NIHR | National Institute for Health Research

Journals Library

Check for updates

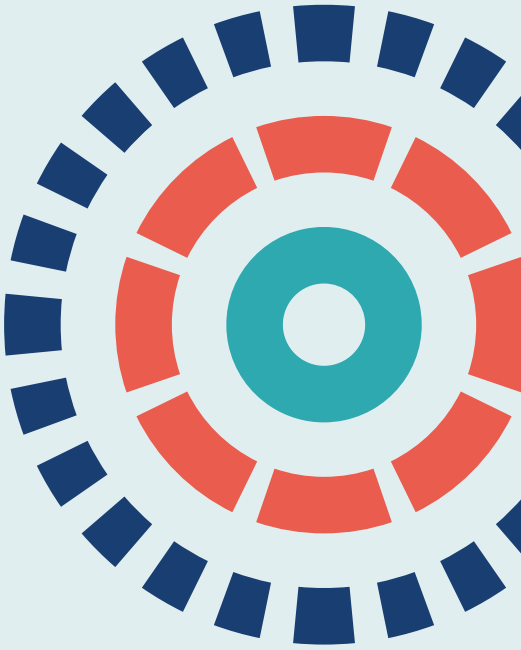
Programme Grants for Applied Research

Volume 7 • Issue 5 • August 2019

ISSN 2050-4322

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

Nigel Bundred, Chris Todd, Julie Morris, Vaughan Keeley, Arnie Purushotham, Adrian Bagust, Philip Foden, Maria Bramley and Katie Riches



DOI 10.3310/pgfar07050

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

Nigel Bundred,[1,2]* Chris Todd,[3] Julie Morris,[1,2,4] Vaughan Keeley,[5] Arnie Purushotham,[6] Adrian Bagust,[7] Philip Foden,[1] Maria Bramley[8] and Katie Riches[5]

[1]Department of Academic Surgery, Manchester University NHS Foundation Trust, Manchester, UK
[2]Manchester Academic Health Sciences Centre (MAHSC), Manchester, UK
[3]School of Health Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK
[4]Clinical Trials Co-ordination Unit, The Christie NHS Foundation Trust, Manchester, UK
[5]Department of Palliative Medicine, Derby Teaching Hospitals NHS Foundation Trust, Derby, UK
[6]Breast Unit, Guy's and St Thomas' NHS Foundation Trust, London, UK
[7]Management School, University of Liverpool, Liverpool, UK
[8]Oncology Research, Pennine Acute Hospitals NHS Trust, Manchester, UK

*Corresponding author

Declared competing interests of authors: none

Published August 2019
DOI: 10.3310/pgfar07050

This report should be referenced as follows:

Bundred N, Todd C, Morris J, Keeley V, Purushotham A, Bagust A, *et al*. Individualising breast cancer treatment to improve survival and minimise complications in older women: a research programme including the PLACE RCT. *Programme Grants Appl Res* 2019;**7**(5).

Programme Grants for Applied Research

ISSN 2050-4322 (Print)

ISSN 2050-4330 (Online)

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full PGfAR archive is freely available to view online at www.journalslibrary.nihr.ac.uk/pgfar. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Programme Grants for Applied Research* journal
Reports are published in *Programme Grants for Applied Research* (PGfAR) if (1) they have resulted from work for the PGfAR programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Programme Grants for Applied Research programme

The Programme Grants for Applied Research (PGfAR) programme, part of the National Institute for Health Research (NIHR), was set up in 2006 to produce independent research findings that will have practical application for the benefit of patients and the NHS in the relatively near future. The Programme is managed by the NIHR Central Commissioning Facility (CCF) with strategic input from the Programme Director.

The programme is a national response mode funding scheme that aims to provide evidence to improve health outcomes in England through promotion of health, prevention of ill health, and optimal disease management (including safety and quality), with particular emphasis on conditions causing significant disease burden.

For more information about the PGfAR programme please visit the website: http://www.nihr.ac.uk/funding/programme-grants-for-applied-research.htm

This report

The research reported in this issue of the journal was funded by PGfAR as project number RP-PG-0608-10168. The contractual start date was in February 2010. The final report began editorial review in October 2017 and was accepted for publication in August 2018. As the funder, the PGfAR programme agreed the research questions and study designs in advance with the investigators. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The PGfAR editors and production house have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).

Abstract

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

Nigel Bundred,[1,2]* Chris Todd,[3] Julie Morris,[1,2,4] Vaughan Keeley,[5] Arnie Purushotham,[6] Adrian Bagust,[7] Philip Foden,[1] Maria Bramley[8] and Katie Riches[5]

[1]Department of Academic Surgery, Manchester University NHS Foundation Trust, Manchester, UK
[2]Manchester Academic Health Sciences Centre (MAHSC), Manchester, UK
[3]School of Health Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK
[4]Clinical Trials Co-ordination Unit, The Christie NHS Foundation Trust, Manchester, UK
[5]Department of Palliative Medicine, Derby Teaching Hospitals NHS Foundation Trust, Derby, UK
[6]Breast Unit, Guy's and St Thomas' NHS Foundation Trust, London, UK
[7]Management School, University of Liverpool, Liverpool, UK
[8]Oncology Research, Pennine Acute Hospitals NHS Trust, Manchester, UK

*Corresponding author Bundredn@manchester.ac.uk

Background: Over 44,000 women are diagnosed with breast cancer annually in the UK. The research comprised three workstreams (WSs) focused on older women.

Maximising survival: WS1 – to identify the role of older women's and surgeons' preferences in cancer treatment decisions and whether comorbidity or fitness for surgery has an impact on survival.

Minimising complications: WS2 – to assess multifrequency bioimpedance (BEA) compared with perometry in identifying women predisposed to develop lymphoedema after axillary node clearance (ANC) surgery. WS3 – to assess, in women at risk of lymphoedema, whether or not applying compression garments prevents the onset of lymphoedema.

Design: WS1 – a prospective, consecutive cohort of surgical consultations with women aged ≥ 70 years with operable breast cancer. Interviews and questionnaire surveys of surgeons' and women's perceptions of responsibility for treatment decisions (Controlled Preference Score), effects related to survival and secondary outcomes. WS2 – women undergoing ANC for cancer in 21 UK centres underwent baseline and subsequent BEA, and perometer arm measurements and quality-of-life (QoL) assessments. WS3 – a randomised controlled trial testing standard versus applying graduated compression garments to the affected arm, for 1 year, in WS2 patients developing arm swelling.

Setting: Breast outpatient clinics in hospitals with specialist lymphoedema clinics.

Participants: WS1 – patients aged ≥ 70 years with newly diagnosed, operable, invasive breast cancer. WS2 – women with node-positive cancer scheduled to undergo ANC. WS3 – WS2 participants developing a 4–9% increase in arm volume.

Interventions: WS1 – observational study. WS2 – observational study. WS3 – application of graduated compression garments to affected arm, compared with standard management, for 1 year.

Outcomes: WS1 – self-report and clinically assessed health, QoL, complications and survival. WS2 – perometer and bioimpedance spectroscopy (BIS) measurements, QoL and health utility; and sensitivity and specificity of BIS for detecting lymphoedema compared with perometer arm measurements; in addition, a health economics assessment was performed. WS3 – time to the development of lymphoedema [≥ 10% relative arm-volume increase (RAVI)] from randomisation.

Results: WS1 – overall, 910 women were recruited, but numbers in the substudies differ depending on consent/eligibility. In a study of patient/surgeon choice, 83.0% [95% confidence interval (CI) 80.4% to 85.6%] had surgery. Adjusting for health and choice, only women aged > 85 years had reduced odds of surgery [odds ratio (OR) 0.18, 95%CI 0.07 to 0.44]. Patient role in treatment decisions made no difference to receipt of surgery. A qualitative study of women who did not have surgery identified three groups: 'patient declined', 'patient considered' and 'surgeon decided'. In a survival substudy, adjusting for tumour stage, comorbidity and functional status, women undergoing surgery had one-third the hazard of dying from cancer. Serious complications from surgery were low and not predicted by older age. In a substudy of the effect of surgical decision-making on HRQoL, 59 (26%) received preferred treatment decision-making style. In multivariate analyses, change in HRQoL was associated neither with congruence ($p = 0.133$) nor with receipt of surgery ($p = 0.841$). In a substudy of receipt of chemotherapy in women aged ≥ 65 years, adjusting for tumour characteristics, health measures and choice, women aged ≥ 75 years had reduced odds of chemotherapy (OR 0.06, 95%CI 0.02 to 0.16). WS2 – lymphoedema by 24 months was detected in 21.4% of women by perometry (24.4% sleeve application) and in 39.4% by BIS. Perometer and BIS measurements correlated at 6 months ($r = 0.61$). Specificity for sleeve application was greater for perometry (94% CI 93% to 96%) at 24 months, as was a positive predictive value of 59% (95% CI 48% to 68%). Lymphoedema diagnosis reduced QoL scores. Sleeve application in the absence of RAVI of > 9% did not improve QoL or symptoms. A composite definition of lymphoedema was developed, comprising a 9% cut-off point for perometer and self-reported considerable swelling. Diagnostic accuracy was ≥ 94% at 6, 12 and 24 months. WS3 – the PLACE (Prevention of Lymphoedema After Clearance of External compression) trial recruited 143 patients, but recruitment was slow and closed early on the advice of the Independent Data Monitoring Committee. A qualitative substudy identified a number of barriers to recruitment.

Conclusions: Half of older patients felt that they influenced decisions about their treatment. No relationship between decision preference being fulfilled and HRQoL in elderly patients diagnosed with cancer occurred, and older age did not predict complications. Primary surgery reduced the hazard of dying of cancer by two-thirds, independent of age, health and tumour characteristics. Women aged ≥ 75 years have reduced odds of receiving chemotherapy. Lymphoedema (along with a BMI of > 30 kg/m^2, cigarette smoking and chemotherapy) reduces QoL. Changes in arm volume of > 9% predicted lymphoedema requiring and benefiting from sleeve application. The PLACE trial qualitative work provides a number of insights into problems of recruitment that were specific to this trial (stigma of compression garments) but that are also generalisable to other RCTs.

Limitations: Both WS1 and WS2 were large, multicentre, UK cohort, observational studies. The WS3 PLACE trial has not reported yet but closed with approximately half of the patients originally planned.

Future work: Research producing objective measures for sleeve prescription in the NHS is required.

Trial registration: Current Controlled Trials ISRCTN48880939.

Funding: This project was funded by the National Institute for Health Research (NIHR) Programme Grants for Applied Research programme and will be published in full in *Programme Grants for Applied Research*; Vol. 7, No. 5. See the NIHR Journals Library website for further project information. Additional support for WS1 came from a Breast Cancer Campaign Grant and a NIHR Postdoctoral Fellowship. ImpediMed (Carslbad, CA, USA; www.impedimed.com) provided bioimpedance L-Dex® machines and electrodes for the study and Sigvaris provided the external compression garments free of charge for the (PLACE) trial.

Contents

List of tables

List of figures

List of supplementary material

Report Supplementary Material 1 Individual data values

Supplementary material can be found on the NIHR Journals Library report project page (www.journalslibrary.nihr.ac.uk/programmes/PGfAR/RP-PG-0608-10168/#/documentation).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

ADL	activities of daily living
ALMANAC	Axillary Lymphatic Mapping Against Nodal Axillary Clearance
ANC	axillary node clearance
ANOVA	analysis of variance
AUC	area under the curve
AUROC	area under the receiver operating characteristic
BCC	Breast Cancer Campaign
BEA	multifrequency bioimpedance
BIS	bioimpedance spectroscopy
BMI	body mass index
CI	confidence interval
CPS	Controlled Preference Score
CTU	Clinical Trials Unit
EMM	estimated marginal mean
EQ-5D	EuroQol-5 Dimensions
EQ-5D-3L	EuroQol-5 Dimensions, three-level version
EQ VAS	EuroQol visual analogue scale
ER	estrogen receptor
FACT-B	Functional Assessment of Cancer Therapy – Breast Cancer
FACT-B+4	Functional Assessment of Cancer Therapy – Breast Cancer, version 4
GEE	general estimating equation
HR	hazard ratio
HRQoL	health-related quality of life
IDMC	Independent Data Monitoring Committee
IRR	incidence rate ratio
LN	log normalised
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NPV	negative predictive value
NSQIP	National Surgical Quality Improvement Program
OR	odds ratio
PET	primary endocrine therapy
PLACE	Prevention of Lymphoedema After Clearance by External compression
PPI	patient and public involvement
PPV	positive predictive value
QALY	quality-adjusted life-year
QoL	quality of life
RAVI	relative arm-volume increase
RCT	randomised controlled trial
ROC	receiver operating characteristic
SD	standard deviation
SF-6D	Short Form Questionnaire-6 Dimensions
SF-12	Short Form questionnaire-12 items
TOI	Trial Outcome Index
WLE	wide local excision
WS	workstream

Plain English summary

Annually, over 44,000 women are diagnosed with breast cancer in the UK. Many older women do not receive appropriate management and a disproportionate number of deaths (6500) occur among elderly patients. Patients who are cured can suffer complications of treatment, such as lymphoedema (gross swelling of the arm).

Complications could be avoided by better identification of patients which takes account of variation in risk of recurrence and susceptibility to complications.

To understand the management of older patients, a study of surgical consultations from newly diagnosed patients with operable cancer attending breast units asked who made their decisions about need for surgery, and their subsequent survival was studied.

Risk of arm swelling (lymphoedema) after armpit surgery for breast cancer was studied in a 1100-patient multicentre study, and a trial was undertaken that looked at the benefit of compression garment sleeves to prevent lymphoedema developing in patients after surgery.

Decisions about surgery were made by the surgeons; patient fitness did not predict surgery or complications of treatment. Surgery was associated with a 70% reduction in cancer deaths. Older women were less likely to receive chemotherapy.

Arm swelling was common after surgery, but only 24% of women developed lymphoedema. Women developing lymphoedema had a reduced quality of life up to 2 years after surgery. Baseline measurements and monitoring identified those women most likely to develop lymphoedema.

The PLACE (Prevention of Lymphoedema After Clearance by External compression) trial has not yet reported its results.

Older breast cancer patients need optimal management. Individualised monitoring after surgery allows treatment of arm swelling to improve quality of life.

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 ≥ 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 > or = 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 Charleson 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 ≥ 65 years demonstrated that women aged ≥ 75 years have lower chemotherapy and radiotherapy rates than women aged 65–69 years. Adjusting for tumour characteristics, health measures and choice, women aged ≥ 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 ≥ 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 ≥ 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 ≥ 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 ≥ 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 ≥ 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 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.

Funding

Funding for this study was provided by the Programme Grants for Applied Research programme of the NIHR. Additional support for WS1 came from a Breast Cancer Campaign Grant and a NIHR Postdoctoral Fellowship. ImpediMed (Carslbad, CA, USA; www.impedimed.com) provided bioimpedance L-Dex® machines and electrodes for the study and Sigvaris provided the external compression garments free of charge for the PLACE trial.

SYNOPSIS

Individualised care aims to improve outcomes, maximising the effectiveness of therapy while minimising its toxicity, taking account of patient variability in terms of recurrent risk (high or low) and patient phenotype (more or less susceptible to complications) and patient choice. In line with the priorities of the NHS Cancer Reform Strategy,[1] we addressed current inequalities of care for older women and how to identify and reduce instances of common complications to improve quality of life (QoL). Improved survival has been achieved for most patients aged < 70 years. Undertreatment is common in older patients because practitioners remain concerned about the risk of complications of therapy. Undertreatment is associated with early death within 1 year for patients aged ≥ 70 years and with early recurrence within 5 years.

We investigated perceptions of the surgical decision-making process in order to predict complications and assess the value of surgery for improved survival in the treatment of elderly breast cancer patients in a prospective cohort study in Greater Manchester. In addition, we analysed survival and complication rates in relation to baseline, treatment and process variables to identify the role of age, health status, choice and treatment, etc., in outcome. The elderly patient project was complementary to a Breast Cancer Campaign (BCC) and National Institute for Health Research (NIHR) Fellowship project, focusing on patients' perceptions of responsibility for surgical discussion in women attending breast units across Greater Manchester and the North West. Two elderly patient cohorts were put together for the subsequent survival data generated at 4 years. This allowed us to understand whether the woman received standard or non-standard treatment, whether this decision was the patient's or the surgeon's, and whether it had an impact on her overall survival. It has allowed us to try to identify predictors of surgical risk, which would provide a tool to assess the risk of adverse outcome (fitness for surgery) as part of a complex intervention. Surgery reduced the risk of death [hazard ratio (HR) 0.3] and improved cancer-free survival (regardless of underlying comorbidity).

Multifrequency bioimpedance (BEA) electrical analysis, also referred to as bioimpedance spectroscopy (BIS), is believed to identify lymphoedema development when a 10-fold change (standard deviation from baseline) is detected after axillary node clearance (ANC) surgery. It is claimed to predict lymphoedema by up to 10 months earlier than arm swelling in a small study. We assessed patients' BEA in 1100 women compared with arm measurement (perometry) for the prediction of lymphoedema and found a positive predictive value (PPV) of 54% but were unable to confirm that BEA monitoring was helpful technology in the prediction of development of lymphoedema. We found a higher risk of lymphoedema in patients developing early arm swelling (4–9% increase on perometry), along with the number of metastatic nodes removed and QoL subscale scores at surgery. A predictive scoring index for lymphoedema has been developed based on these variables.

The PLACE (Prevention of Lymphoedema After Clearance by External compression) trial aimed to prevent lymphoedema after axillary node clearance by applying external compression garments in patients with early arm-volume increase (4–9%). We recruited 143 patients, but recruitment was slow and the IDMC recommended that the trial close to further recruitment while maintaining follow-up of participants, as the rate of lymphoedema in the study was 40% (lower than anticipated).

The rate of lymphoedema in BEA was also lower than expected on follow-up, which we have attributed to the reiterative information and explanation given to patients to protect the arm, combined with the simple lymphatic massage and drainage that the patients were taught after surgery. We intend, however, to continue to follow up patients in the PLACE trial to assess the outcomes on lymphoedema development. Eligible women for our studies were identified preoperatively in nine study sites across the UK initially, but this was increased to 21 sites to improve and expedite recruitment.

During the project, a number of changes occurred, both in staff and to the work planned. The initial Programme Grant co-ordinator was Charlotte Stockton, who left after 36 months and was replaced

by Sarah Ashton. Sarah Ashton left after a further 18 months and was replaced by Donna Watterson. Initially, seven NHS sites were planned, but, to improve recruitment to workstream (WS) 3, 14 more sites were added (*Figure 1*).

Workstream 1

The elderly patient study was a prospective cohort study assessing the role of the surgeon and the patient and their agreement as to who made decisions about the use of surgery for their early breast cancer in an elderly population > 70 years of age. It was planned that predictors of surgical risk identified from this study, in terms of either patient fitness or other health parameters, would allow us to develop a screening tool and that we would then conduct feasibility randomised controlled trial (RCT) to determine whether more, appropriate, surgery occurred when assessment of surgical risk took place.

As no predictors of surgical risk were identified, the planned feasibility study could not go ahead and was replaced by further follow-up of the cohort, with several additional analyses of the data as per board approval in January 2016, including outcomes and overall survival in proportion to health risk factors. A comparative analysis with previous work from 1999 and subsequent years was considered, but after a meeting with the NIHR to review, it was agreed that there was greater clinical utility in extending the congruence analysis, to indicate whether desired treatment decision-making had an effect on post-surgical health-related quality of life (HRQoL) (see *Appendix 6*), and the impact on non-surgical and surgical patients, on the surgery in terms of overall survival *Appendix 7*. These data have now been published (see *Appendix 5*).

Workstreams 2 and 3

There was a 6-month delay in the start of recruiting to WS2a and WS3, due to the staggered opening of all initial seven sites and the delay in research and development in certain sites to approve the BEA device, even though it was an external diagnostic device.

Workstream 2a

Comparing bioimpedance with perometer recruited 1100 patients.

Workstream 2b

The diagnostic test accuracy analysis protocol was requested at a NIHR stakeholder meeting in January 2016 to establish the diagnostic test accuracy of bioimpedance, compared with perometry, for the diagnosis of arm lymphoedema and to explore composite measurements to develop a clearer working definition of lymphoedema and implications of alternative definitions. Two hundred and sixty-six patients had a compression garment fitted for lymphoedema in the study (221 by 24 months) and an analysis was performed to understand how this intervention was triggered. Changes in personnel at the Clinical Trials Unit (CTU) also contributed to delay in statistical analysis as a result of data checking, management and cleaning issues within the unit.

Workstream 3

The PLACE trial had a target of 270 patients, but recruitment was slower than anticipated. The PLACE trial was opened at 14 additional centres including King's Mill Hospital, Macclesfield; Russell Hall Hospital, Dudley; Singleton Hospital, Swansea; Royal Albert Edward Infirmary, Wigan; Homerton University Hospital,

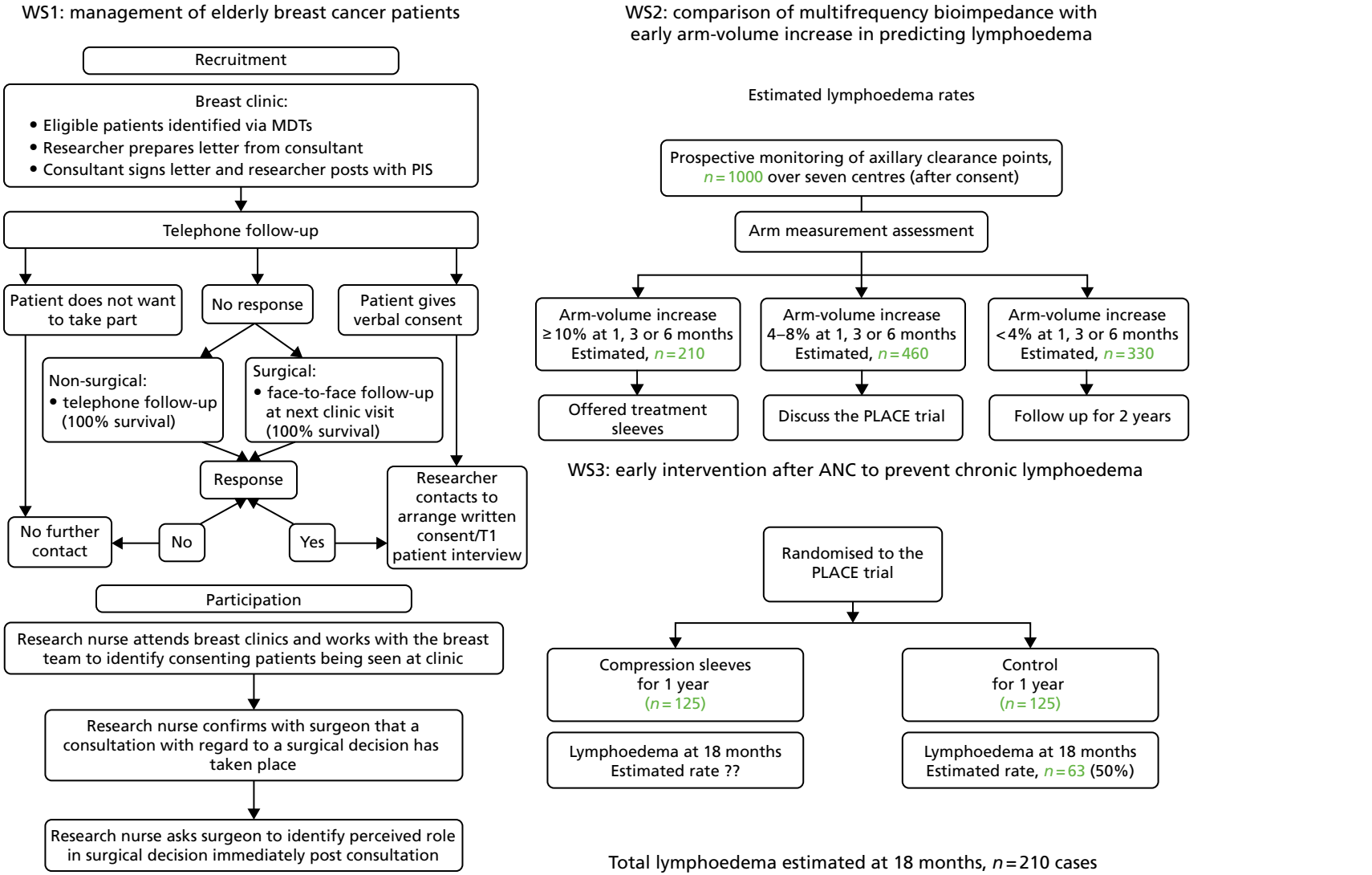


FIGURE 1 Kaplan–Meier curve for breast cancer-specific survival for patients treated with and without breast surgery. Survival in 910 early breast cancer patients in an elderly population according to surgical treatment.

London; Macclesfield District General Hospital; Bronglais General Hospital; Peterborough City Hospital; and the George Eliot Hospital, Nuneaton. We explored several other centres, and some of these later centres were open to recruitment only with the addition of tape measurements to assess arm-volume increase. We allowed patients who had had a sentinel node biopsy and who had an arm-volume increase of 4–9% to be recruited to the study (see *Appendix 18*), as an American study looking at only sentinel node biopsy patients[2] reported that these patients had a very high risk of lymphoedema when an arm-volume increase of 4–9% was seen after sentinel node biopsy within 6 months. To provide insight to improve recruitment, a qualitative study was carried out by Karen Spencer, Research Associate, who came into post in August 2015. A number of findings were made that could help improve recruitment procedures, but before we could initiate those findings, the Independent Data Monitoring Committee (IDMC) recommended that as BEA recruitment was complete, and the PLACE trial had recruited only 121 patients, we should close the study to further recruitment as it would not reach its target of 270 patients. In the event, recruitment stayed open until all patients who had been approached to take part in the PLACE trial through BEA decided whether or not to go in the trial. In total, 139 patients were recruited and remain on follow-up. The overall risk of lymphoedema in the study (control and sleeve arm) is 40%, but the IDMC's decision was taken with data from 65 patients with 2-year follow-up, informed by the CTU statistician (without any chief investigator input). In the light of the extended review of the data (not yet fully quality checked by the CTU) on 139 patients, it is clear that the trial needs to complete follow-up of all patients for 2 years and that the data need to be reviewed. Initial statistical power calculation was that if the difference in lymphoedema was 40% in a control arm and nil or 1% in the sleeve arm, there would be a statistical difference demonstrated with 125 patients.

Additionally, Taghian A *et al*. (Massachusetts General Hospital, 2016, personal communication) are running a randomised trial of compression sleeves in patients with 4–9% arm increases after sentinel node biopsy or ANC, in Boston, Massachusetts, and have agreed to meta-analyse their data with this study's data. They currently have around 50 patients recruited to their trial, and it may well be that between the two studies we will have sufficient power to answer the question when follow-up is finished. We have provided the data from WS1, and the publications associated with it, as well as a report, which includes short-term (3.8 years) survival and effects of congruence on QoL, and the finding that having surgery reduced the risk of death from breast cancer by 30%. Data queries from all PLACE trial patients have been updated to allow the PLACE trial data to be finally analysed 2 years after the last patient was randomised in November 2016 (i.e. November 2018).

The number of patients recruited to BEA means that the data permitted us to provide insight into the diagnostic accuracy of BEA, and were presented to the National Institute for Health and Care Excellence (NICE) as part of a Medical Technologies Evaluation Programme in January 2017 for the selection and use of L-Dex® (Carslbad, CA, USA; www.impedimed.com) for detection of lymphoedema (see *Report Supplementary Material 1*). The NICE review panel appreciated the quality of the evidence and have reported their findings.

Workstream 1: management of elderly breast cancer patients

In line with the priorities of the NHS Cancer Reform Strategy,[1] WS1 on the management of older breast cancer patients sought to address inequalities of care for older women. Over recent years, improved survival has been achieved for most patients aged < 70 years. Our earlier work revealed undertreatment to be common in older patients, and practitioners remain concerned about the risk of complications of therapy. Undertreatment is associated with early recurrence and death;[3,4] therefore, we proposed to complement our work investigating patient views by investigating surgeons' perceptions of the surgical decision-making process for the same consultations as those reported by patients. We also planned to develop a risk screening tool based on follow-up of our cohort, which could be administered pre treatment to predict the risk of complications allowing optimisation of treatment for elderly patients with breast cancer.

Study design

In the original application to NIHR, this WS comprised two studies complementing studies funded by BCC and a NIHR fellowship. The original plans had to be modified during the lifetime of the programme (see below).

Study 1

This study complemented the BCC project (protocol submitted to the NIHR with an original application reference of 2008NovPR35) focusing on patients' perceptions of responsibility for the surgical decision. The BCC study was a prospective cohort study of 550 women aged ≥ 70 years consecutively recruited from newly diagnosed patients with operable (stage I–IIIa) breast cancer attending breast units in Greater Manchester over 21 months. The BCC study collected data on women's preferences through an interview conducted at home. Study 1 complemented the BCC work by measuring surgeons' perceptions of who made the treatment decision for the same index cases and related to the same consultations. Thus, we were able to collect a measure of agreed responsibility for treatment decisions. Regardless of whether an older woman received standard or non-standard treatment, we were able to establish whether this decision was a result of the patient's or the surgeon's choice. Data on surgeons' perceptions of responsibility for the surgical decision for individual consultations had to be collected by brief, immediately post-consultation interviews, a resource-intensive method.

Study 2

As part of the research funded by the BCC, NIHR Fellowship and this programme, we planned to identify predictors of surgical risk using multivariate modelling of data from our cohort. For study 2, we planned to 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 Medical Research Council complex intervention framework and guidelines. However, our modelling revealed no significant clinically novel predictors of surgical risk and therefore we were not able to build a viable screening tool, and hence could not proceed to conduct the planned feasibility trial (see *Modelling surgical risk*). We thus consulted with programme board and proposed and received board approval for further follow-up of the cohort (IMPACT study) and several additional analyses of the data to investigate outcomes so as to investigate the impact of lack of treatments on older breast cancer patients in the UK.[4] In addition, we undertook an analysis looking at the relationship between congruence (patient getting the treatment decision-making style she preferred) and HRQoL at follow-up.

Workstream 1, aim 1 studies: does patient choice or poor health explain lack of surgery?

The results of study 1 are reported in Lavelle *et al.*'s[5] paper.

In this first study we investigated whether the lack of surgery for older patients can be explained by patient choice/poor health in a prospective cohort study of 800 women aged ≥ 70 years diagnosed with operable (stage I–IIIa) breast cancer at 22 English breast cancer units in 2010–13 by using interviews and case note review. The outcome measure was surgery for operable breast cancer (stage I–IIIa) < 90 days from diagnosis. Logistic regression adjusting for age, health measures, tumour characteristics, sociodemographics and patients'/surgeons' perceived responsibility for treatment decisions was undertaken.[6–9]

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 (OR 0.18, 95% CI 0.07 to 0.44). Each point increase in activities of daily living (ADL) score (worsening functional status) reduced the odds of surgery by over one-fifth (OR 0.23, 95% CI 0.15 to 0.35). The patient's role in the treatment decisions made no difference to whether or not they received surgery; those who were active/collaborative were as likely to get surgery as those who were passive, that is, they left the decision up to the surgeon. Lower surgery rates among older women with breast cancer are unlikely to be due to patients actively opting out of having this treatment. However, poorer health explains the difference in surgery between women aged 75–84 years and younger women. The lack of surgery for women aged ≥ 85 years persists even when health and patient choice are adjusted for, revealing that inappropriate undertreatment persists in old age.

To understand these results more fully, we undertook an in-depth qualitative interview study of a group of women who did not receive primary surgery to try to identify how the decision not to have surgery was arrived at.[10] Twenty-eight in-depth interviews were conducted with women aged > 70 years who had operable breast cancer but were receiving primary endocrine therapy (PET) as their primary treatment and had not received, and were not scheduled to receive, surgery. The interviews focused on their perceptions of why they were being treated with PET rather than surgery. Interviews were transcribed verbatim and were analysed using framework analysis. The explanations given varied, but based on reasons for proffered, patients could be divided into three groups: 'patient declined', 'patient considered' or 'surgeon decided'. The 'patient declined' group ruled out surgery to treat their breast cancer as they were not interested in maximising survival and rejected surgery citing age or concerns about impact of treatment on level of functioning. The 'patient considered' group had considered surgery, but chose PET. These patients viewed this as offering them two options; if PET failed, then they could have surgery. The 'surgeon decided' group was started on PET by the surgeon and in most cases the surgeon asserted that the patient's comorbidities were incompatible with surgery.

We conclude that older women are a diverse group and have various reasons for forgoing surgery. Discussions about breast cancer treatment should be patient centred and adapted to differing patient priorities. This issue of patient centeredness is particularly important when we consider the congruence between women's preferences for involvement in treatment decision-making and their actual involvement, which was addressed in study 2 and is reported below.

As can be seen in *Appendix 5*, there is little congruence between patients' preferred and actual roles in the treatment decision-making process, as revealed by their Controlled Preference Score (CPS) scores. Only 163 out of 673 patients (24%) actually received their preferred role in the decision-making, and the vast majority (125; 77%) of these were when they indicated that they wanted decision to be made by the surgeon and indicated this to be the case in actuality. Using Cohen's kappa, we identify there is only a 'slight' level of agreement ($\kappa = 0.039$) between preferred and actual role in decision-making.[11] The majority of patients indicated that their actual role was more passive than they would have preferred (442 patients; 66%); only 68 patients (10%) indicated that their actual role was more active than they would have preferred.

These data strongly suggest that it is the surgeon (or at least the surgical team) that is steering the decision in most cases. As revealed by data reported in Lavelle *et al*.[5] (see *Table 3*), patients are far more likely than surgeons to indicate that treatment options were not discussed during the consultation. In 112 out of 473 consultations, the patient and surgeon agreed that they did not discuss treatment options. In only 24 out of 136 (17.6%) consultations scored by the surgeons as treatment options not being discussed did patients indicate otherwise; on the other hand, of the 267 consultations scored by patients as not including discussion of treatment options, the surgeons indicated differently in 155 (58%).

Modelling surgical risk

The original plans to identify surgical risk factors create and test a risk assessment tool could not be followed up, because in the final models the novel risk factors proved not to contribute significantly or, if significant, increased the odds only fractionally. These results are reported by Sowerbutts *et al.*[10]

In brief, the ability of pre-treatment health measures to predict complications was investigated in a prospective cohort study of a consecutive series of 664 women aged at least 70 years undergoing surgery for operable (stage I–IIIa) breast cancer at 22 English breast units between 2010 and 2013.[12–14] Data on treatment, surgical complications, health measures and tumour characteristics were collected by case note review and/or patient interview. Outcome measures were all complications and serious complications within 30 days of surgery. One or more complications were experienced by 41% of patients, predominantly seroma or primary or minor infections. Complications were serious in 6.5% of patients. More extensive surgery predicted a higher number of complications, but not serious complications. 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. In conclusion, 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. Health measures that predict surgical risk were identified in multivariable models, but the effects were weak, with 95% CIs close to unity. They were therefore judged not suitable for building a clinically useful risk screening tool.

Workstream 1, aim 2 studies: impact of lack of treatments on older breast cancer patients in the UK

Introduction

For these studies we used our established cohort of patients aged ≥ 65 years and diagnosed with early-stage invasive breast cancer in 22 trusts in England from 1 July 2010 to 31 March 2013. The extent to which lack of surgery is explained by patient health and choice has been investigated using a range of pre-treatment health measures, tumour characteristics and demographics collected prospectively from patient interview and case note review.[1] However, follow-up of subsequent adjuvant treatment (radiotherapy and/or chemotherapy following surgery) and the impact of lack treatment on survival and long-term HRQoL were not within the remit, resources or timescale of this previous work.

Background

Older women in the UK experience the highest incidence and worst survival for breast cancer, and are less likely to have standard treatment.[1,3,4] The impact of lack of treatment on older patients' survival needs to be investigated. There is good evidence that poor survival is a particular problem for older breast cancer

patients in the UK. Møller *et al.*[4] found that the 5-year relative survival for women aged ≥ 80 years is 61% in the UK, compared with 74% in Norway and Sweden. They conclude that this 'leads to important questions about the adequacy of care provided for the oldest patients'. However, Møller *et al.* did not investigate access to treatment on survival. Moreover, the proportion of patients with comorbidities/frailty and later-stage breast cancer increases with age, and both of these factors also affect survival, and so these variables should also be investigated/adjusted for.

Treatment for breast cancer is based on clinical trials that excluded older women. Moreover, recent trials specific to older patients have closed as a result of failure to recruit.[13] The deficit of evidence on the risks/benefits of treatment for the age group most affected by breast cancer remains. Given the increasing proportion of older people in our population,[11,14,15] this presents a growing problem, and studies of older women's response to therapy are required in order to provide patients, physicians and policy-makers with evidence on which to base decisions about treatment. Surgery is the mainstay of treatment for early breast cancer and yet rates reduce among those aged ≥ 75 years. Omission of surgery leads to lack of local control, particularly at 2 years post diagnosis.[16] Although the only previous trial investigating surgery versus no surgery for older breast cancer patients planned to investigate costs, it closed as a result of failure to recruit.[6]

Aims

Workstream 1 set out to address the following research aims in the second set of studies:

- to investigate the extent to which primary surgery for older women with early breast cancer increases survival and HRQoL and is effective as measured by quality-adjusted life-years (QALYs)
- to investigate follow-up adjuvant treatment (radiotherapy and/or chemotherapy post surgery) for older breast cancer patients regarding:
  - the extent to which adjuvant treatment increases survival and HRQoL and is effective
  - the extent to which lack of adjuvant treatment can be explained by patient health and choice.

Methods

Table 1 and *Figure 2* (see *Appendix 1*) summarise the outcome variables, explanatory variables and main methods for each of the above aims, along with a flow diagram specifying the logic and numbers of patients in the specific analyses performed. Data on our established cohort of 944 women aged ≥ 65 years consecutively diagnosed, from 1 July 2010 to 31 March 2013, already include a wide range of health measures, patient choice, tumour characteristics, demographics and hospital resource variables collected at diagnosis via pre-treatment patient interview and case note review. Follow-up of the cohort involved a further case note review (up to 3 years following diagnosis), postal survey (at 3–4 years post diagnosis – ideally all patients would be surveyed at 3 years, but timings are fixed by diagnosis dates of cohort) and mortality flagging (*Figure 19*).

Only patients recruited/diagnosed from 1 July 2010 to 31 December 2012 are included in this study ($n = 910$) because recruitment was phased out in the final 6 months of the project, with the majority of sites stopping recruitment from 31 December 2012. Only another 34 out of the 944 patients were recruited from 31 December 2012 to 31 March 2013. The inclusion of these final 34 patients in this study is not necessary to support the analyses and would have increased study costs substantially, as it would have required a further wait of 3 months (with concomitant staff salaries, etc.) before the analysis could be conducted with only 34 more patients included (see *Appendix 1*).

We conducted further case note reviews to follow up each of the included 910 participants up to 3 years post diagnosis, recording adjuvant treatments received. The pro formas for collecting data from case notes were developed and piloted in consultation with clinicians and a health economist (to ensure the correct cost allocation for various procedures). Inter-rater reliability and data quality checks were undertaken on

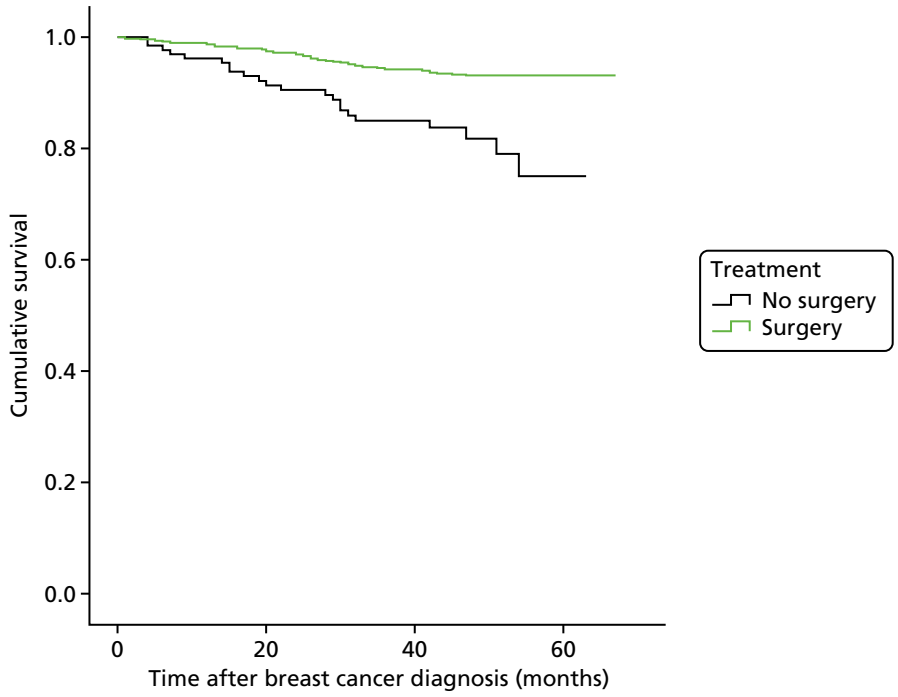
TABLE 1 Baseline characteristics by observed and expected for breast cancer-specific deaths ($n = 910$; 71 breast cancer-specific deaths)

Variable	Category	*n*	Per cent	Deaths (*n*)		Log-rank test[a] *p*-value[b]
				Observed	Expected	
Primary surgery	Yes	772	84.8	49	61.99	
	No	138	15.2	22	9.01	< 0.001
Age group (years)	65–69	136	15.0	6	11.14	
	70–74	265	29.1	18	21.78	
	75–79	225	24.7	13	17.94	
	80–84	148	16.3	14	10.89	
	≥ 85	136	15.0	20	9.26	0.001
Grade	1	168	18.5	7	13.28	
	2	489	53.7	28	38.70	
	3	183	20.1	32	13.36	< 0.001
	Missing	70	7.7	4	5.67	< 0.001
ER or PR positive	Yes	774	85.1	50	60.77	
	No	81	8.9	17	5.90	< 0.001
	Missing	55	6.0	4	4.33	< 0.001
Tumour stage	I	403	44.3	19	32.06	
	II and IIIa	507	55.7	52	38.94	0.002
Charlson Comorbidity Index	0	473	52.0	38	37.98	
	1	268	29.5	21	20.53	
	≥ 2	169	18.6	12	12.49	0.985
Functional status	Independent (1–2)	758	83.3	55	60.38	
	Dependent (3–4)	148	16.3	16	10.38	0.061
	Missing	4	0.4	0	0.24	0.153
	Total	910	100	71	71	

ER, estrogen receptor; PR, progesterone receptor.
a The log-rank test tests the equality of survivor function across groups.
b *p*-values for each variable for complete data reported first followed by data including missings if relevant.

10% of cases. Pro formas satisfied kappa > 0.6, showing substantial to perfect agreement and data input errors of < 0.3%.[11]

The HRQoL survey undertaken at diagnosis was repeated. Ideally, this would have been at 3 years in all women, but timings are fixed to diagnosis date and the first woman was recruited into the study on 1 July 2010. As participants have already consented to further follow-up, ethics approval only required a substantial amendment to specify the follow-up instruments, etc. Patients who did not return the survey were followed up by telephone and reposting 2 weeks later and offered telephone support or a face-to-face interview to complete the survey.



Number at risk					
No surgery	138 (15%)	129 (14%)	114 (13%)	98 (12%)	84 (11%)
Surgery	772 (85%)	761 (86%)	734 (87%)	710 (88%)	689 (89%)

FIGURE 2 Kaplan–Meier breast cancer-specific survival curve for patients not treated with surgery vs. treated with surgery for breast cancer.

The Office for National Statistics mortality flagging via NHS Digital provided information on both date and cause of death. This enabled analyses of breast cancer survival, the primary outcome of interest.

Outcome/dependent variables

The following outcome measures were specified a priori:

- aim A (extent to which primary surgery increases survival, HRQoL and is effective)
- aim Bi (extent to which adjuvant treatment increases survival and HRQoL and is effective)
- survival to 3 years post diagnosis
- HRQoL at 3–4 years from diagnosis (see above and *Appendices 5–7* for explanation of timings)
- QALYs at 3–4 years post diagnosis
- aim Bii (extent to which lack of adjuvant treatment can be explained by patient health and choice)
- receipt of radiotherapy in addition to primary surgery
- receipt of chemotherapy in addition to primary surgery.

Explanatory variables

Explanatory variables include measures of health, patient choice, tumour characteristics and demographic variables. Adjusting for these in the analyses enabled us to account for case mix, health status and preferences of older women. Health measures have been selected based on ease of administration, validity, reliability, acceptability to older people, availability of normative data and prediction of non-standard management and/or treatment outcomes.[3,11,15,16] Tumour characteristics have been selected on the basis of management guidelines including TNM stage, grade and steroid receptor status. Choice was determined using the CPS, which has been selected as a validated measure of patient choice.[6–8,14]

Analyses

Aim A

The impact of surgery on survival and HRQoL and its effectiveness was investigated in the full sample of 910 women (see *Figure 2*). For aim Bi, the impact of the adjuvant treatments of radiotherapy and chemotherapy in addition to surgery on these outcomes was tested within a subsample of 759 patients who had surgery (*Figure 3*). Cox (proportional hazards) regression was used to examine the effect of surgery and adjuvant treatment on survival, adjusting for age, tumour stage, steroid receptor status, comorbidity and functional status. The impact of treatment on difference in HRQoL at diagnosis compared with 3–4 years was adjusted for age, health, choice and tumour characteristics by multiple linear regressions. As recommended by NICE, effectiveness was measured by the difference in QALY gain of treatment adjusted for various age, health, choice and tumour variables (QALY gain of treatment = quality of life lifetime with treatment – quality of life lifetime without treatment). To calculate QALYs, the Short Form Questionnaire-6 Dimensions (SF-6D) utility measure was derived from the SF-12v2, generated using preference weights obtained from a sample of the general population in the UK and following the procedures described at www.sheffield.ac.uk/scharr/sections/heds/mvh/sf-6d (accessed 29 April 2019).

Aim Bii

To assess the extent to which lack of adjuvant treatment can be explained by patient health and choice, surgical patients were included in a logistic regression analysis of receipt of adjuvant chemotherapy and radiotherapy (*Figure 20*), adjusting for health measures, patient preference, tumour characteristics and demographic variables. Tumour characteristics include those used to determine chemotherapy status in clinical guidelines (steroid receptor status, tumour stage and grade).[13,17] As clinical guidelines indicate that radiotherapy is necessary after lumpectomy but not always necessary following mastectomy,[13,17] multivariate logistic regression predicting receipt of radiotherapy was also limited to the number of patients in the cohort receiving lumpectomy.

Results

Aim A

To investigate the extent to which primary surgery for older women with early-stage breast cancer increases survival and HRQoL and is effective.

Sample

All 910 participants could be included in the survival analyses (see *Figure 2*). Of these, 643 returned the survey at 3–4 years (mean 3.3 years post diagnosis, minimum 3.0 years, maximum 4.4 years), giving an overall response rate of 71%. However, of the 910 participants in the overall sample, 839 completed the Short Form questionnaire-12 items (SF-12) at baseline, of whom 617 returned the survey at 3–4 years, including 501 completed SF-12 surveys. Only those returning completed SF-12 surveys at baseline (diagnosis) and 3–4 years post diagnosis could be included in the analyses of difference in HRQoL from baseline to 3–4 years post diagnosis ($n = 501$). However, those participants who did not return a survey at 3–4 years because they had died could be included in the QALY calculation and, thus, in the cost-effectiveness analyses ($n = 640$). Survival results are presented in *Appendix 4*.

In short, of the 910 women in the study, 178 died before the end point of the study: 71 of breast cancer and 107 of other causes (*Table 2* relates to breast cancer deaths only). Patients who had primary surgery (vs. those who did not) had 0.36 times the hazard of dying of breast cancer (95% CI 0.20 to 0.66; $p = 0.001$) adjusting for other factors. In univariate analysis, women aged ≥ 85 years had an increased hazard of breast cancer death compared with those aged 65–69 years (HR 4.02, 95% CI 1.61 to 10.01; $p = 0.003$). However, when adjusted for surgery, tumour characteristics and general health, this was at best only borderline significant at the 5% level ($p = 0.053$). Surgery for older breast cancer patients reduces the hazard of breast cancer death by two-thirds, independent of age, comorbidity and tumour characteristics.

TABLE 2 Multiple regression of difference in HRQoL (SF-6D) 3–4 years post diagnosis from baseline ($n = 501$)

	Coefficient	SE	*t*	$p > t$	95% CI
Primary surgery					
No	(ref)				
Yes	–0.012	0.024	–0.47	0.636	–0.060 to 0.036
Age group (years)					
65–69	(ref)				
70–74	–0.015	0.018	–0.81	0.420	–0.050 to 0.021
75–79	0.020	0.019	1.04	0.301	–0.018 to 0.058
80–84	–0.015	0.022	–0.67	0.504	–0.059 to 0.029
≥ 85	–0.004	0.027	–0.17	0.867	–0.057 to 0.048
Grade					
1	(ref)				
2	0.004	0.017	0.26	0.794	–0.029 to 0.038
3	–0.019	0.021	–0.88	0.382	–0.061 to 0.023
Missing	0.019	0.028	0.67	0.501	–0.036 to 0.073
ER or PR positive					
Yes	(ref)				
No	–0.012	0.024	–0.51	0.613	–0.059 to 0.035
Missing	0.032	0.029	1.1	0.272	–0.025 to 0.089
Tumour stage					
I	(ref)				
II and IIIa	–0.002	0.013	–0.17	0.866	–0.028 to 0.023
Charlson Comorbidity Index					
0	(ref)				
1	0.009	0.015	0.61	0.545	–0.020 to 0.038
≥ 2	–0.030	0.018	–1.65	0.101	–0.066 to 0.006
Functional status					
Independent (1–2)	(ref)				
Dependent (3–4)	0.108	0.023	4.77	< 0.001[a]	0.064 to 0.153

ER, estrogen receptor; PR, progesterone receptor; ref, reference; SE, standard error.
a These values are statistically significant.

Health-related quality-of-life results

The average age of the 501 participants in this sample was 75.6 years [standard deviation (SD) 6.4 years]. Their mean SF-6D utility scores (0–1, increase = better health) at diagnosis (0.75, SD 0.15) were higher than 3–4 years later (0.70, SD 0.14), indicating reduced HRQoL for participants over this time (paired *t*-test $p < 0.001$). The average decrease in the utility score was –0.05 (SD 0.14). Of the 501 participants, 461 (92.0%) had primary surgery and 40 (8.0%) did not. Although the decrease in utility appears greater for those having surgery (mean –0.06, SD 0.14) than for those not having surgery (mean –0.02, SD 0.16), this difference was not significant (*t*-test $p = 0.175$), indicating that having primary surgery does not affect HRQoL in the 3- to 4-year term. This result was confirmed by multiple regression analyses (*Table 3*) in which only functional status at diagnosis predicted changes in HRQoL. Participants dependent in ADL at diagnosis experienced an increase in HRQoL compared with those who were independent, possibly due to having additional help from supportive services.

TABLE 3 Multiple regression of QALY gain from primary surgery ($n = 640$)

	Coefficient	SE	*t*	$p > t$	95% CI
Primary surgery					
No	(ref)				
Yes	0.393	0.089	4.43	< 0.001	0.219 to 0.567
Age group (years)					
65–69	(ref)				
70–74	–0.038	0.081	–0.47	0.637	–0.198 to 0.121
75–79	–0.096	0.086	–1.12	0.263	–0.264 to 0.072
80–84	–0.350	0.095	–3.69	< 0.001	–0.536 to –0.164
≥ 85	–0.420	0.106	–3.98	< 0.001	–0.627 to –0.212
Grade					
1	(ref)				
2	0.019	0.074	0.26	0.796	–0.126 to 0.164
3	–0.117	0.090	–1.3	0.193	–0.293 to 0.059
Missing	0.123	0.120	1.02	0.306	–0.113 to 0.360
ER or PR positive					
Yes	(ref)				
No	–0.260	0.095	–2.73	0.007	–0.446 to –0.073
Missing	–0.209	0.117	–1.79	0.074	–0.439 to 0.021
Tumour stage					
I	(ref)				
II and IIIa	–0.026	0.055	–0.47	0.637	–0.134 to 0.082
Charlson Comorbidity Index					
0	(ref)				
1	–0.108	0.063	–1.73	0.084	–0.231 to 0.015
≥ 2	–0.158	0.075	–2.11	0.035	–0.305 to –0.011
Functional status					
Independent (1–2)	(ref)				
Dependent (3–4)	–0.072	0.096	–0.75	0.454	–0.260 to 0.116
Baseline utility (SF-6D)	2.149	0.207	10.36	< 0.001	1.742 to 2.556

ER, estrogen receptor; PR, progesterone receptor; ref, reference; SE, standard error.

Quality-adjusted life-years

As recommended by NICE, effectiveness was measured by the difference in QALY gain of treatment adjusted for various age, health, choice and tumour variables (QALY gain of treatment = quality of life × lifetime with treatment – quality of life × lifetime without treatment). QALYs were calculated using the standard procedure described by Manca *et al.*[18] Lifetime was defined as the time from completion of the SF-12 at baseline (diagnosis) to completion of the follow-up survey 3–4 years later or time to death. Adjustment for baseline HRQoL was made within multiple regression analyses.

The average age of the 640 participants in this sample was 76.5 years (SD 6.8 years). Of these participants, 558 (87.2%) had primary surgery and 82 (12.8%) did not. The average QALY gain was significantly greater for those who had primary surgery (2.08, SD 0.76) than for those who did not (1.32, SD 0.84) (*t*-test $p < 0.001$). In the multiple regression analyses, surgery increased QALYs gained by 0.39 (95% CI 0.22 to 0.57), adjusting for baseline utility score as well as age, comorbidity, functional status and tumour characteristics ($p < 0.001$) (see *Table 3*).

Aim Bi

To investigate the extent to which adjuvant treatment (radiotherapy and/or chemotherapy) increases survival and HRQoL and is effective for older breast cancer patients undergoing primary surgery. The results reported in this section are more fully explored in *Appendix 3*.

Sample

Of the 910 participants, 896 had their case notes reviewed and 759 had primary surgery and so could be included in the survival analyses (see *Figure 3*). Of these, 574 returned the survey at 3–4 years (mean 3.3 years post diagnosis, minimum 3.0 years, maximum 4.4 years), giving an overall response rate of 76%.

However, of the 759 participants in the overall sample, 718 completed the SF-12 at baseline, of whom 555 returned the survey at 3–4 years, including 454 completed SF-12s. Only those returning completed SF-12 surveys at baseline (diagnosis) and 3–4 years post diagnosis could be included in the analyses of difference in HRQoL from baseline to 3–4 years post diagnosis ($n = 454$). However, those participants who did not return a survey at 3–4 years because they had died could be included in the QALY calculation and thus the effectiveness analyses ($n = 640$).

Survival results

The primary end point is breast cancer-specific mortality, which was defined as time from diagnosis to death due to breast cancer based on underlying cause of death provided by NHS Digital.[19] Participants who died of other causes were censored at their date of death. Participants were classified as having adjuvant treatment if they received this within 12 months of diagnosis. Therefore, treatment had to be followed up for a minimum of 12 months post diagnosis. Participants who moved away or whose care was transferred to another hospital within 12 months post diagnosis were censored on the date of their last breast clinic visit.

Of the 759 women in the study (mean age 75.99 years, 95% CI 75.53 to 76.44 years), 113 died before the end point of the study (5 February 2016): 48 of breast cancer and 65 of other causes. The mean follow-up time was 3.68 years (95% CI 3.59 to 3.77 years). The baseline characteristics of the sample are detailed in *Table 4*.

The number of observed breast cancer deaths significantly exceeded those expected for participants whose tumours were of higher grade or stage and steroid receptor negative and warranted chemotherapy and mastectomy [vs. wide local excision (WLE)] (see *Table 4*). As the number of events (48) per degree of freedom from explanatory variables needs to exceed five in the final model (26), the maximum number of variables could not exceed nine. Therefore, in addition to adjuvant therapy, only variables significant at the 5% level in the univariate analyses were entered into the Cox's proportional hazards model (*Table 5*). In this multivariate analysis, breast cancer survival was determined more by tumour characteristics (i.e. grade and receptor status) than by receipt of chemotherapy and radiotherapy.

Health-related quality-of-life results

The average age of the 454 participants in this sample was 75.1 years (SD 6.2 years). Their mean SF-6D utility scores (0–1, increase = better health) at diagnosis (0.76, SD 0.15) were higher than at 3–4 years (0.70, SD 0.14), indicating reduced HRQoL for participants over this time (paired *t*-test $p < 0.001$). The average decrease in the utility score was –0.06 (SD 0.14). Of the 454 participants, 66 (14.5%) had chemotherapy and 313 (68.9%) had radiotherapy.

TABLE 4 Baseline characteristics by observed and expected breast cancer-specific deaths ($n = 759$)

Variable	Category	*n*	Per cent	Deaths (*n*)		Log-rank test[a] *p*-value[b]
				Observed	Expected	
Chemotherapy	Yes	99	87.0	11	6.27	
	No	660	13.0	37	41.73	0.043
Radiotherapy	Yes	491	64.7	27	31.54	
	No	268	35.3	21	16.46	0.167
Type of surgery	Mastectomy	353	46.5	34	21.63	
	Wide local excision	406	53.5	14	26.37	< 0.001
Age group (years)	65–69	129	17.0	6	8.20	
	70–74	244	32.2	17	16.24	
	75–79	188	24.8	7	12.10	
	80–84	121	15.9	10	7.07	
	≥ 85	77	10.1	8	4.39	0.137
Grade	1	142	18.7	3	9.09	
	2	397	52.3	17	25.71	
	3	158	20.8	26	9.13	< 0.001[a]
	Missing	62	8.2	2	4.07	< 0.001[a]
ER or PR positive	Yes	631	83.1	28	40.37	
	No	77	10.1	17	4.43	< 0.001[a]
	Missing	51	6.7	3	3.21	< 0.001[a]
Tumour stage	I	358	47.2	13	23.24	
	II and IIIa	401	52.8	35	24.76	0.003[a]
Charlson Comorbidity Index	0	421	55.5	33	26.87	
	1	216	28.5	10	13.54	
	≥ 2	122	16.1	5	7.59	0.202
Functional status	Independent (1–2)	679	89.5	42	43.1	
	Dependent (3–4)	77	10.1	6	4.76	0.555
	Missing	3	0.4	0	0.14	0.780
	Total	759	100%	48	48	

ER, estrogen receptor; PR, progesterone receptor.
a The log-rank test tests the equality of survivor function across groups.
b *p*-values for each variable for complete data are reported first followed by data including missings if relevant.

The difference in utility from diagnosis (baseline) to 3–4 years later does not differ significantly with receipt of chemotherapy (*t*-test $p = 0.188$) or radiotherapy (*t*-test $p = 0.221$), indicating that having these adjuvant therapies does not affect HRQoL in the long term. This result was confirmed by multiple regression analyses (*Table 6*) in which only functional status at diagnosis predicted changes in HRQoL. Participants dependent in ADL at diagnosis experienced an increase in HRQoL compared with those who were independent, possibly because of additional help from supportive services.

TABLE 5 Cox's proportional hazards regression of breast cancer-specific survival of patients undergoing surgery ($n = 759$)

	Coefficient	SE	*t*	$p > t$	95% CI
Chemotherapy					
No	(ref)				
Yes	0.891	0.322	–0.32	0.749	0.439 to 1.809
Radiotherapy					
No	(ref)				
Yes	0.979	0.335	–0.06	0.951	0.501 to 1.913
Surgery type					
Mastectomy	(ref)				
WLE	0.475	0.185	–1.91	0.056	0.221 to 1.019
Grade					
1	(ref)				
2	1.604	1.012	0.75	0.454	0.466 to 5.524
3	4.822	3.087	2.46	0.014[a]	1.375 to 16.910
Missing	0.930	0.878	–0.08	0.939	0.146 to 5.916
ER or PR positive					
Yes	(ref)				
No	2.720	0.949	2.87	0.004[a]	1.373 to 5.390
Missing	1.785	1.133	0.91	0.361	0.515 to 6.194
Tumour stage					
I	(ref)				
II and IIIa	1.502	0.527	1.16	0.246	0.756 to 2.987

ER, estrogen receptor; PR, progesterone receptor; ref, reference; SE, standard error.
a These values are statistically significant.

Quality-adjusted life-years

As recommended by NICE, effectiveness was measured by the difference in QALY gain of treatment adjusted for various age, health, choice and tumour variables (QALY gain of treatment = quality of life × lifetime with treatment – quality of life × lifetime without treatment). QALYs were calculated using the standard procedure described by Manca *et al.*[18] Lifetime was defined as time from completion of the SF-12 at baseline (diagnosis) to completion of the follow-up survey 3–4 years later or time to death. Adjustment for baseline HRQoL was made within multiple regression analyses.

The average age of the 548 participants in this sample was 75.6 years (SD 6.4 years). Of these participants, 15.0% had chemotherapy and 363 (66.2%) had radiotherapy. The average QALY gain was not significantly different for those who had chemotherapy (*t*-test $p = 0.844$). Participants having radiotherapy did appear to have significantly greater QALYs (2.17, SD 0.70) than those who did not (1.93, SD 0.85) (*t*-test $p = 0.001$). However, this gain did not persist in the multiple regression analyses, adjusting for baseline utility score as well as surgery type, age, comorbidity, functional status and tumour characteristics (*Table 7*).

TABLE 6 Multiple regression of difference in HRQoL (SF-6D) at 3–4 years post diagnosis from baseline for surgical patients ($n = 454$)

	Coefficient	SE	*t*	$p > t$	95% CI
Chemotherapy					
No	(ref)				
Yes	–0.007	0.021	–0.33	0.742	–0.048 to 0.034
Radiotherapy					
No	(ref)				
Yes	–0.016	0.019	–0.86	0.392	–0.054 to 0.021
Surgery type					
Mastectomy	(ref)				
WLE	0.016	0.019	0.84	0.400	–0.021 to 0.053
Age group (years)					
65–69	(ref)				
70–74	–0.020	0.018	–1.11	0.269	–0.057 to 0.016
75–79	0.019	0.020	0.92	0.356	–0.021 to 0.059
80–84	–0.024	0.024	–1.00	0.316	–0.072 to 0.023
≥ 85	–0.015	0.030	–0.49	0.623	–0.074 to 0.044
Grade					
1	(ref)				
2	0.008	0.018	0.42	0.673	–0.028 to 0.043
3	–0.017	0.023	–0.75	0.452	–0.063 to 0.028
Missing	0.014	0.029	0.48	0.629	–0.043 to 0.071
ER or PR positive					
Yes	(ref)				
No	–0.011	0.025	–0.44	0.658	–0.060 to 0.038
Missing	0.025	0.029	0.84	0.400	–0.033 to 0.082
Tumour stage					
I	(ref)				
II and IIIa	0.002	0.014	0.16	0.869	–0.026 to 0.031
Charlson Comorbidity Index					
0	(ref)				
1	–0.005	0.015	–0.35	0.724	–0.036 to 0.025
≥ 2	–0.031	0.019	–1.60	0.111	–0.069 to 0.007
Functional status					
Independent (1–2)	(ref)				
Dependent (3–4)	0.107	0.026	4.17	< 0.001	0.057 to 0.158

ER, estrogen receptor; PR, progesterone receptor; ref, reference; SE, standard error.

TABLE 7 Multiple regression of QALY gain from adjuvant chemotherapy and radiotherapy ($n = 548$)

	Coefficient	SE	*t*	$p > t$	95% CI
Chemotherapy					
No	(ref)				
Yes	–0.038	0.087	–0.44	0.659	–0.210 to 0.133
Radiotherapy					
No	(ref)				
Yes	0.033	0.076	0.43	0.669	–0.117 to 0.183
Surgery type					
Mastectomy	(ref)				
WLE	0.107	0.076	1.41	0.158	–0.042 to 0.257
Age group (years)					
65–69	(ref)				
70–74	–0.041	0.081	–0.51	0.609	–0.200 to 0.117
75–79	–0.063	0.088	–0.71	0.478	–0.237 to 0.111
80–84	–0.349	0.101	–3.46	0.001	–0.547 to –0.151
≥ 85	–0.419	0.120	–3.49	0.001	–0.654 to –0.183
Grade					
1	(ref)				
2	0.017	0.078	0.21	0.832	–0.137 to 0.170
3	–0.198	0.096	–2.06	0.040	–0.388 to –0.009
Missing	0.093	0.123	0.76	0.450	–0.149 to 0.335
ER or PR positive					
Yes	(ref)				
No	–0.213	0.094	–2.25	0.025	–0.398 to –0.027
Missing	–0.201	0.117	–1.72	0.087	–0.431 to 0.029
Tumour stage					
I	(ref)				
II and IIIa	–0.011	0.061	–0.17	0.862	–0.130 to 0.109
Charlson Comorbidity Index					
0	(ref)				
1	–0.091	0.065	–1.39	0.164	–0.219 to 0.037
≥ 2	–0.074	0.081	–0.92	0.358	–0.233 to 0.085
Functional status					
Independent (1–2)	(ref)				
Dependent (3–4)	0.011	0.116	0.09	0.927	–0.218 to 0.239
Baseline utility (SF-6D)	2.327	0.214	10.89	< 0.001	1.908 to 2.747

ER, estrogen receptor; PR, progesterone receptor; ref, reference.

Workstream 1 summary

In overview:

1. The studies of preference reveal that in about half of consultations the patient and surgeon both chose the same person as making the surgical decision, but the actual agreement between the surgeons and patients is low. In univariate 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. Patient role in treatment decisions makes no difference to whether or not they receive surgery. Women who were active/collaborative were as likely to get surgery as those who left the decision to the surgeon. The qualitative study of women who did not receive primary surgery revealed three approaches: 'patient declined', 'patient considered' and 'surgeon decided'.
2. Older age did not predict complications, and 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, even though age seems to be a factor taken into account by surgeons, especially for the 'oldest old' group as revealed in our study of choice. We were unable to build a pre-treatment risk screening tool as originally planned.
3. In our study of survival, the number of observed cancer deaths exceeded those expected for participants whose tumours were of higher grade or stage and steroid receptor negative, 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. Given these findings, it is hard to see on what basis surgery should be withheld from older women who are fit for surgery.
4. Following surgery, changes in HRQoL were not associated with getting the treatment decision-making style they preferred. Thus, it seems that the outcomes of consultation with the surgeon in terms of preferences were not detrimental per se to the women's QoL in the longer term.
5. Many older women do not receive chemotherapy and radiotherapy following surgery, even though they may benefit from these therapies. Can this lack of chemotherapy and radiotherapy be explained by patient choice or health? We demonstrated that women aged ≥ 75 years have lower chemotherapy and radiotherapy rates than women aged 65–69 years. After adjusting for tumour characteristics, health measures and choice, women aged ≥ 75 years still have reduced odds of receiving chemotherapy, whereas age has no impact on the radiotherapy rates of older women. Therefore, lower chemotherapy rates in older women cannot be explained by health or patient choice.

Overall, although over the last decade there have been improvements in the access older women have to breast cancer services, there are still substantial gains to be made by ensuring that treatment decisions are based on 'fitness' and ability to benefit, rather than on age.

Workstream 2: comparison of multifrequency bioimpedance with early arm-volume increase in predicting lymphoedema by 18 months

Sentinel lymph node biopsy staging reduces the need for axillary node clearance (ANC), but 30% of breast cancer patients are node positive and require ANC to remove diseased nodes.[18,20]

Lymphoedema (gross swelling of the arm) occurs when the lymphatic system is unable to keep up with the normal demands of tissue homeostasis, resulting in fluid accumulating in the interstitial spaces of the subcutaneous tissue.[21–23] If excess protein in the interstitial fluid (that causes the oedema) is allowed to persist, chronic inflammation can lead to fibrotic, thickened skin and tissues and progressive lymphoedema.[21–23] Up to 40% of patients report arm swelling by 18 months post ANC.[20,22,24]

The consequences of lymphoedema are multidimensional and can involve physical and psychosocial morbidity. Recurrent infections of the arm (cellulitis) may occur, causing progression of the lymphoedema by further damage to the lymph vessels.[23,25,26] Patients report the limb being heavy and painful, experiencing impaired limb function and reduced shoulder mobility.[21–23] A clinical end point of a > 10% increase in ipsilateral arm volume (vs. contralateral arm) is an accepted criterion for a diagnosis of lymphoedema.[21–24,27]

Most women present with established lymphoedema 1–2 years after surgery.[21–23,28] Its management is calculated to cost £350 per patient per year and £10M per annum to the NHS budget, including the cost of treating recurring infection with antibiotics and more intensive treatments when acute exacerbations occur.[23] Intervention before arm swelling becomes chronic may prevent the complications of lymphoedema after ANC. Recent evidence from a prospective cohort study in which preoperative perometer monitoring identified 43 women after ANC with an early RAVI of > 3%, in whom provision of compression garments prevented any further RAVI at 6 months' follow-up (no lymphoedema developed), has led to claims that the standard of postoperative care should routinely include prospective arm measurement to intervene in the development of so-called 'preclinical' lymphoedema. However, this lacks a robust evidence base and the proposed intervention has never been tested in a multicentre randomised trial setting.[29]

An alternative definition of lymphoedema is the application of compression sleeve garments, as some women develop hand or lower arm swelling that does not reach the overall 10% arm-volume increase but represents clinical practice by lymphoedema practitioners.

Multifrequency bioimpedance electrical analysis is a non-invasive technique to measure total water content, which involves passing extremely small electrical currents through the body and measuring the impedance (or resistance) to the flow of these currents. In recent years the BEA technique has been refined to measure the impedance over a range of frequencies from 4 to 1000 kHz. By mathematically modelling the measured data, the impedance at zero frequency (i.e. the impedance of the extracellular fluid alone) can be determined.[22,30,31] BEA is used to quantitatively compare the degree of fluid accumulation in the arms using a leg as the reference limb, and a 3SD change in BEA is claimed to accurately diagnose lymphoedema. Small single-centre prospective studies in Australia have claimed that BEA predicts lymphoedema development up to 10 months ahead of arm-volume changes with a sensitivity of 98% and a specificity of 100%.[30,31]

Bioimpedance electrical analysis can be measured with a handheld device and is marketed as safe, accurate and diagnostic for lymphoedema (in the absence of confirmed arm swelling of > 10%) to justify early treatment intervention in women after axillary surgery. BEA correlates with arm measurement in lymphoedema

patients, but is reported to be more sensitive than and equally as specific as arm circumference measures, particularly in women whose ANC involves the non-dominant arm lymphatics.[30,31]

We assessed BEA monitoring compared with perometer arm measurements in women after ANC. BEA monitoring during the study was used to determine its value in predicting response to compression garment therapy.[22,23] Within the study we assessed reproducibility of both methods across all centres and robustly established both intra- and interobserver error rates for both methods in the study population.

Training in the use of L-DEX U400 BIS devices was provided for all centres with the appropriate software and electrodes to carry out a health technology assessment (see BEA protocol).[32,33]

All women undergoing ANC in the UK breast units underwent preoperative 1-, 3-, 6-, 12- and 18-monthly bilateral arm measurements with a perometer (Pero-Systems 350S) and circumferential arm tape measurements as well as perometer measurements.

All centres monitored women undergoing ANC from pre-surgery baseline with perometer measurements and BEA to compare the sensitivity and specificity of both techniques for predicting chronic lymphoedema development. Identifying the most sensitive and specific method for detecting chronic lymphoedema would enhance selection of patients for intervention with arm sleeves should the intervention prove cost-effective.

Study design

Women undergoing ANC for breast cancer were approached for baseline (preoperative) and subsequent BEA monitoring, along with perometer arm measurements, in initially seven centres with an increase to 21 across the UK (see flow diagram in protocol[34]). First, a comparison of the sensitivity and specificity of BEA versus perometer measurement was made in women who developed arm swelling of > 10% by 6 months [based on the ALMANAC (Axillary Lymphatic Mapping Against Nodal Axillary Clearance) trial, we estimated this in advance at 210/1000 (21%) of the initial group]. Second, women with an arm-volume increase of 4–8% at 1, 3 or 6 months where effectively the BEA 6 months readings were to be compared with final 18-month perometer scores to assess the prediction of lymphoedema at 18 months by BEA. Third, women with a < 4% perometer arm-volume increase up to 6 months were to be used to determine the sensitivity and specificity of BEA 6-month measures compared with the perometer 6-month measurement in predicting the 18-month outcome.

Sample size calculation

We were required to screen 1000 patients to enrol enough women into the PLACE trial using perometer measurements, which allowed us to determine if BEA had a > 80% sensitive and a > 80% specific accuracy. Currently the specificity of arm swelling measured by perometer is 87% specific for subsequent lymphoedema at 18 months with a sensitivity of 54% (assessed from ALMANAC data).[34]

Older age, increases in body mass index (BMI) and postoperative radiotherapy are claimed to increase lymphoedema development.[21–23,28–31] We built a multivariate model predicting lymphoedema from the following potential predictor variables: BMI, dominant limb, postoperative radiotherapy, previous sentinel node biopsy, cigarette smoking, weight gain and age. This allowed us to identify what factors, as well as early arm-volume changes or BEA, predict subsequent development of lymphoedema. Although we anticipated 1000 patients recruited by 24 months of the programme to allow us to build a multivariate model, delays to sites opening meant that 1100 were recruited by June 2015. Multiple logistic regression modelling techniques were used to identify significant predictors of lymphoedema at early (18 months) and late time points (24 months) in the participants.

Workstream 2 multifrequency bioimpedance study: results of a multicentre prospective study

Among the 1100 women recruited to the trial undergoing ANC surgery for breast cancer from nine centres in England, the median age was 56 years (range 22–90 years). They have undergone preoperative and subsequent regular measurements post surgery (1, 3, 6, 9 and 12 months, then 6-monthly) of arm volume by perometry (Perometer 350 NT; www.pero-system.de) and multifrequency BIS (L-Dex® U400; www.impedimed.com) and currently have a minimum 24 months' follow-up surveillance. Change in arm volume was calculated using relative arm-volume change (RAVI).

The primary end point of lymphoedema was defined as a ≥ 10% limb volume change, compared with the contralateral arm, by perometry.[24,29] BIS L-Dex change of 10 was considered the diagnostic criterion for lymphoedema. There is considerable variation in the definitions of lymphoedema and methods of measurement, ranging from the more conservative ≥ 10% limb volume change by perometry, through volume increases of 200 ml by perometry, to the more liberal increase of 2 cm in circumference.[20,24] For the purposes of this study, we used a > 10% arm-volume increase (RAVI) since baseline (compared with the contralateral arm) as measured by perometer on at least two occasions to identify women with lymphoedema secondary to ANC.[29]

We also used a clinical definition of compression sleeve application (excluding patients who had sleeves applied as part of the intervention arm in the PLACE trial). Lymphoedema determined by BIS was defined as an increase of ≥ 10 units from baseline.

Arms were measured using a 350S perometer with standard perometer software supplied by Pero-System, Wuppertal, Germany. The average of two perometer measurements was used at each visit to exclude intraobserver variability. BIS intracellular fluid was measured using the L-Dex® U400 BIS devices on loan from ImpediMed Ltd (Pinkenba, QLD, Australia).[30,31]

At least 50% of breast cancer patients gain weight in the first year after diagnosis, which is associated with increased risk of lymphoedema. Nonetheless, if careful contralateral arm measurements are not performed, weight gain, rather than lymphoedema, can lead to inappropriate fitting of compression sleeves. BIS results are unaltered by weight gain and we tested whether the BIS results were sensitive and/or more specific than perometer measurements in detecting early and later arm swelling.

Self-reported symptoms and quality-of-life measures

Patients were asked to complete a lymphoedema questionnaire, which used three items from the Lymphedema and Breast Cancer Questionnaire about heaviness, numbness and swelling, and the Functional Assessment of Cancer Therapy – Breast Cancer, version 4 (FACT-B+4) Questionnaire (www.facit.org/FACITOrg/Questionnaires) and the EuroQol-5 Dimensions (EQ-5D) (www.euroqol.org/about-eq-5d.html) to assess self-reported upper limb symptoms, physical functioning disease-specific QoL and health utility. All questionnaires were completed preoperatively and then again at 3 and 6 months post surgery, with the exception of the EQ-5D, which was not completed at 3 months post surgery.

Statistical analysis

Statistical analysis included sensitivity and specificity analysis of the BIS L-Dex score against the 'gold standards' of perometer assessment at 6, 18 and 24 months (and subsequently clinical sleeve application) using statistical techniques recommended by Bland and Altman.[35] The BIS value cut-off level was checked using receiver operating characteristic (ROC) analysis and confirmed using later results. An assessment of the relationship between the two methods of measurement up to 2 years in predicting lymphoedema was performed. The analysis for the current report involved comparison of the baseline and 6-, 18- and 24-month post-surgery measurements using paired *t*-tests, and comparison between groups defined by lymphoedema status using independent *t*-tests, and data were described using means and ranges,

sensitivity and specificity, and univariate and multivariate analyses. ROC analysis, Cox proportional hazards regression, log-rank testing and generalised estimating equation (GEE) regression were performed for univariate and multivariate analyses. The GEE regression was chosen as the inference was at the population level so the GEE marginal effects were of interest. Descriptive methods were used for all other data presented.

Results

Out of the 1100 patients entered into the study (median follow-up 36 months, minimum 24 months), the mean age was 55.7 years (range 22 to 90 years), 47.0% had a mastectomy and ANC, 90.5% were node positive, 70.9% had a histology of infiltrating ductal carcinoma and the majority (80.6%) were estrogen receptor (ER) positive (*Table 8*). Eighty-three per cent received postoperative radiotherapy, 67.3% received chemotherapy and 82.4% were given endocrine treatment. Fifty-eight patients (5%) had no post-1-month perometer measurements. Overall, 497 patients have completed 60 months' follow-up, 105 have died and 204 have been lost to follow-up (or withdrawn from the study).

TABLE 8 Multifrequency bioimpedance demographics (*N* = 1100)

Demographic	*n* (%)
Age (*N* = 1088)	
Mean (SD) [range]	55.7 (12.4) [22 to 90]
BMI (kg/m^2) (pre-op) (*N* = 1071)	
Median (IQR) [range]	27.3 (24.0 to 31.2) [16.6 to 60.0]
Weight gain at 3 months (as % of baseline) (*N* = 916)	
Mean (SD) [range]	–0.1 (4.0) [–12.8 to 24.2]
Side of ANC (*N* = 1096)	
Right : left	550 (50.2) : 546 (49.8)
Dominant hand (*N* = 1096)	
Right : left	998 (91.0) : 98 (9.0)
Smoking history (*N* = 1094)	
Never	651 (59.5)
Ex-smoker	319 (29.2)
Current smoker	124 (11.3)
Previous SN biopsy: yes	368 (34.3)
Type of ANC surgery (*N* = 1089)	
ANC	257 (23.6)
WLE + ANC	309 (28.4)
Mastectomy + ANC	512 (47.0)
Other	11 (1.0)
Histology (*N* = 1087)	
Infiltrating ductal	771 (70.9)
Infiltrating lobular	125 (11.5)
DCIS	27 (2.5)

TABLE 8 Multifrequency bioimpedance demographics (*N* = 1100) (*continued*)

Demographic	*n* (%)
LCIS	2 (0.2)
Mixed invasive	91 (8.4)
Other	71 (6.5)
Pathological tumour size, (mm) (*N* = 1078)	
Median (IQR) [range]	26.0 (18.0 to 40.0) [0 to 220]
Grade (*N* = 1080)	
1	63 (5.8)
2	477 (44.2)
3	501 (46.4)
Ungraded	39 (3.6)
Number of nodes removed (*N* = 1088)	
Median (IQR) [range]	17.0 (13.0 to 23.0) [1 to 56]
Number of nodes involved (*N* = 1088)	
Median (IQR) [range]	2.0 (1.0 to 5.8) [0 to 46]
Node positive	985 (90.5)
ER negative : ER positive	208 (19.4) : 864 (80.6)
HER-2 (*N* = 1072)	
Negative	811 (75.7)
Amplified	82 (7.6)
3+	179 (16.7)
ER, HER–2 combination (*N* = 1066)	
ER negative, HER-2 negative	152 (14.3)
ER negative, HER-2 3+	56 (5.3)
ER positive, HER-2 negative	735 (68.9)
ER positive, HER-2 3+	123 (11.5)
Post-operative radiotherapy: yes (*N* = 1062)	878 (82.7)
Post-operative chemotherapy: yes (*N* = 1060)	713 (67.3)
Post-operative endocrine therapy: yes (*N* = 1061)	874 (82.4)
Any disease recurrence: yes	134 (12.3)
Time (years) to first disease recurrence, median (IQR) [range]	1.44 (0.60 to 2.63) [0.05 to 5.04]
Time (years) in study (from definitive surgery) (*N* = 1072)	
Median (IQR) [range]	3.00 (1.98 to 4.03) [0.06[a] to 5.51]

DCIS, ductal cancer in situ; HER-2, human epidermal growth factor receptor 2; IQR, interquartile range; LCIS, lobular cancer in situ; SN, sentinel node.

a There were 17 patients who withdrew (or were lost to follow-up) from the study prior to (or on the date of) definitive surgery and have negative values when using the surgery date as the start point.

Lymphoedema assessment within the protocol was defined as the development of an arm-volume increase (RAVI) of > 10% but, on reviewing the data, compression sleeves were being applied outside the protocol indications. For some patients, significant swelling of the lower arm or hand or swelling of < 10% RAVI but associated with symptoms led to the application of a compression sleeve by the lymphoedema practitioner. We ascertained this by retrieving the perometer readings for all patients with a sleeve applied. Compression garment application was another surrogate marker of lymphoedema and potentially a better clinical marker. Time to lymphoedema for RAVI of > 10% at follow-up and that for sleeve application are presented.

The median time to developing lymphoedema was 11.3 months (range 2.3–63.1 months). Lymphoedema incidence (sleeve application and RAVI of > 10%) is shown in *Tables 9* and *10*. The incidence of lymphoedema differed by the definition of either a clinical sleeve application by a lymphoedema nurse or the perometer RAVI of > 10% after 24 months' follow-up.

Using Kaplan–Meier estimates for time to diagnosis of lymphoedema, 14.6% using RAVI and 17.7% by sleeve application were diagnosed by 12 months, and 21.4% and 24.4% were diagnosed by 24 months, respectively (*Figure 9*).

There was clinical lymphoedema diagnosis/applied sleeve in 24.4% patients by 24 months, compared with 21.4% with RAVI of > 10% during follow-up. The majority of this difference appeared to occur between 6 and 12 months, when more sleeves were applied. This was partly due to the patients who were not eligible for the PLACE trial but had a perometer value RAVI of > 9% and who therefore went on to compression sleeves.

TABLE 9 Lymphoedema rates using perometer RAVI of ≥ 10% rate (primary end point)

	Follow-up date (months)					
	≤ 3	> 3 and ≤ 6	> 6 and ≤ 9	> 9 and ≤ 12	> 12 and ≤ 18	> 18 and ≤ 24
n at risk	1001	925	848	798	722	647
Perometer RAVI of ≥ 10%						
During interval	33	54	27	24	31	25
Total number	33	87	114	138	169	194
Kaplan–Meier[a] probability of event (%)	3.4	9.0	11.9	14.6	18.2	21.4

a 1–Kaplan–Meier estimates.

TABLE 10 Lymphoedema rates defined by clinical lymphoedema/applied sleeve

	Follow-up date (months)					
	≤ 3	> 3 and ≤ 6	> 6 and ≤ 9	> 9 and ≤ 12	> 12 and ≤ 18	> 18 and ≤ 24
n at risk	999	928	856	789	697	622
Lymphoedema						
During interval	29	48	46	43	31	24
Total number	29	77	123	166	197	221
Kaplan–Meier[a] probability of event (%)	3.0	8.0	12.9	17.7	21.3	24.4

a 1–Kaplan–Meier estimates.

Lymphoedema by 24 months detected in 21.4% of women by perometry whereas using BIS definition in 39.4%. A moderate correlation between perometer and BIS at 6 months ($r = 0.61$) was found, with a sensitivity of 76% (95% CI 64% to 84%), specificity of 85% (95% CI 83% to 88%) and PPV of BIS of 31% (95% CI 25% to 39%) (*Table 11*). Sensitivity remained similar at 24 months (75%, 95% CI 64% to 83%), though specificity was higher (91%, 95% CI 89% to 93%), as was PPV of BIS (54%, 95% CI 44% to 63%). The sensitivity and specificity values for BIS fall below the percentage of 95% required according to the study protocol.

Women who developed a RAVI of > 5 to < 10% by 6 months required lymphoedema treatment in 35% of cases by 24 months, whereas a RAVI of < 3% was associated with an 8% lymphoedema rate at 24 months ($p < 0.001$).

The sensitivity and specificity of BIS and perometer were compared according to sleeve application using sleeve application as the clinical diagnosis of lymphoedema, as well as against the protocol defined perometer, RAVI of > 10%. There were 226 patients with an appropriately applied sleeve, which included patients with a sleeve applied and patients who had > 10% lymphoedema and were offered a sleeve by the lymphoedema nurse but declined it because they already had metastatic disease and were about to die. In addition, 51 patients had their sleeve applied as part of the PLACE trial; nine patients contralateral sleeve application and these patients were excluded from the analysis.

Perometer and bioimpedance spectroscopy comparison

After reviewing the perometer and lymphoedema nursing data from all patients with RAVI of > 10% or a sleeve applied, 226 patients fitted the clinical lymphoedema definition of sleeve appropriately fitted or RAVI of > 10%. There were 25 patients with sleeves applied who were deemed not to have clinical lymphoedema because there was insufficient evidence in the notes; 29 patients did not have a sleeve applied but were deemed to have clinical lymphoedema (predominantly localised lower arm swelling or RAVI of > 10%).

TABLE 11 Sensitivity and specificity of perometer and BIS at 6, 18 and 24 months

	No lymphoedema (perometer definition: RAVI of < 10%)	Lymphoedema (perometer definition: RAVI of > 10%)	Total
By 6 months			
BIS (< 10)	698 (82%) true negative	27 (31%) false negative	725
BIS (≥ 10)	153 (18%) false positive	59 (69%) true positive	212
Total	851	86	937
After 6 months up to 18 months			
BIS (< 10)	600 (81%)	25 (32%)	625
BIS (≥ 10)	138 (19%)	53 (68%)	191
Total	738	78	816
After 6 months up to 24 months			
BIS (< 10)	572 (79%)	32 (32%)	604
BIS (≥ 10)	150 (21%)	68 (68%)	218
Total	722	100	822

Perometer by 6 months

The perometer by 6 months variable includes those women with lymphoedema at 3 or 6 months.

For those with lymphoedema according to the RAVI of ≥ 10% definition, the BIS value used is the one at the time of the lymphoedema diagnosis. For those without lymphoedema according to the RAVI of ≥ 10% definition, the largest BIS value at either time point was used (*Figure 3*).

At all time points BIS identified high numbers of false-positive patients with a lymphoedema diagnosis (using RAVI of > 10%).

Relative arm-volume increase after 6 months up to 18 months

The RAVI after 6 months up to 18 months variable excludes those with lymphoedema up to and including 6 months.

For those with lymphoedema according to the RAVI of ≥ 10% definition, the BIS value used is the one at the time of the lymphoedema diagnosis. For those without lymphoedema according to the RAVI of ≥ 10% definition, the BIS value is the largest value from 9 to 18 months (*Figure 4*).

Relative arm-volume increase of > 10% after 6 up to 24 months (excludes those with lymphoedema up to and including 6 months)

For those with lymphoedema according to the RAVI of ≥ 10% definition, the BIS value used is the one at the time of lymphoedema diagnosis. For those without lymphoedema, the BIS value used is the largest value between 9 and 24 months (*Figure 5*).

Clinical lymphoedema/appropriately applied sleeve from 6 up to 18 months

The clinical lymphoedema/applied sleeve between 6 and 18 months variable excludes those with lymphoedema up to and including 6 months (see *Table 12* and *Figure 6*).

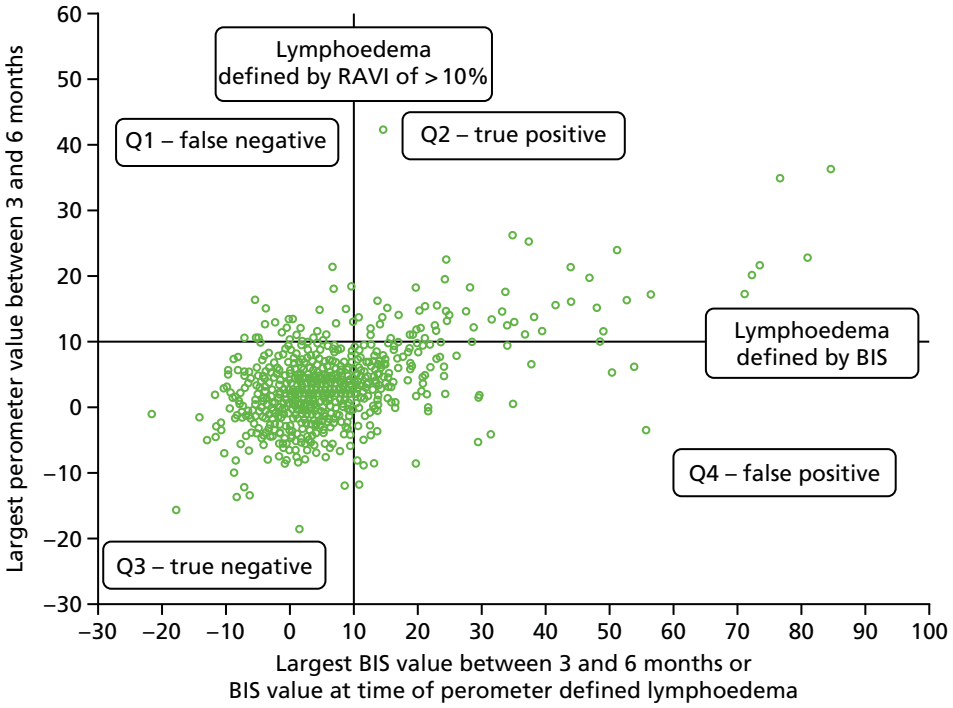


FIGURE 3 Comparison of perometer and BIS at 6 months. Q1, RAVI only of ≥ 10; Q2, both ≥ 10; Q3, neither ≥ 10; Q4, BIS only of ≥ 10. Sensitivity, 69% (59/86; 95% CI 58% to 77%); specificity, 82% (698/851; 95% CI 79% to 84%); PPV, 28% (59/212; 95% CI 22% to 34%); NPV, 96% (698/725; 95% CI 95% to 97%). NPV, negative predictive value.

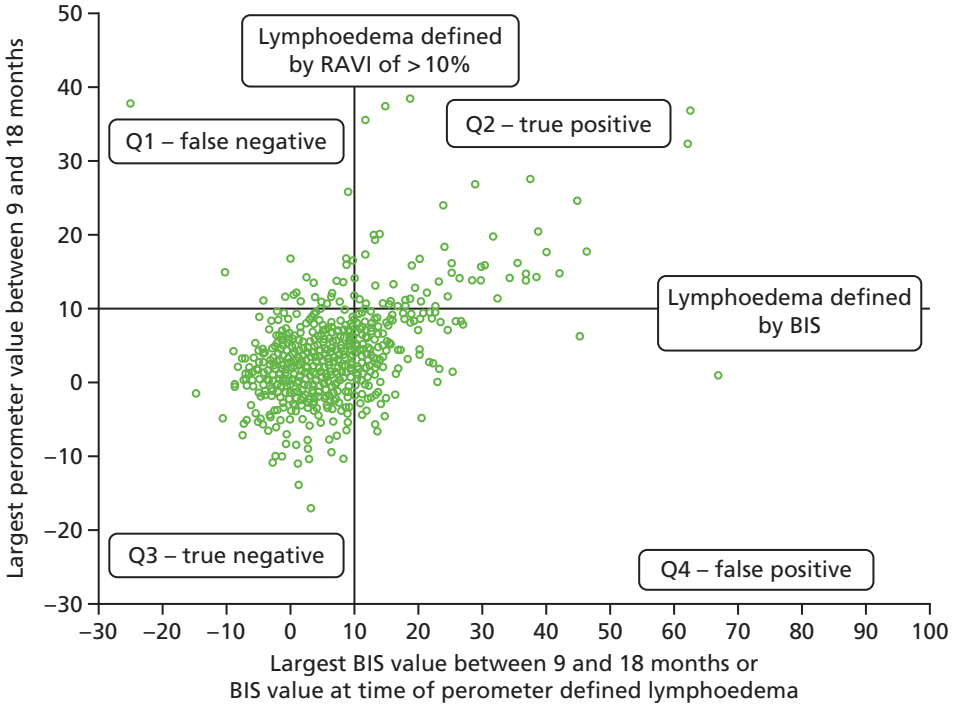


FIGURE 4 Comparison of RAVI and BIS at 18 months. Q1, RAVI only of ≥ 10; Q2, both ≥ 10; Q3, neither ≥ 10; Q4, BIS only of ≥ 10. Sensitivity, 68% (53/78; 95% CI 57% to 77%); specificity, 81% (600/738; 95% CI 78% to 84%); PPV, 28% (53/191; 95% CI 22% to 34%); NPV, 96% (600/625; 95% CI 94% to 97%). NPV, negative predictive value.

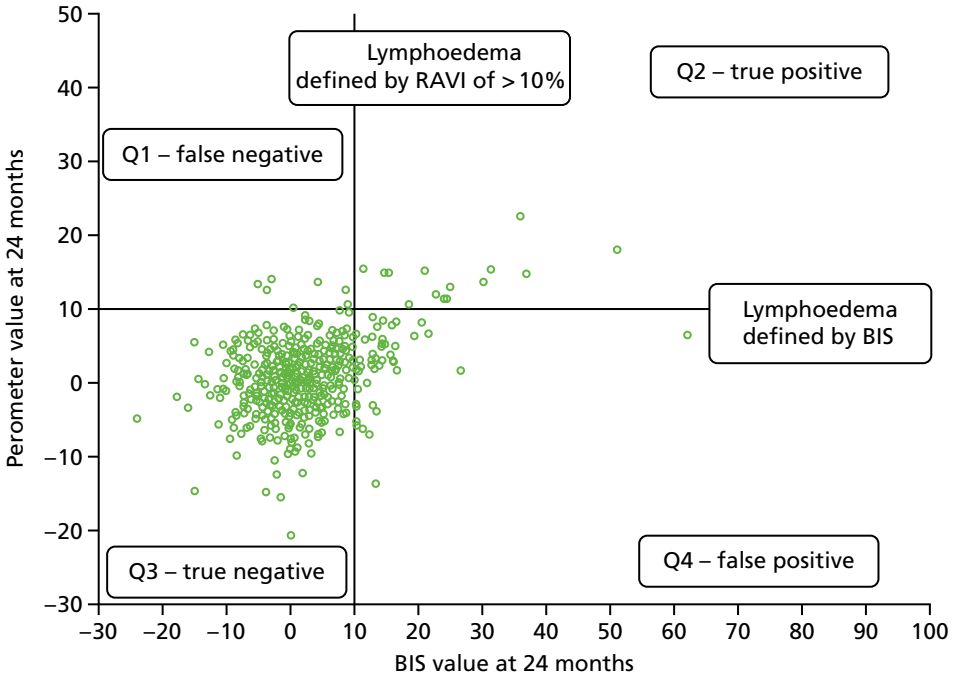


FIGURE 5 Comparison of RAVI and BIS after 6 months up to 24 months. Q1, RAVI only of ≥ 10; Q2, both ≥ 10; Q3, neither ≥ 10; Q4, BIS only of ≥ 10. Sensitivity, 68% (15/22; 95% CI 58% to 76%); specificity, 79% (572/722; 95% CI 76% to 82%); PPV, 31% (68/218; 95% CI 25% to 38%); NPV, 95% (572/604; 95% CI 93% to 96%). NPV, negative predictive value.

TABLE 12 Relative arm-volume increase change compared with sleeve/clinical lymphoedema

By 6 months	No sleeve or clinical lymphoedema	Sleeve or clinical lymphoedema	Total
RAVI (< 10%)	820 (94%)	45 (60%)	865
RAVI (≥ 10%)	55 (6%)	30 (40%)	85
Total	875	75	950

Sensitivity, 40% (30/75; 95% CI 30% to 51%); specificity, 94% (820/875; 95% CI 92% to 95%); PPV, 35% (30/85; 95% CI 26% to 46%); negative predictive value, 95% (820/865; 95% CI 93% to 96%).

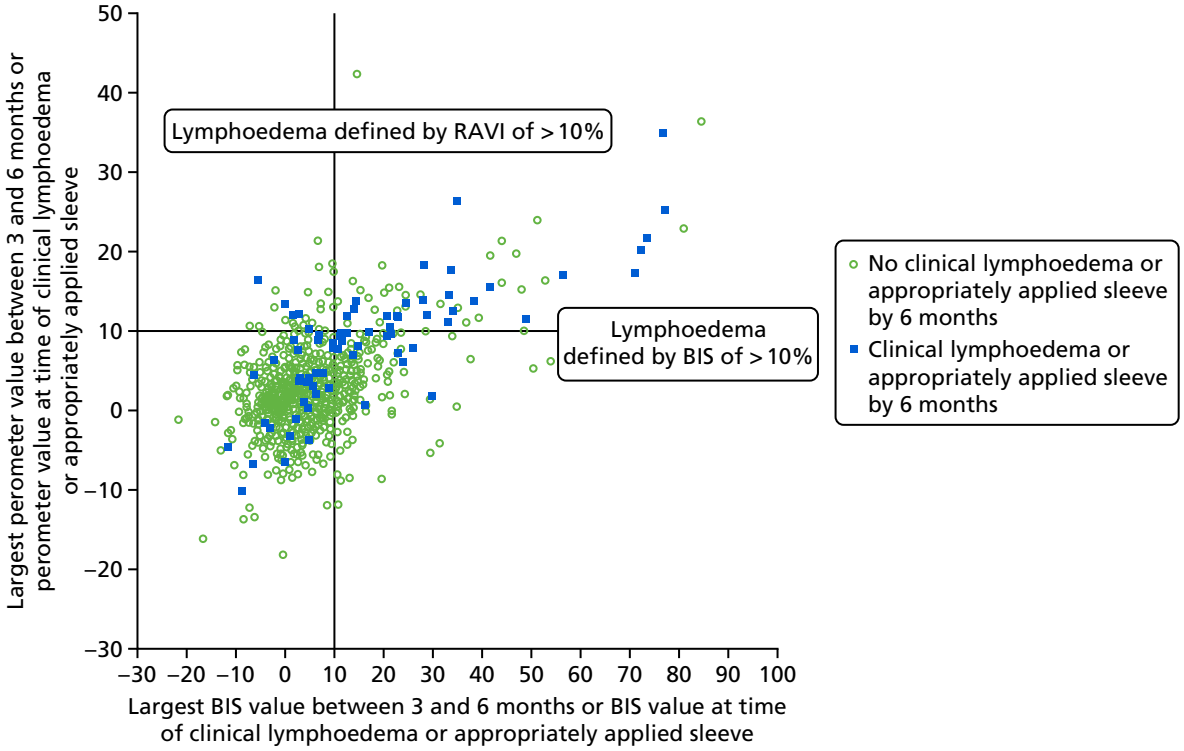


FIGURE 6 Comparison of RAVI of > 10% and BIS of > 10% with sleeve application. NB those with no clinical lymphoedema or applied sleeve by 6 months may have had an applied sleeve at a later time point.

At all time points, BIS would have resulted in more sleeves being applied than RAVI of > 10% incorrectly with lower specificity (*Tables 12–15*). RAVI of > 10% was better at identifying patients who could be reassured and did not need surveillance proving cost-effective to the NHS. It ruled out patients unlikely to develop lymphoedema and has a higher PPV at 18 months.

TABLE 13 Bioimpedance spectroscopy compared with sleeve/clinical lymphoedema

By 6 months	No sleeve or clinical lymphoedema	Sleeve or clinical lymphoedema	Total
BIS (< 10)	690 (80%) true negative	34 (46%) false negative	724
BIS (≥ 10)	170 (20%) false positive	40 (54%) true positive	210
Total	860	74	934

Sensitivity, 54% (40/74; 95% CI 43% to 65%); specificity, 80% (690/860; 95% CI 77% to 83%); PPV, 19% (40/210; 95% CI 25% to 39%); negative predictive value, 95% (690/724; 95% CI 94% to 97%).

TABLE 14 Relative arm-volume increase of > 10% and sleeve/clinical lymphoedema

After 6 months up to 18 months	No sleeve or clinical lymphoedema	Sleeve or clinical lymphoedema	Total
RAVI (< 10%)	693 (95%) true negative	72 (62%) false negative	765
RAVI (≥ 10%)	33 (5%) false positive	45 (38%) true positive	78
Total	726	117	843

Sensitivity, 38% (45/117; 95% CI 30% to 48%); specificity, 95% (693/726; 95% CI 94% to 97%); PPV, 58% (45/78; 95% CI 47% to 68%); negative predictive value, 91% (693/765; 95% CI 88% to 92%).

TABLE 15 Bioimpedance spectroscopy and sleeve/clinical lymphoedema

After 6 months up to 18 months	No sleeve or clinical lymphoedema	Sleeve or clinical lymphoedema	Total
BIS (< 10)	581 (82%) true negative	52 (47%) false negative	633
BIS (≥ 10)	126 (18%) false positive	59 (53%) true positive	185
Total	707	111	818

Sensitivity, 53% (59/111; 95% CI 44% to 62%); specificity, 82% (581/707; 95% CI 79% to 85%); PPV, 32% (59/185; 95% CI 26% to 39%); negative predictive value, 92% (581/633; 95% CI 89% to 94%).

For those with lymphoedema, the BIS and perometer values used are those at the time of lymphoedema diagnosis. For those without lymphoedema, the BIS and perometer values used are the largest value between 9 and 18 months.

Up to 6 months: sleeve application in at least one-third of patients appeared to be as a result of a composite of significant arm symptoms (swelling and heaviness) together with arm-volume increases. The PPV for RAVI of > 10% at both time points is superior to BIS, although the negative predictive values (NPVs) are similar (*Figure 7*).

Clinical lymphoedema/applied sleeve after 6 months up to 24 months

The clinical lymphoedema/applied sleeve after 6 up to 24 months variable excludes those with lymphoedema up to and including 6 months.

For those with lymphoedema, the BIS and RAVI values used are those at the time of lymphoedema diagnosis. For those without lymphoedema, the BIS and RAVI values used are the largest value between 9 and 24 months (*Table 16*).

It is apparent that perometer is more specific (94–96%) than BIS (80–91%) at all time points. In other words, RAVI measurement gets more diagnoses of sleeve application correct and fewer wrong, particularly at 6 months. Thus, it is noticeable that at 6 months BIS of > 10 had 170 false positives, yet identified only 40 out of the 74 sleeves that were applied, whereas perometer identified 30 out of the 75 sleeves applied but overdiagnosed only 55 rather than 170 patients (*Table 17*). The differences in sleeve application numbers reflect the fact that some patients did not have a BIS measurement. BIS use would have meant that patients had far more sleeves applied than those using RAVI of > 10%, but neither method was particularly sensitive (see *Figure 8*).

We then looked at the sensitivity and specificity of RAVI and BIS at 6, 18 and 24 months (i.e. comparing both methods with each other). Once again, BIS of > 10 identified those patients with a RAVI of > 10% measurement in 68–76% of cases.

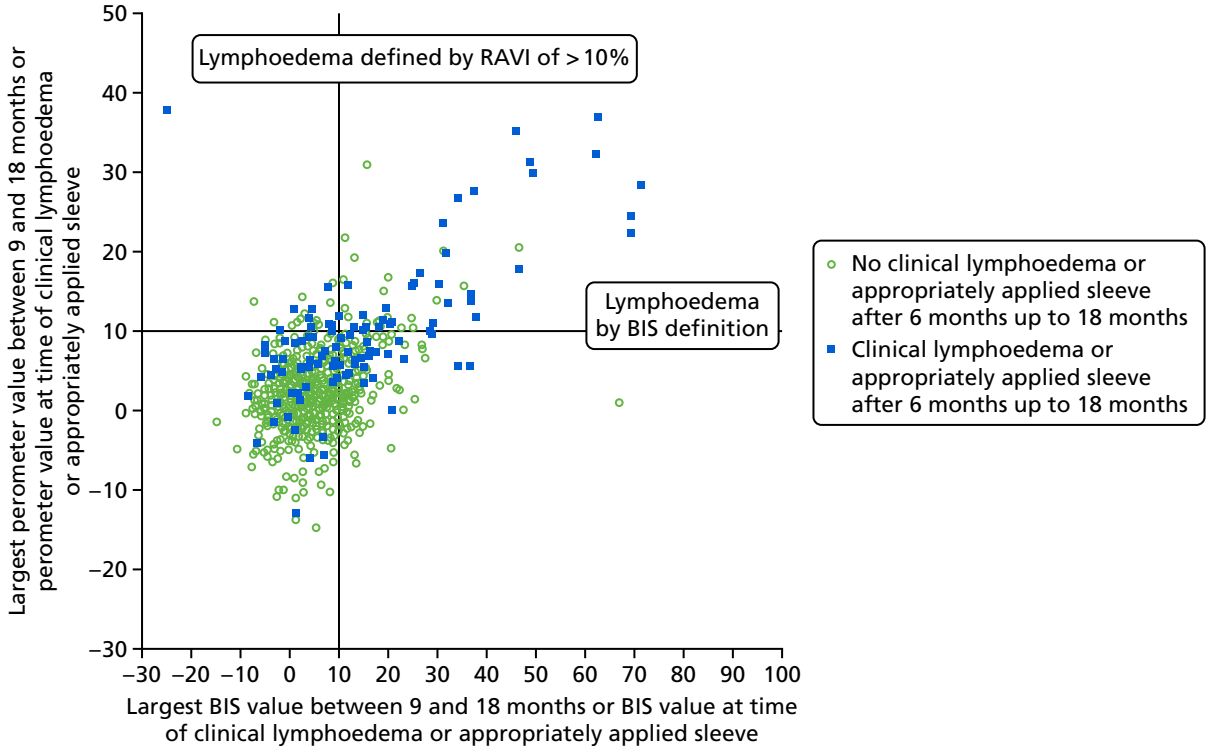


FIGURE 7 Comparison of RAVI of > 10% and BIS with sleeve application (6–18 months). Note that those with no clinical lymphoedema or appropriately applied sleeve by 6 months may have had clinical lymphoedema or an applied sleeve at a later time point.

TABLE 16 Relative arm-volume increase of > 10% and sleeve/clinical lymphoedema

After 6 months up to 24 months	No sleeve or clinical lymphoedema	Sleeve or clinical lymphoedema	Total
RAVI (< 10%)	667 (94%)	86 (61%)	753
RAVI (≥ 10%)	39 (6%)	55 (39%)	94
Total	706	141	847
Sensitivity, 39% (55/141; 95% CI 31% to 47%); specificity, 94% (667/706; 95% CI 93% to 96%); PPV, 59% (55/94; 95% CI 48% to 68%); NPV, 89% (667/753; 95% CI 86% to 91%).			

TABLE 17 Bioimpedance spectroscopy and sleeve/clinical lymphoedema

After 6 months up to 24 months	No sleeve or clinical lymphoedema	Sleeve or clinical lymphoedema	Total
BIS (< 10)	556 (80%)	65 (49%)	621
BIS (≥ 10)	136 (20%)	69 (51%)	205
Total	692	134	826
Sensitivity, 51% (69/134; 95% CI 43% to 60%); specificity, 80% (556/692; 95% CI 77% to 83%); PPV, 34% (69/205; 95% CI 28% to 40%); NPV, 90% (556/621; 95% CI 87% to 92%).			

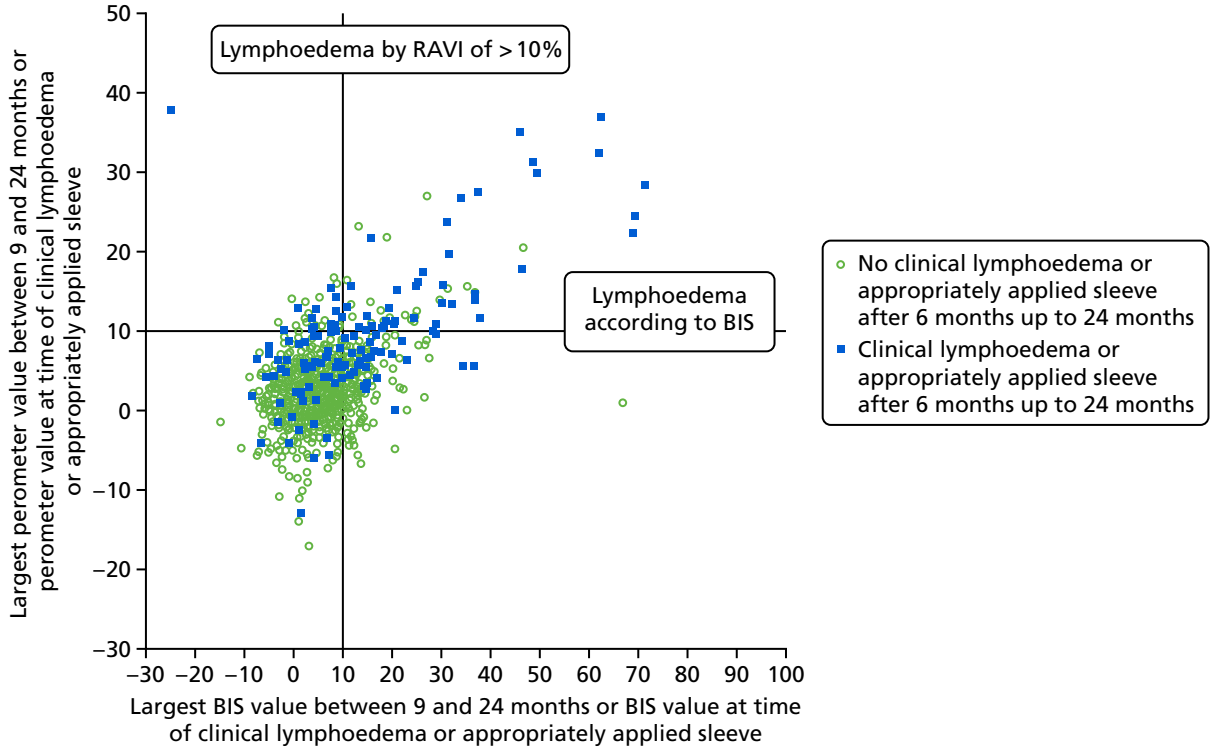


FIGURE 8 Comparison of RAVI of > 10% and BIS with sleeve application (6–24 months). Note that those women with no clinical lymphoedema or appropriately applied sleeve after 6 months and up to 24 months may have had clinical lymphoedema or a sleeve applied at a later time point.

Combined relative arm-volume increase or bioimpedance spectroscopy versus clinical lymphoedema/appropriately applied sleeve

We considered whether combining RAVI of > 10% and BIS of > 10% improved the diagnosis of lymphoedema compared with sleeve application. At all time points it reduced PPV, although sensitivity increased slightly (*Table 18*).

Clinical lymphoedema/applied sleeve after 6 months up to 24 months (excludes those with lymphoedema up to and including 6 months)

The BIS and RAVI values used are those at the time of the indicated lymphoedema. For those without lymphoedema, the BIS and RAVI values used are the largest value between 9 and 24 months (*Table 19*).

The 85 patients with lymphoedema are made up of 39 with both RAVI and BIS of ≥ 10, 30 with only BIS of ≥ 10 and 16 with only RAVI of ≥ 10%.

TABLE 18 Combined RAVI or BIS vs. sleeve/clinical lymphoedema

By 6 months	No sleeve or clinical lymphoedema	Sleeve or clinical lymphoedema	Total
RAVI of < 10% and BIS of < 10	663 (78%)	28 (38%)	691
RAVI of > 10% or BIS of ≥ 10	192 (22%)	45 (62%)	237
Total	855	73	928

Sensitivity, 62% (45/73; 95% CI 50% to 72%); specificity, 78% (663/855; 95% CI 75% to 80%); PPV, 19% (45/237; 95% CI 15% to 24%); NPV, 96% (663/691; 95% CI 94% to 97%).

TABLE 19 Combined RAVI or BIS vs. sleeve/clinical lymphoedema

After 6 months up to 24 months	No sleeve or clinical lymphoedema	Sleeve or clinical lymphoedema	Total
RAVI and BIS of < 10	537 (78%)	52 (38%)	589
RAVI or BIS of ≥ 10	154 (22%)	85 (62%)	239
Total	691	137	828

Sensitivity, 62% (85/137; 95% CI 54% to 70%); specificity, 78% (537/691; 95% CI 74% to 81%); PPV, 36% (85/239; 95% CI 30% to 42%); NPV, 91% (537/589; 95% CI 89% to 93%).

Predictive value of bioimpedance spectroscopy value by 6 months against lymphoedema by 18 or 24 months

Lymphoedema defined by RAVI of ≥ 10% and clinical lymphoedema or applied sleeve.

In all of the analyses that follow, any patients diagnosed with a RAVI value of > 10% by 6 months were excluded from the analysis ($n = 87$) and any patients with a clinical lymphoedema or sleeve applied before 6 months were excluded from the analysis (*Table 20*).

There is a significant relationship between both BIS category by 6 months and lymphoedema defined by perometer of ≥ 10% by 18 months ($p < 0.001$) and clinical lymphoedema or applied sleeve by 18 months ($p < 0.001$).

For lymphoedema defined by RAVI of > 10% the significant relationship appears to be as a result of the higher rate of lymphoedema, 24%, in those with BIS score of ≥ 10 (which is the BIS definition of lymphoedema).

For clinical lymphoedema/applied sleeve there appears to be a small increase in lymphoedema rate across the BIS < 3, ≥ 3 to < 5, and ≥ 5 to < 10 categories from 7% to 16% across the three categories. The significant relationship appears mainly to be as a result of the higher rate of lymphoedema, 36%, in those with BIS of ≥ 10 (*Table 21*).

There is a relationship between both BIS category by 6 months and lymphoedema defined by perometer of ≥ 10% ($p < 0.001$) and clinical lymphoedema or applied sleeve by 24 months ($p < 0.001$).

For lymphoedema defined by perometer of ≥ 10% there appears to be little difference in the lymphoedema rate in the < 3, ≥ 3 to < 5, and ≥ 5 to < 10 categories; the rate was between 9% and 15% in each of those categories. The relationship appears to be as a result of the higher rate of lymphoedema, 30%, in those with BIS of ≥ 10.

TABLE 20 Bioimpedance spectroscopy value by 6 months against lymphoedema by 18 months

	Lymphoedema defined by perometer RAVI > 10%		Clinical lymphoedema or appropriately applied sleeve	
BIS value by 6 months	No lymphoedema by 18 months ($n = 662$)	Lymphoedema by 18 months ($n = 77$)	No lymphoedema by 18 months ($n = 643$)	Lymphoedema by 18 months ($n = 114$)
< 3	327 (93%)	23 (7%)	324 (93%)	25 (7%)
> 3 to < 5	80 (91%)	8 (9%)	78 (90%)	9 (10%)
> 5 to < 10	156 (92%)	14 (8%)	145 (84%)	27 (16%)
> 10	99 (76%)	32 (24%)	96 (64%)	53 (36%)

TABLE 21 Bioimpedance spectroscopy value by 6 months against lymphoedema by 24 months

	Lymphoedema defined by RAVI of > 10%		Clinical lymphoedema or appropriately applied sleeve	
BIS value by 6 months	No lymphoedema by 24 months ($n = 596$)	Lymphoedema by 24 months ($n = 101$)	No lymphoedema by 24 months ($n = 577$)	Lymphoedema by 24 months ($n = 137$)
< 3	298 (91%)	30 (9%)	297 (91%)	31 (9%)
> 3 to < 5	68 (85%)	12 (15%)	66 (85%)	12 (15%)
> 5 to < 10	142 (87%)	21 (13%)	128 (78%)	36 (22%)
> 10	88 (70%)	38 (30%)	86 (60%)	58 (40%)

For clinical lymphoedema or applied sleeve, there is an increase in the lymphoedema rate across all four categories, with smaller increases across the first three categories and a larger increase in the rate of lymphoedema in those with BIS of ≥ 10, which is the diagnostic category for lymphoedema according to BIS.

Prediction of lymphoedema

Two analyses were performed: one looked at the situation described above (lymphoedema after 6 months and up to 2 years), and the other looked at the time to first lymphoedema including all follow-up data (1-month visit was excluded as per the protocol, version 5.2, and the NIHR Programme Grants for Applied Research programme response letter). Both RAVI (> 10%) and sleeve application were considered in these analyses.

Factors predicting lymphoedema from baseline

For RAVI of > 10% as the end point, univariate analysis revealed BMI ($p = 0.004$), age ($p = 0.013$), previous sentinel node biopsy ($p = 0.027$), ER status ($p = 0.006$: ER negativity: HR 1.59, 95% CI 1.14 to 2.21), and number of nodes involved ($p < 0.001$) all predicted lymphoedema development. If one only considers those with confirmed or absent lymphoedema by 24 months, 25% (47/190) of ER-negative patients and 18% (141/794) of ER positive patients developed lymphoedema.

The multivariable analysis included number of nodes involved (HR 1.04, 95% CI 1.02 to 1.06), age ≥ 70 years compared with age < 70 years (HR 1.67, 95% CI 1.10 to 2.55), BMI of > 30 kg/m^2 (HR 1.62, 95% CI 1.14 to 2.32) and ER negativity (HR 1.56, 95% CI 1.11 to 2.19) in the model for predicting lymphoedema development (*Table 22*).

Sleeve application from baseline 24 months (excluding 1-month lymphoedema)

Univariate analysis revealed that only two factors predicted the sleeve application, node positivity (per-node increase) (HR 1.04, 95% CI 1.02 to 1.05) and adjuvant radiotherapy (HR 2.08, 95% CI 1.30 to 3.33), and both were independent in the multivariable analysis with a HR of 1.03 (95% CI 1.01 to 1.05; $p < 0.001$) and a HR of 1.93 (95% CI 1.20 to 3.10; $p = 0.007$), respectively (*Table 23*).

Lymphoedema development after 6 months' surveillance (i.e. 6 months up to 2 years and the time to first lymphoedema within that time)

Patients with lymphoedema at 3 or 6 months are excluded because the inclusion of the RAVI variable, which is determined at 6 months, means there would need to be a ≥ 10% category RAVI variable but this is also used as the outcome event. In addition, excluding these patients is part of the study protocol (version 5.2) and the NIHR Programme Grants for Applied Research programme response letter.

The RAVI of ≥ 10% univariate analysis revealed that BMI ($p < 0.002$), number of nodes involved (median 2, range 0–41; $p < 0.001$), largest RAVI change by 6 months ($p < 0.001$; HR 5.58 for ≥ 5% to < 10% vs. < 3%, 95% CI 3.61 to 8.62) and BIS of > 10% ($p < 0.001$) all predicted lymphoedema development from 6 months up to 2 years.

TABLE 22 Relative arm-volume increase of ≥ 10% definition of lymphoedema from baseline: time to lymphoedema assessed for those with a perometer RAVI of ≥ 10% after 1 up to 24 months

	Analysis			
	Univariate		Multivariable	
Variable	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age (per year increase)	1.01 (1.00 to 1.03)	0.013	1.01 (1.00 to 1.02)	0.074
BMI (kg/m^2) at baseline (reference ≤ 25)		0.004		0.005
> 25 to ≤ 30	1.18 (0.82 to 1.71)	0.38	0.99 (0.68 to 1.44)	0.95
> 30	1.76 (1.24 to 2.51)	0.002	1.62 (1.14 to 2.32)	0.008
ER negative	1.59 (1.14 to 2.21)	0.006	1.56 (1.11 to 2.19)	0.010
Nodes positive (per-node increase)	1.04 (1.03 to 1.06)	< 0.001	1.04 (1.02 to 1.06)	< 0.001
Adjuvant CT (yes)	1.19 (0.87 to 1.62)	0.27	–	–
Adjuvant RT (yes)	1.43 (0.93 to 2.19)	0.10	–	–
Previous SN biopsy	0.70 (0.51 to 0.96)	0.027	–	–

CT, chemotherapy; RT, radiotherapy; SN, sentinel node.

TABLE 23 Sleeve application from baseline 24 months (excluding 1-month lymphoedema)

	Analysis			
	Univariate		Multivariable	
Variable	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age (per year increase)	1.00 (0.99 to 1.01)	0.71	–	–
BMI (kg/m^2) at baseline (reference ≤ 25)		0.53	–	–
> 25 to ≤ 30	0.99 (0.71 to 1.39)	0.96		
> 30	1.18 (0.84 to 1.66)	0.35		
ER negative	0.80 (0.54 to 1.17)	0.25	–	–
Nodes positive (per-node increase)	1.04 (1.02 to 1.05)	< 0.001	1.03 (1.01 to 1.05)	0.001
Adjuvant CT (yes)	1.34 (0.98 to 1.82)	0.065	–	–
Adjuvant RT (yes)	2.08 (1.30 to 3.33)	0.002	1.93 (1.20 to 3.10)	0.007
Previous SN biopsy	0.98 (0.73 to 1.31)	0.89	–	–

CT, chemotherapy; RT, radiotherapy; SN, sentinel node.

The multivariable analysis included RAVI change by 6 months ($p < 0.001$; HR 5.22 for ≥ 5% to < 10%, 95% CI 3.22 to 8.47) along with 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), BMI of > 30 kg/m^2 (HR 1.87, 95% CI 1.16 to 3.02) and BIS > 10% ($p = 0.069$) in the model for predicting lymphoedema development after 6 months up to 2 years (*Table 24*).

Smoking, type of surgery, weight gain and histological tumour type were not significant [$n = 1100$: those with lymphoedema ≤ 6 months have been excluded]. Factors predicting time to lymphoedema (sleeve applied) after 6 months surveillance (excluding lymphoedema at 6 months).

TABLE 24 Predictors of lymphoedema (defined by RAVI > 10%) after 6 months

	Analysis			
	Univariate		Multivariable	
Variable	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age (per year increase)	1.01 (0.99 to 1.02)	0.31	–	–
BMI (kg/m^2) at baseline (reference ≤ 25)		0.002		0.008
> 25 to ≤ 30	0.81 (0.48 to 1.36)	0.42	0.96 (0.56 to 1.67)	0.90
> 30	1.78 (1.13 to 2.79)	0.013	1.87 (1.16 to 3.02)	0.010
ER negative	1.27 (0.79 to 2.05)	0.33	–	–
Nodes positive (per-node increase)	1.05 (1.03 to 1.08)	< 0.001	1.05 (1.02 to 1.07)	< 0.001
Adjuvant CT (yes)	1.24 (0.81 to 1.88)	0.32	1.61 (1.01 to 2.55)	0.044
Adjuvant RT (yes)	1.43 (0.80 to 2.55)	0.23	–	–
Previous SN biopsy	0.68 (0.44 to 1.03)	0.069	–	–
Arm measurements – 6 months (reference < 3% increase)		< 0.001		< 0.001
RAVI ≥ 3 to < 5% increase	1.88 (1.06 to 3.33)	0.030	1.87 (1.03 to 3.41)	0.041
RAVI ≥ 5 to < 10% increase	5.58 (3.61 to 8.62)	< 0.001	5.22 (3.22 to 8.47)	< 0.001
BIS at 6 months (reference < 3% increase)		< 0.001		0.069
≥ 3 to < 5% increase	1.48 (0.74 to 2.95)	0.26	1.54 (0.77 to 3.11)	0.22
≥ 5 to < 10% increase	1.37 (0.79 to 2.39)	0.26	1.25 (0.70 to 2.24)	0.44
≥ 10% increase	3.70 (2.30 to 5.95)	< 0.001	1.98 (1.18 to 3.33)	0.010

CT, chemotherapy; RT, radiotherapy; SN, sentinel node.

For applied sleeves as the clinical definition of lymphoedema, univariate analysis revealed that adjuvant radiotherapy ($p = 0.008$), adjuvant chemotherapy ($p = 0.005$), ER status ($p = 0.076$), ER negativity (HR 0.63, 95% CI 0.38 to 1.05), BIS of ≥ 10% ($p < 0.001$) and RAVI of ≥ 10% ($p < 0.001$) all predicted time to lymphoedema after 6 months to 24 months.

The multivariable analysis included adjuvant radiotherapy ($p = 0.021$), adjuvant chemotherapy ($p = 0.003$), ER status ($p = 0.012$), ER negativity (HR 0.51, 95% CI 0.30 to 0.86), BIS of ≥ 10% ($p < 0.001$) and perometer of ≥ 10% ($p < 0.001$) independently predicted time to lymphoedema after 6 months to 24 months (*Table 25*).

At 1 month, because both chemotherapy and radiotherapy had not commenced, the prediction was not as good as that at 6 months. Early changes in arm volume (RAVI) had the highest HR and were the best single predictor of subsequent lymphoedema.

Quality-of-life analyses: FACT-B scores

There are nine FACT-B+4 summary scores:[27] physical well-being (PWB; score range 0–28), social/family well-being (SWB; score range 0–28), emotional well-being (EWB; score range 0–24), functional well-being (FWB; score range 0–28), breast cancer subscale (BCS; score range 0–40), arm subscale (ARM; score range 0–20), FACT-G total score (FACT-G = PWB + SWB + EWB + FWB; score range 0–108), FACT-B total score (FACT-B = PWB + SWB + EWB + FWB + BCS, score range 0–148), and Trial Outcome Index (TOI = PWB + FWB + BCS; score range 0–96). Descriptive summary data are shown in *Appendix 16*.

A simple comparison of the QoL data at each time point separately revealed that patients with lymphoedema at 6 months (by either definition) had significantly lower FACT-B+4, TOI and ARM subscale scores (*Table 26* and *27*). Poorer ARM subscale scores were also found at 12, 18 and 24 months (*Table 28*).

TABLE 25 Time to lymphoedema from 6 months to 24 months (excluding lymphoedema to 6 months): clinical lymphoedema/applied sleeve

	Analysis			
	Univariate		Multivariable	
Variable	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age (per year increase)	1.00 (0.99 to 1.01)	> 0.99	–	–
BMI (kg/m^2) at baseline (reference ≤ 25)		0.76	–	–
> 25 to ≤ 30	1.09 (0.72 to 1.65)	0.67		
> 30	1.18 (0.77 to 1.80)	0.45		
ER negative	0.63 (0.38 to 1.05)	0.076	0.51 (0.30 to 0.86)	0.012
Nodes positive (per-node increase)	1.04 (1.02 to 1.06)	< 0.001	–	–
Adjuvant CT (yes)	1.78 (1.19 to 2.66)	0.005	1.92 (1.24 to 2.96)	0.003
Adjuvant RT (yes)	2.23 (1.23 to 4.03)	0.008	2.03 (1.11 to 3.71)	0.021
Previous SN biopsy	0.93 (0.65 to 1.33)	0.68	–	–
Arm measurements – perometer at 6 months (reference < 3% increase)		< 0.001		< 0.001
RAVI of ≥ 3% to < 5% increase	1.94 (1.15 to 3.26)	0.013	1.57 (0.92 to 2.69)	0.099
RAVI of ≥ 5% to 10% increase	3.84 (2.47 to 5.96)	< 0.001	3.13 (1.97 to 4.98)	< 0.001
RAVI of ≥ 10% increase	12.56 (7.84 to 20.14)	< 0.001	7.90 (4.78 to 13.06)	< 0.001
Arm measurements BIS at 6 months (reference < 3% increase)		< 0.001		< 0.001
≥ 3% to < 5% increase	1.27 (0.60 to 2.67)	0.53	1.48 (0.69 to 3.14)	0.31
≥ 5% to 10% increase	2.39 (1.47 to 3.89)	< 0.001	2.51 (1.50 to 4.20)	< 0.001
≥ 10% increase	5.65 (3.63 to 8.79)	< 0.001	4.06 (2.51 to 6.58)	< 0.001

CT, chemotherapy; RT, radiotherapy; SN, sentinel node.

TABLE 26 FACT-B at 6, 12, 18 and 24 months, respectively

	Lymphoedema, mean (SD)		
Time (no : yes)	No	Yes	*p*-value
Perometer of > 10%			
Lymphoedema at 6 months (660 : 58)	107.4 (21.5)	101.0 (21.4)	0.030
Lymphoedema at 12 months (628 : 55)	112.0 (21.1)	103.7 (22.8)	0.005
Lymphoedema at 18 months (566 : 59)	113.6 (20.2)	106.2 (21.5)	0.008
Lymphoedema at 24 months (541 : 68)	114.1 (20.1)	108.0 (25.3)	0.059
Sleeve application			
Lymphoedema by 6 months (683 : 60)	107.1 (21.5)	99.6 (23.5)	0.011
Lymphoedema by 12 months (577 : 121)	112.9 (20.4)	104.6 (24.3)	0.001
Lymphoedema by 18 months (518 : 124)	114.1 (19.9)	107.3 (21.6)	0.001
Lymphoedema by 24 months (466 : 151)	114.8 (19.8)	108.5 (23.8)	0.003

TABLE 27 FACT-B TOI at 6, 12, 18 and 24 months, respectively

	Lymphoedema, mean (SD)		
Time (no : yes)	No	Yes	*p*-value
Perometer of > 10%			
Lymphoedema at 6 months (690 : 63)	64.7 (15.5)	58.0 (16.1)	0.001
Lymphoedema at 12 months (585 : 123)	70.0 (14.2)	63.6 (17.0)	< 0.001
Lymphoedema at 18 months (523 : 128)	70.9 (14.0)	65.6 (14.6)	< 0.001
Lymphoedema at 24 months (472 : 152)	71.5 (13.7)	67.0 (16.5)	0.003
Sleeve application			
Lymphoedema at 6 months (669 : 59)	65.0 (15.4)	58.1 (15.3)	0.001
Lymphoedema at 12 months (637 : 56)	69.3 (14.6)	62.9 (16.2)	0.002
Lymphoedema at 18 months (570 : 63)	70.4 (14.2)	64.6 (14.2)	0.002
Lymphoedema at 24 months (546 : 70)	71.1 (13.9)	65.2 (17.8)	0.009

TABLE 28 FACT-B Arm subscale changes with time and lymphoedema

	Lymphoedema, median, IQR (range)		
Time (no : yes)	No	Yes	*p*-value
RAVI of > 10%			
Lymphoedema at 6 months (688 : 60)	16, 13–18 (0–20)	14, 10–16 (0–20)	< 0.001
Lymphoedema at 12 months (654 : 56)	16, 14–18 (0–20)	14, 10–17 (0–20)	< 0.001
Lymphoedema at 18 months (583 : 64)	16, 14–18 (0–20)	14, 10–17 (0–20)	< 0.001
Lymphoedema at 24 months (558 : 74)	17, 14–19 (0–20)	15, 10–17 (0–20)	< 0.001
Sleeve application			
Lymphoedema by 6 months (712 : 63)	16, 13–18 (0–20)	15, 10–16 (0–19)	< 0.001
Lymphoedema by 12 months (598 : 127)	16, 14–19 (0–20)	15, 11–17 (0–20)	< 0.001
Lymphoedema by 18 months (531 : 134)	17, 14–19 (1–20)	14, 11–16 (0–20)	< 0.001
Lymphoedema by 24 months (483 : 157)	17, 14–19 (0–20)	15, 12–17 (0–20)	< 0.001

IQR, interquartile range.

At all time points, a significantly higher percentage of patients reporting swelling symptoms was found for those with lymphoedema, and a significantly higher percentage of patients reporting heaviness symptoms was found at 6, 18 and 24 months. Lower FACT-B+4, TOI and ARM subscale scores were found in the two smaller restricted subsets of patients defined by 'no sleeve' usage. These lower scores were significant for TOI (*Table 27*), and for the ARM subscale at 6, 12, 18 and 24 months. Likewise, a higher percentage of patients with reported swelling and patients with reported heaviness symptoms were found for those with lymphoedema in the smaller restricted subsets of patients defined by 'no sleeve' usage, and these remained significant (*Table 29*). The absolute change in FACT-B+4 ($p = 0.04$), TOI ($p = 0.046$) and ARM subscale ($p = 0.009$) scores between 6 and 24 months were significantly related to having lymphoedema at 24 months.

TABLE 29 Lymphoedema self-report symptoms with time and lymphoedema: swelling and heaviness

Time (no : yes)	Lymphoedema, % (*n*)		*p*-value
	No	Yes	
RAVI > 10% (swelling)			
Lymphoedema at 6 months (601 : 55)	31 (186)	91 (50)	< 0.001
Lymphoedema at 12 months (591 : 53)	37 (219)	91 (48)	< 0.001
Lymphoedema at 18 months (524 : 61)	36 (187)	89 (54)	< 0.001
Lymphoedema at 24 months (525 : 70)	35 (185)	87 (61)	< 0.001
Sleeve application (swelling)			
Lymphoedema by 6 months (620 : 60)	30 (189)	90 (54)	< 0.001
Lymphoedema by 12 months (540 : 119)	31 (167)	89 (106)	< 0.001
Lymphoedema by 18 months (473 : 127)	28 (134)	88 (112)	< 0.001
Lymphoedema by 24 months (449 : 153)	28 (126)	80 (123)	< 0.001
RAVI > 10% (heaviness)			
Lymphoedema at 6 months (620 : 57)	38 (233)	67 (38)	< 0.001
Lymphoedema at 12 months (590 : 53)	40 (237)	66 (35)	< 0.001
Lymphoedema at 18 months (523 : 59)	39 (202)	85 (50)	< 0.001
Lymphoedema at 24 months (516 : 67)	40 (208)	73 (49)	< 0.001
Sleeve application (heaviness)			
Lymphoedema by 6 months (640 : 60)	37 (239)	68 (41)	< 0.001
Lymphoedema by 12 months (544 : 112)	37 (203)	67 (75)	< 0.001
Lymphoedema by 18 months (477 : 121)	35 (169)	74 (90)	< 0.001
Lymphoedema by 24 months (441 : 149)	37 (164)	64 (95)	< 0.001

Generalised estimating equation regression analysis to further analyse the changes in quality-of-life scores over time

FACT-B Trial Outcome Index

Owing to the negative skew of the TOI variable, a transformation [log normalised (LN) (120 – TOI)] was used for the GEE analysis to obtain a better approximation to a normal distribution. In a regression model including the time variable, the estimated marginal mean (EMM) of TOI at each time point is presented in *Table 30*. A total of 997 patients had some data in the model. There was a change in TOI over time ($p < 0.001$).

TABLE 30 FACT-B TOI estimated marginal mean at each time point

Time point	Estimated marginal mean of TOI	95% CI
Pre surgery	68.0	67.2 to 68.9
3 months	63.5	62.5 to 64.5
6 months	65.4	64.4 to 66.4
12 months	70.2	69.2 to 71.1
18 months	70.6	69.6 to 71.5
24 months	71.0	70.0 to 71.9

A GEE 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 (*Table 31* and *Figure 10*).

The EMMs from the interaction term in the GEE analysis are presented below and in *Table 31*.

The main effect for the time variable was significant ($p < 0.001$). The main effect for the lymphoedema status by 6 months variable was significant ($p = 0.028$), showing that there was a difference between the lymphoedema status groups overall. Patients who developed lymphoedema by 6 months did not initially have poorer QoL (TOI) scores than those who did not develop lymphoedema, but by 6 months their scores were poorer and they remained poorer until 24 months, when the difference was no longer significant.

It is noteworthy that those without lymphoedema at 6 months begin to regain their QoL (TOI) at 3 months, improving to be above pre-surgery levels by 12 months, whereas those who develop lymphoedema continue

TABLE 31 FACT-B TOI EMMs at each time point for those with and without lymphoedema by 6 months

Time point	Estimated marginal mean of TOI (95% CI)		
	Without lymphoedema by 6 months ($n = 883$)	With lymphoedema by 6 months ($n = 87$)	*p*-value
Pre surgery	68.3 (67.4 to 69.2)	67.0 (63.9 to 70.0)	0.42
3 months	63.8 (62.7 to 64.8)	61.4 (57.8 to 64.8)	0.19
6 months	66.0 (64.9 to 67.1)	60.1 (56.4 to 63.5)	0.001
12 months	70.7 (69.8 to 71.7)	65.3 (61.8 to 68.5)	0.001
18 months	71.1 (70.2 to 72.1)	65.4 (61.9 to 68.6)	0.001
24 months	71.4 (70.4 to 72.4)	67.6 (64.0 to 71.0)	0.033

The *p*-values in this table have not been adjusted for multiple testing.

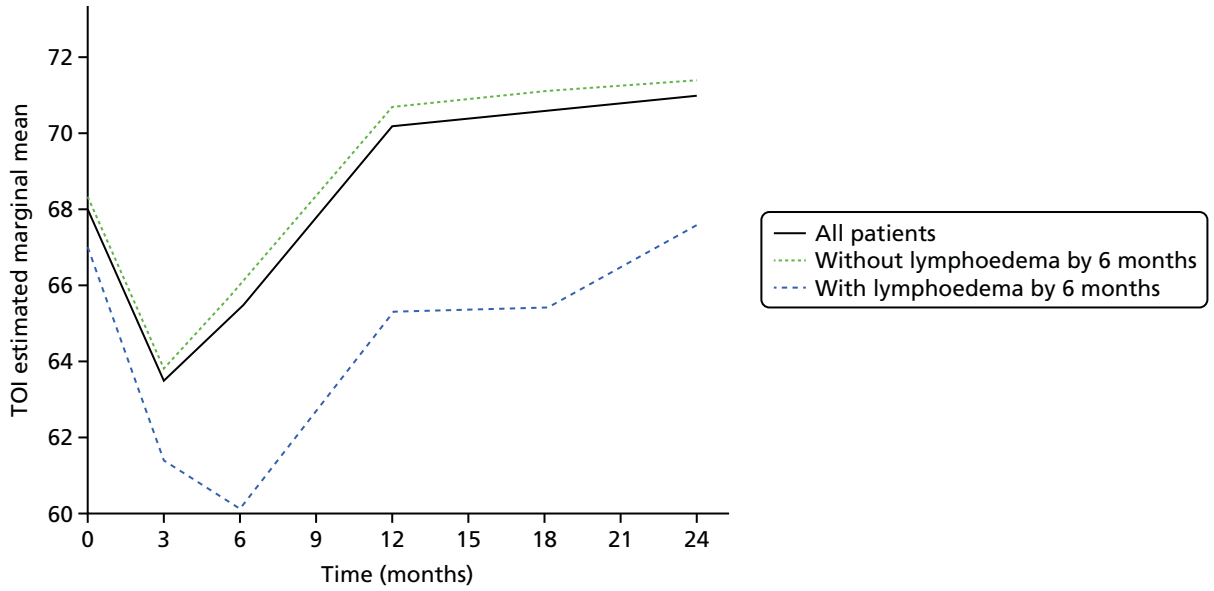


FIGURE 9 The FACT-B TOI EMMs over time for all patients and those with and those without lymphoedema at 6 months.

to have worsening QoL until 6 months and do not regain QoL to pre-surgery levels until 24 months, and do not surpass their pre-surgery QoL scores. This is an important finding, as it clearly and robustly indicates poorer QoL in the group who develop lymphoedema following surgery.

FACT-B total scores

Owing to the negative skew of the FACT-B total score variable, a transformation [LN(160 – FACT-B)] was used for the GEE analysis to obtain a better approximation to a normal distribution.

There was a change in FACT-B total over time ($p < 0.001$), and a borderline difference in the overall level of the FACT-B scores between those with and without lymphoedema ($p = 0.055$) over time (*Figure 10*). Although the difference between patients with and without lymphoedema indicated deficits in QoL from 3 months onwards, the pattern of change over time between groups was different ($p < 0.001$). The EMMs from the GEE analysis are in *Table 32*. By 6 months patients without lymphoedema regained their pre-surgery levels of total FACT-B score, whereas those who developed lymphoedema had persistent FACT-B QoL deficiency until 12 months after surgery (see *Table 32* and *Figure 10*).

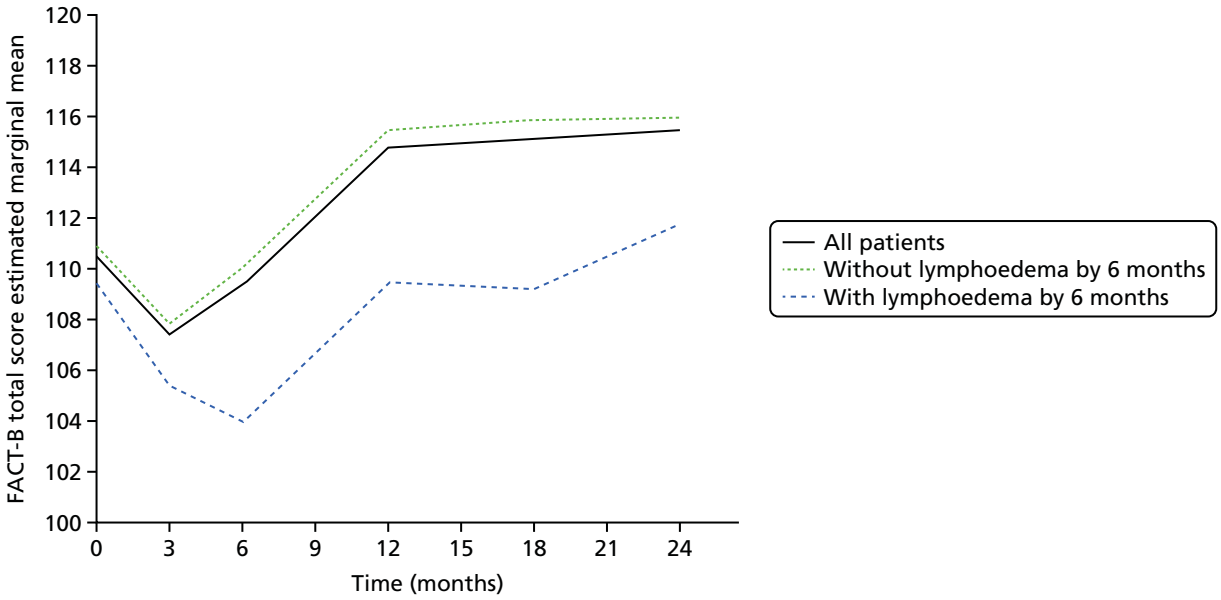


FIGURE 10 The FACT-B total score EMMs over time for all patients and those with and without lymphoedema at 6 months.

TABLE 32 The FACT-B total scores EMM at each time point for those with and without lymphoedema by 6 months

Time point	EMM of FACT-B total score (95% CI)		*p*-value
	Without lymphoedema by 6 months ($n = 882$)	With lymphoedema by 6 months ($n = 87$)	
Pre surgery	110.9 (109.7 to 112.2)	109.4 (105.0 to 113.4)	0.48
3 months	107.8 (106.3 to 109.2)	105.3 (100.3 to 109.9)	0.32
6 months	110.1 (108.6 to 111.5)	104.0 (98.7 to 108.8)	0.018
12 months	115.5 (114.1 to 116.8)	109.5 (104.5 to 114.0)	0.012
18 months	115.9 (114.5 to 117.2)	109.2 (104.2 to 113.7)	0.005
24 months	116.0 (114.6 to 117.4)	111.8 (106.5 to 116.7)	0.11

The *p*-values in this table have not been adjusted for multiple testing.

ARM subscale

Owing to the negative skew of the ARM subscale variable, a transformation [LN(22 – ARM)] was used for the GEE analysis to obtain a better approximation to a normal distribution (data for 995 patients).

There was a change in scores over time ($p < 0.001$) for FACT-B ARM scores (*Figure 11* and *Table 34*), and a difference in the overall level of the ARM scores between those with and without lymphoedema ($p = 0.002$). The pattern of change over time was different between the two groups ($p < 0.001$). For ARM subscale values, all patients' values declined which did not return to baseline by 24 months implying a long-term arm symptom increase with ANC Surgery. ARM scores were persistently worse in those patients who developed lymphoedema, and there was a decrease in ARM subscale EMMs from pre surgery to 3 months in both those with and those without lymphoedema by 6 months. The EMM of those without lymphoedema by 6 months remained similar level to the EMM at 3 months before increasing slightly at 24 months but remained below the pre-surgery EMM. The EMM score at 24 months increased, although it remained below the pre-surgery EMM (*Table 33*).

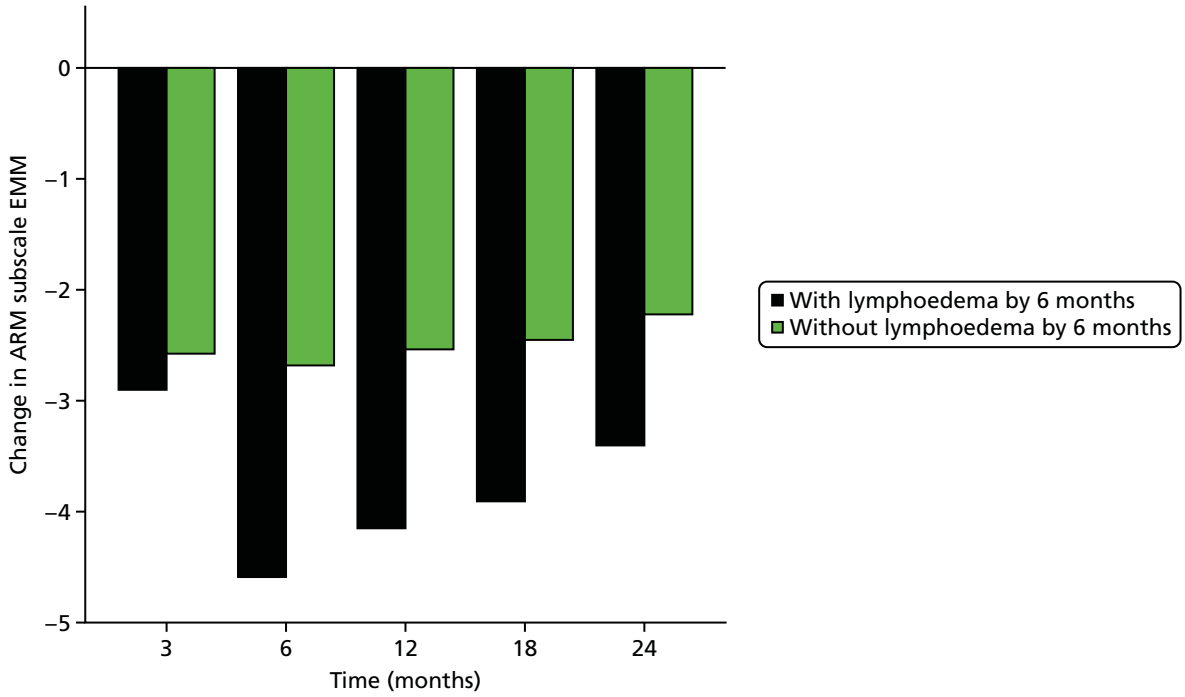


FIGURE 11 Change in FACT-B ARM scores EMMs for patients with and without lymphoedema at 6 months.

TABLE 33 ARM subscale scores EMM at each time point for those with and without lymphoedema by 6 months

Time point	EMM of ARM subscale (95% CI)		*p*-value
	Without lymphoedema by 6 months ($n = 882$)	With lymphoedema by 6 months ($n = 87$)	
Pre surgery	18.7 (18.6 to 18.9)	18.6 (17.9 to 19.1)	0.62
3 months	16.2 (15.9 to 16.4)	15.7 (14.7 to 16.5)	0.29
6 months	16.0 (15.8 to 16.3)	14.0 (13.0 to 14.8)	< 0.001
12 months	16.2 (15.9 to 16.4)	14.4 (13.4 to 15.3)	< 0.001
18 months	16.3 (16.0 to 16.5)	14.7 (13.5 to 15.6)	0.001
24 months	16.5 (16.3 to 16.8)	15.2 (14.2 to 16.0)	0.003

The *p*-values in this table have not been adjusted for multiple testing.

Clinical lymphoedema/appropriately applied sleeve

Whether the clinical lymphoedema or applied sleeve variable is considered or the RAVI of > 10% definition of lymphoedema, the multivariable analysis results are similar. The only difference of note is that type of surgery is no longer associated with FACT-B at 12 months, although the direction of effect is the same as when the RAVI of > 10% definition of lymphoedema was included in the model.

In addition to lymphoedema, the analysis identified BMI, current smoking and older age, which had not previously been reported to influence FACT-B scores.

A similar analysis at 6 months found that chemotherapy significantly influenced scores, but the effect was lost in multivariate analysis by 12 months (see *Table 34*).

TABLE 34 FACT-B+4: analysis of factors influencing the QoL scores

	Analysis			
	Univariate		Multivariable ($n = 683$)	
Variable	EMM (95% CI)	*p*-value	EMM (95% CI)	*p*-value
Lymphoedema in first 12 months				
No	116.9 (115.4 to 118.4)		114.3 (112.1 to 116.5)	
Yes	109.9 (105.9 to 113.6)	< 0.001	106.4 (101.7 to 110.8)	< 0.001
Adjuvant CT				
No	117.9 (115.4 to 120.2)	0.051	–	–
Yes	114.9 (113.1 to 116.6)		–	
Adjuvant RT				
No	116.6 (113.2 to 119.7)	0.60	–	–
Yes	115.6 (114.0 to 117.1)		–	
BMI (kg/m^2) at baseline				
≤ 25	120.3 (118.1 to 122.4)	< 0.001	116.5 (113.4 to 119.3)	< 0.001
> 25 to ≤ 30	114.8 (112.4 to 117.1)		109.4 (105.7 to 112.9)	
> 30	110.3 (107.1 to 113.2)		105.0 (100.8 to 108.9)	
Type of surgery				
ANC/other	118.4 (115.7 to 120.9)	0.012	112.5 (108.7 to 115.9)	0.063
WLE + ANC	116.8 (114.2 to 119.3)		110.9 (107.1 to 114.5)	
Mastectomy + ANC	113.4 (111.2 to 115.6)		108.1 (104.8 to 111.2)	
Smoking				
Never	117.1 (115.3 to 118.8)	0.012	113.9 (111.5 to 116.3)	0.018
Ex-smoker	114.7 (112.0 to 117.2)		111.1 (107.9 to 114.2)	
Current	109.1 (103.0 to 114.5)		106.2 (99.5 to 112.1)	
Age (years)				
< 50	113.8 (111.1 to 116.3)	0.058	107.8 (103.9 to 111.5)	0.002
≥ 50	116.7 (115.0 to 118.4)		113.1 (110.4 to 115.6)	

CT, chemotherapy; RT, radiotherapy.

This is the first large prospective analysis of factors affecting QoL using FACT-B+4 in breast cancer patients and has identified several new factors, such as smoking and BMI, which influence QoL. BMI was also found to have important effects on QoL in the health economic analysis, strengthening the case for encouraging weight loss strategies after cancer diagnosis.

Relationship between the lymphoedema checklist variables at 6 months and changes in quality of life from baseline and relative arm-volume increase/bioimpedance spectroscopy from 1 month

The lymphoedema checklist is a patient self-reported symptom checklist; the constituent symptoms were compared with QoL changes in the study.

Greater reductions (from baseline to 6 months) in FACT-B, TOI and ARM subscale scores were found in those with swelling, heaviness ($p < 0.001$) and numbness ($p < 0.035$ FACT-B; $p = 0.051$ TOI; and $p < 0.001$ ARM).

For patients reporting swelling at 6 months, the reductions (from baseline to 6 months) in FACT-B ($p < 0.001$), TOI ($p < 0.001$) and ARM subscale ($p < 0.001$) were greater than for those not reporting swelling.

For patients reporting numbness at 6 months, the reductions (from baseline to 6 months) in FACT-B ($p = 0.035$), TOI ($p = 0.051$) and ARM subscale ($p < 0.001$) were greater than for those not reporting numbness.

For patients reporting heaviness at 6 months, the reductions (from baseline to 6 months) in FACT-B ($p < 0.001$), TOI ($p < 0.001$) and ARM subscale ($p < 0.001$) were greater than for those not reporting heaviness.

Greater increases (from 1 month to 6 months) in the exact RAVI value and exact BIS values were found in those with swelling (both $p < 0.001$), and in those with heaviness (RAVI $p = 0.038$ and exact BIS $p = 0.004$).

There were greater increases (from 6 to 24 months) in the exact RAVI value in those with swelling ($p < 0.001$), and in those with heaviness (RAVI $p = 0.001$) both during the time period and the responses at 24 months. No association was seen between 6 and 24 months with exact BIS values and swelling, numbness or heaviness.

In summary, RAVI of > 10% or changes in RAVI more closely related to patient-reported symptoms of arm swelling and heaviness throughout the BEA study.

Associations between changes in quality of life from baseline to 6 months and perometry/bioimpedance spectroscopy at 6 months

There was a negative association between changes in TOI and RAVI ($r = –0.10$; $p = 0.024$) and BIS ($r = –0.14$; $p = 0.001$) at 6 months. Larger reductions in QoL scores were found in patients who have had larger RAVI/BIS increases.

Associations between changes in quality of life from baseline to 6 months and changes in perometry/bioimpedance spectroscopy from 1 month to 6 months

There was a negative association between changes in TOI and changes in RAVI ($r = –0.10$; $p = 0.024$) and BIS ($r = –0.14$; $p = 0.001$), and between changes in FACT-B and changes in BIS ($r = –0.11$; $p = 0.011$). Thus, again greater reductions in QoL scores were found in those patients who had bigger increases in RAVI/BIS values.

Quality-of-life overview

These results demonstrate significant and persisting impact of lymphoedema on QoL following diagnosis and treatment for breast cancer. This is true for overall disease-specific HRQoL indicators reflected in the FACT-B TOI and total FACT-B+4 scores and is pronounced in specific symptoms associated with lymphoedema reflected in the ARM subscale scores. While overall QoL (TOI) does return to (or exceed) pre-surgery levels by

12 months for those without lymphoedema and 24 months for those with lymphoedema, the arm-specific measures indicate deficits for all ANC patients continuing until at least 24 months.

Most QoL studies in breast cancer have been cross-sectional and have not used instruments designed specifically for lymphoedema. Most reported reduced QoL with onset of lymphoedema.[23,26,27] The ALMANAC QoL study, reported by Fleissig *et al.*, found similar TOI and FACT-B+4 reductions in the ANC arm and considered them due to surgery.[26] Whereas 66% of their patients were node negative and the majority did not receive chemotherapy, in contrast in the BEA study, all were node positive and 66% received chemotherapy. There was a significant relationship between chemotherapy and QoL during the 6 months of treatment, but patients developing lymphoedema in the first 6 months had a greater reduction in QoL than those who did not develop lymphoedema. Whereas after the period during which chemotherapy was administered, QoL returned to pre-surgical levels by 12 months in patients who did not develop lymphoedema, the QoL deficit was prolonged after the development of lymphoedema until at least 24 months. Current smoking, BMI and age also affected QoL scores. Self-reported symptoms were associated with lymphoedema development but were not discriminatory predictors on their own.[24] Subjective symptoms such as heaviness and particularly 'considerable' swelling correlated with QoL deficits, RAVI and BIS increase and are probably clear and simple markers of adverse effects for many patients.[23,26,27] Such simple to complete self-reported measures could play an important part in clinical practice if widely adapted and combined with objective measures, and as seen below they may also contribute significantly to predicting the development of lymphoedema.

Composite scoring model to define lymphoedema

Reference standard

In a review document published in 2011, the Agency for Health Research and Quality[24] concluded that, although rarely identified as gold standards, the frequency of use of different measures of limb volume or circumference would suggest that these measures are the de facto gold standards for diagnosing secondary lymphoedema.[24]

The proposed reference standard for this diagnostic test accuracy study is perometry (also known as infrared optoelectric volumetry). Infrared light is used to measure the volume of a limb, at repeated sites along the limb. Numerous studies have reported perometry as a reliable and valid method for determining limb volume with excellent intra- and inter-rater reliability.[6,9,36] Perometry has superseded the use of water displacement as a reference standard. Its adoption into standard clinical practice has been hindered by the relatively high cost of the perometer.

It is acknowledged that in studies of diagnostic test accuracy the reference standard is rarely 100% accurate in practice. An imperfect reference standard can lead to difficulties in the interpretation of test results. If we could assume, based on evidence, that perometry alone provides adequate classification of the target condition, then we had intended to proceed with the diagnostic test accuracy with a reference standard of perometry alone. However, the reference standard did not predict sleeve application and was considered to provide inadequate classification. Given the degree of imperfection of the reference standard, we then considered whether additional information provided adequate classification in the form of a composite reference standard [using, for example, the addition of clinical presentation (application of a sleeve for treatment), presence or absence of arm lymphoedema at 6, 18, 24 months, etc.].[37–39]

There is currently no gold standard for the definition of lymphoedema. Proposed definitions include a 200 ml limb volume difference; a 10% difference in arm volume; and a 2.0 cm circumferential difference at any point on the arm. Widely accepted as diagnostic criteria, the measurements are not equivalent, but constitute explicit, observable clinical definitions.[23,24] The 2011 report for by the Agency for Health Research and Quality concluded that based on the evidence in the extracted studies, there does not appear to be a gold standard to formally grade or measure the severity of lymphoedema.[24]

We aimed to identify discriminatory factors for a composite index.[39–41]

Diagnostic criteria for lymphoedema

The RAVI of > 10% is the most conservative criterion for diagnosis of lymphoedema, with two-thirds of patients complaining of heaviness or swelling by 24 months. *Figure 12* and *Table 35* are the same data shown diagrammatically and in tabular form. We considered whether a combination of RAVI and self-reported symptoms might better define lymphoedema, and used both sleeve application and RAVI of > 10% as the basis for redefining lymphoedema diagnosis. Overall, 86% of patients with a RAVI of > 9 and 10% had a sleeve fitted ($\kappa = 0.60$).

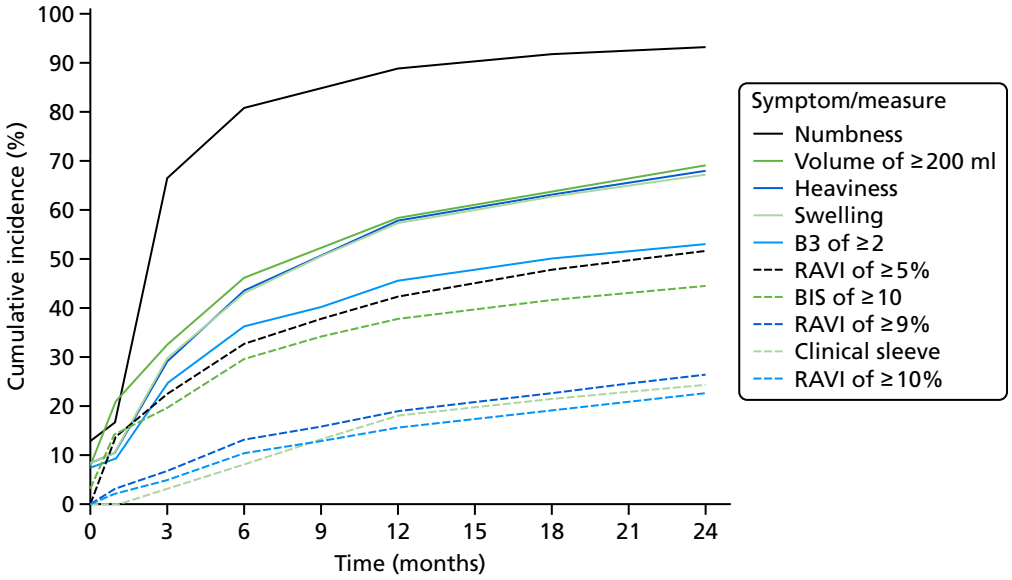


FIGURE 12 Temporal changes in self-reported symptoms from ARM subscale and objective measures of arm swelling (≥ 10%, ≥ 9%, ≥ 5%, ≥ 200 ml) compared with sleeve application (clinical lymphoedema).

TABLE 35 Changes in self-reported symptoms (heaviness, numbness and swelling) from ARM subscale and objective measures of arm swelling over time

	Month (%)							
Symptom/measure	0	1	3	6	9	12	18	24
Numbness	12.9	17.1	66.8	80.8	84.7	88.8	91.7	93.3
≥ 200 ml	8.3	21.2	32.6	46.1	52.5	58.4	64.3	69.1
Heaviness	8.7	10.6	29.4	43.4	50.6	57.8	63.1	68.0
Swelling	8.4	10.7	29.7	43.1	50.7	57.4	62.9	67.3
B3 ≥ 2 (from FACT-B+4)	7.6	9.4	24.8	36.3	40.2	45.6	50.2	53.3
≥ 5% vol	0.0	14.0	22.5	32.6	37.8	42.5	47.8	51.9
BIS of ≥ 10	3.8	15.0	19.7	29.8	34.2	37.8	41.8	44.6
≥ 9% vol	0.0	3.3	6.9	13.2	16.0	19.1	22.8	26.5
Clinical sleeve	0.0	0.2	3.2	8.4	13.2	18.2	21.6	24.5
≥ 10% vol	0.0	2.2	5.0	10.5	13.0	15.7	19.4	22.8

Cohort of patients who had clinical lymphoedema or appropriately applied sleeve only (excluding the PLACE trial patients)

A total of 223 patients had clinical lymphoedema (appropriately applied sleeve) by 24 months (79 by 6 months, 168 by 12 months); this excludes those who had a sleeve applied during the PLACE trial.

There were significant increases in the proportion of women with swelling, numbness and heaviness from the time point previous to sleeve fitting to the time point the sleeve was fitted. There was a decrease in the ARM subscale from the FACT-B+4 QoL questionnaire from before the sleeve was fitted to the time the sleeve was fitted (*Table 36*).

The rates of symptoms reported in our BEA study are higher than those reported in the ALMANAC trial.[26] The combination of arm swelling symptoms and nurses' perception of poorer QoL of these women (as reflected by their QoL scores) may have led to the application of compression sleeves in these patients even though the RAVI was < 10% (*Table 37*). The perometer measurements for these patients are retained at each site and the arm-volume changes over the different segments were reviewed with the case note/source documents to understand the basis for sleeve application in the women for whom RAVI was < 10% in order to be able to produce a composite measure of lymphoedema.

TABLE 36 FACT-B Total, FACT-B TOI and FACT-B ARM subscale scores at time of sleeve-indicated lymphoedema or appropriately applied sleeve and measurement prior to fitting

	Mean (SD), range		
	Time point previous to clinical lymphoedema or appropriately applied sleeve	At time of clinical lymphoedema or appropriately applied sleeve	Paired *t*-test
Perometer ($n = 206$)	6.7 (6.5), –7.0 to 36.4	8.7 (8.5), –16.1 to 37.8	$p = 0.001$[a]
BIS ($n = 199$)	11.3 (14.0), –16.9 to 84.6	15.0 (17.9), –25.1 to 77.2	$p = 0.002$[a]
FACT-B ($n = 169$)	101.7 (23.0), 42.0 to 138.6	103.1 (23.0), 28.0 to 141.0	$p = 0.23$
TOI ($n = 172$)	60.4 (16.4), 20.5 to 88.7	61.6 (16.4), 9.0 to 89.0	$p = 0.15$
ARM ($n = 174$)	14.1 (4.5), 0 to 20	13.3 (4.4), 0 to 20	$p = 0.011$[a]

a These results are statistically significant.

TABLE 37 Self-reported symptoms (heaviness, numbness, and swelling) and objective measures of arm swelling at time of sleeve-indicated lymphoedema or appropriately applied sleeve and measurement prior to fitting

Symptom/measure	Time point previous to clinical lymphoedema or appropriately applied sleeve (%)	At time of clinical lymphoedema or appropriately applied sleeve (%)	McNemar's test
≥ 200 ml ($n = 206$)	57	73	$p < 0.001$[a]
RAVI of ≥ 5% ($n = 206$)	55	71	$p < 0.001$[a]
RAVI of ≥ 10% ($n = 206$)	28	38	$p = 0.014$[a]
BIS of ≥ 10% ($n = 199$)	43	51	$p = 0.081$
Swelling ($n = 163$)	56	88	$p < 0.001$[a]
Numbness ($n = 160$)	70	84	$p = 0.001$[a]
Heaviness ($n = 156$)	47	65	$p < 0.001$[a]

a These results are statistically significant.

We identified localised segmental swelling in the hand or upper, lower arm segments on source perometry measurements such that if the forearm segment had a 10% volume increase (even if the whole arm RAVI was < 10%), a compression sleeve was applied based on these clinical findings, and symptoms.[23]

Even after central review of source perometry data, there remained patients for whom decisions regarding sleeve fitting were determined by lymphoedema nurses based on patient reports of worsening symptoms, rather than on objective measurement of arm swelling. This finding is in line with results of the qualitative study reported in WS3 below.

The RAVI and BIS values increased from before lymphoedema to the time of diagnosis but the mean values for RAVI post sleeve application were < 9%, which implies that, in women with subthreshold arm-volume increases whose symptoms worsened, sleeves were used to treat symptoms in the absence of objective volume criteria defining lymphoedema.

Diagnostic accuracy of composite end-points analysis

Using a definition of clinical lymphoedema (applied sleeve), we assessed sensitivity, specificity, PPV and NPV across a range of diagnostic criteria either alone or in combination for increased diagnostic accuracy.

At all time points examined (6, 9, 12, 18 and 24 months), a combination of RAVI of < 5% and B3 score of 3 or 4 (little or no swelling) provided a NPV of 99% and almost guaranteed that the patient would not develop lymphoedema by 24 months.

Positive predictive value was highest overall using RAVI of > 9% and B3 score of < 2 at 9 months (74%). At other time points the optimal criteria varied between RAVI of > 9 or 10% and B3 score of < 2 (PPV 50% at 12 and 18 months), although between 18 and 24 months BIS of > 10% added to PPV, increasing it from 31% with RAVI of > 9%/B3 of < 2 to 41% with all three scores present.

Diagnostic accuracy for these composite end points (number diagnosed added to number excluded with lymphoedema) was 94% (781/834), 94% (668/709) and 95% (526/553) at 6, 12 and 24 months, respectively for a combination of RAVI of > 9%and B3 score of < 2 (self-reported 'considerable' swelling) (see *Appendix 17* for data analysis).

Using a combination of objective measures (RAVI of > 9%) and self-reported arm swelling (B3 subjective measure) increased diagnostic accuracy for sleeve application. Given that some patients had sleeves applied for arm/shoulder stiffness with little objective swelling, this is a surprisingly good fit for the data.

Changes in quality of life in relation to sleeve application

Overall, for patients who required treatment with a sleeve, an increase in their QoL occurred. Comparing FACT-B+4 at two time points – the time the sleeve was applied and approximately 6 months after – there was a mean increase of 2.96 ($p = 0.021$: *t*-test). Using repeated measures [analyses of variance (ANOVAs) shown in *Table 43*], total FACT-B ($p = 0.015$), ARM ($p < 0.001$) and TOI ($p < 0.001$) all showed that QoL decreased from baseline to the point before their sleeve was applied. FACT-B and TOI showed an improvement at the time at which the sleeve was applied. At 24 months, FACT-B and TOI returned to above pre-surgery levels, but the ARM subscale remained low.

Arm symptoms were not improved as much as overall QoL after sleeve application.

Repeated measures ANOVAs showing the changes in different QoL measurements at various points in relation to the time of sleeve application (*Table 38*).

TABLE 38 Quality-of-life subscale scores at time of pre surgery, before the sleeve was applied, at the time the sleeve was applied and at 24 months

		Estimated marginal mean (95% CI)				
Subscale	*n*	Pre surgery	Before the sleeve was applied	At the time the sleeve was applied	At 24 months	*p*-value
Total FACT-B+4	92	107.0 (102.8 to111.1)	103.5 (99.2 to 107.9)	106.3 (102.2 to 110.4)	109.3 (104.6 to 114.0)	0.015
ARM	74	17.5 (16.5 to18.4)	13.6 (12.6 to 14.6)	12.8 (11.8 to 13.8)	13.1 (12.1 to 14.1)	< 0.001
TOI	94	66.4 (63.5 to 69.3)	61.8 (58.7 to 64.9)	63.5 (60.5 to 66.5)	67.0 (63.7 to 70.3)	< 0.001

The patients split into two groups with regard to QoL changes following sleeve application. One group were patients who met the conventional definition of lymphoedema (having a RAVI of ≥ 9% at sleeve application) and another group contained patients who had a RAVI of < 9% at sleeve application. Patients with complete data sets including (both their RAVI and total FACT-B+4) before and after sleeve application were analysed. Sixty patients with sleeves applied were not included because of missing data.

The patients who had a larger increase in arm volume (median RAVI was 11.7%) had a mean FACT-B score of 106.3 when their sleeve was applied. From sleeve application to the first time point afterwards, approximately 6 months after, their QoL showed a large increase to 112.6 ($p = 0.004$), suggesting that reducing arm swelling by treating lymphoedema is an important factor in improving their QoL.

The group with smaller amounts of arm swelling (i.e. with a median RAVI of 3.6%) had a lower mean FACT-B score of 103.5 when their sleeve was applied, which increased by a small amount, from 105.5 ($p = 0.20$). However, the arm volume in this group continued to increase, suggesting that the sleeve was not an effective treatment.

Effect of self-reported arm swelling on quality-of-life benefit following sleeve application

Within FACT-B+4 there are five questions, which relate directly to lymphoedema, including B3, which relates to arms being either swollen or tender.

Repeated measures ANOVAs of total FACT-B, TOI and ARM at the time of sleeve application and afterwards, split by the patients' B3 score at the time of application B3 scores, are reverse coded, so a score of 0 is 'very much' arm swelling and 4 is 'not at all'.

The initial overall QoL scores for patients with little or no swelling are, as expected, significantly higher than those for patients with considerable self-reported arm swelling. Likewise, patients with little arm swelling have higher QoL scores (FACT-B+4, TOI) at 36 months post surgery.

Patients were grouped based on their self-reported B3 scores at the time of sleeve application. The group with large amounts of arm swelling had B3 scores of 0–2 (81% of those with RAVI of ≥ 9% had a B3 score of 0–2 at sleeve application) and the group with little to no arm swelling had B3 scores of 3–4 (54% of those with RAVI of < 9% had a B3 score of 3–4) ($p \leq 0.005$).

ARM subscale scores increased (improved QoL) when sleeve was applied for 'considerable' arm swelling (B3 score 0–2) but were unaltered when little or no swelling was present (*Figure 13*).

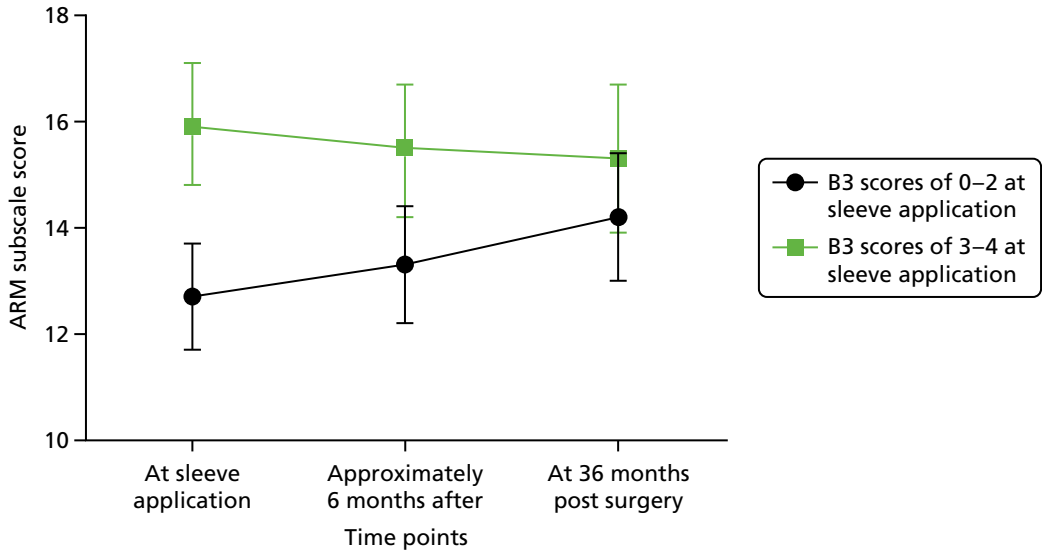


FIGURE 13 Change in the ARM subscale score at the time of sleeve application and afterwards, by B3 score.

In the ARM subscale ($p = 0.044$) analysis, there was an interaction between having a B3 score of 0–2 (more arm swelling) or 3–4 (limited arm swelling) and the time points post sleeve application. The interaction term was significant because of the increase in ARM scores after sleeve application in patients with B3 scores 0–2, whereas there was minimal change in the ARM score post sleeve application in patients with a B3 score of 3–4.

In the patients with considerable swelling, mean FACT-B and TOI increased (QoL improved) following sleeve application. Among the group with B3 scores showing limited or no arm swelling, there were small QoL increases. Patients with small amounts of arm swelling had higher QoL scores throughout until 36 months after their surgery (*Table 39*).

These data indicate that when patients self-report 'considerable' arm swelling, application of a sleeve in 'correctly diagnosed' lymphoedema successfully improves symptoms and QoL scores. However, if a sleeve is applied without self-reported arm swelling and/or with no RAVI of > 9% (definition of lymphoedema), no benefit in arm symptoms or QoL occurs.

The prescription of compression sleeves in 'correctly diagnosed' lymphoedema successfully improves symptoms and QoL. Understanding and developing objective evidence for which patient groups benefit from treatment with a compression sleeve has important implications for compression sleeve prescription and use in the NHS.

Scoring model to predict lymphoedema

The definition of lymphoedema used as the outcome for the logistic regression included both RAVI of > 10% or a sleeve applied after 1 or 6 months up to 24 months.

Of the 1097 patients in the data set, 326 were classified as having either an appropriately applied sleeve or clinical lymphoedema.

Fifty-one patients were identified as being given their sleeve as part of the PLACE trial and nine had a sleeve applied to the contralateral arm (because of deep-vein thrombosis). These 60 patients were excluded from consideration in the following analysis.

There were 266 patients with an appropriately applied sleeve or clinical lymphoedema.

TABLE 39 Self-reported arm swelling and QoL benefit following sleeve application

Subscale	*n*	Estimated marginal mean (95% CI)			*p*-value
		At sleeve application	Approximately 6 months after sleeve was applied	At 36 months post surgery	
FACT-B+4 total					
B3 score of 0–2 (considerable swelling)	36	102.9 (97.1 to 108.7)	105.5 (98.6 to 112.58)	108.9 (102.6 to 115.1)	Time: 0.043 B3 score: 0.045
B3 score of 3–4 (little to no swelling)	26	113.1 (106.3 to 119.9)	115.2 (107.1 to 123.3)	116.3 (109.0 to 123.7)	Interaction: 0.72
TOI					
B3 score of 0–2 (considerable swelling)	37	60.0 (56.2 to 63.8)	64.4 (59.9 to 68.9)	65.8 (61.6 to 69.9)	Time: 0.011 B3 score: 0.002
B3 score of 3–4 (little to no swelling)	27	71.3 (66.9 to 75.7)	72.6 (67.3 to 77.9)	73.4 (68.5 to 78.3	Interaction: 0.33
ARM					
B3 score of 0–2 (considerable swelling)	38	12.7 (11.7 to 13. 7)	13.3 (12.2 to 14.4)	14.2 (13.0 to 15.4)	Time: 0.54 B3 score: 0.002
B3 score of 3–4 (little to no swelling)	30	15.9 (14.8 to 17.1)	15.5 (14.2 to 16.7)	15.3 (13.9 to 16.7)	Interaction: 0.044

Model at 6 months predicting lymphoedema (relative arm-volume increase of > 10%)

The variables considered for the scoring model were RAVI at 6 months (categorical), BIS at 6 months (categorical), TOI at 6 months, FACT-B total at 6 months, ARM subscale at 6 months, lymphoedema checklist questions at 6 months (swelling, numbness, heaviness), B3 at 6 months (categorical: 0–2, considerable swelling vs. 3–4, little to no swelling), age, BMI at 6 months, ER status, number of positive nodes, adjuvant chemotherapy and adjuvant radiotherapy.

A total of 711 patients were included in this analysis.

A scoring model was produced based on the regression coefficients from the final model (*Table 40*). The individual scores are the regression coefficients for binary or categorical variables rounded to the nearest 0.5 and the regression coefficients for continuous variables to two decimal places owing to their per-unit increase interpretation. The total 'diagnostic' score is given by summing the individual scores. A patient with a higher total score is more likely to have a 10% RAVI volume increase.

This scoring model gives an area under the receiver operating characteristic (AUROC) of 0.80 (95% CI 0.74 to 0.85). For a cut-off score of 1.58 – where a patient with a score of $\geq$ 1.58 would be predicted to have a 10% RAVI by perometer – the scoring model would give a sensitivity of 80.0% (68/85), a specificity of 67.7% (424/626), a PPV of 25.2% (68/270) and a NPV of 96.1% (424/441). The cut-off score was chosen to maximise the sum of the sensitivity and specificity, giving equal weight to both.

Prediction scoring predicting lymphoedema (relative arm-volume increase of > 10%) at 6 months (excluding bioimpedance spectroscopy)

Bioimpedance spectroscopy is not widely available in the NHS and therefore we concentrated on models that could be used in any lymphoedema clinic in the UK. A total of 740 patients were included in this analysis (*Table 41*).

TABLE 40 Prediction model for lymphoedema at 6 months (with BIS)

Variable	OR (95% CI)	*p*-value	Score
RAVI at 6 months			
< 3%	1 (–)	< 0.001	0
≥ 3 to < 5%	1.92 (0.96 to 3.86)		0.5
≥ 5 to < 10%	7.36 (4.10 to 13.24)		2
BIS at 6 months			
< 3	1 (–)	0.030	0
≥ 3 to < 5	1.39 (0.57 to 3.38)		0.5
≥ 5 to < 10	1.87 (0.96 to 3.64)		0.5
≥ 10	2.58 (1.35 to 4.93)		1
BMI at 6 months (kg/m^2)			
≤ 25	1 (–)	0.015	0
> 25 to ≤ 30	1.53 (0.80 to 2.91)		0.5
> 30	2.53 (1.34 to 4.77)		1
Number of positive nodes (per-node increase)	1.08 (1.04 to 1.12)	< 0.001	0.08 × number of positive nodes

TABLE 41 Prediction scoring model for lymphoedema at 6 months (includes BIS)

Variable	OR (95% CI)	*p*-value	Score
RAVI at 6 months			
< 3%	1 (–)	< 0.001	0
≥ 3 to < 5%	2.47 (1.27 to 4.79)		1
≥ 5% to < 10%	9.10 (5.24 to 15.79)		2
BMI at 6 months			
≤ 25	1 (–)	0.025	0
> 25 to ≤ 30	1.53 (0.82 to 2.86)		0.5
> 30	2.34 (1.26 to 4.35)		1
Number of positive nodes (per-node increase)	1.08 (1.04 to 1.11)	< 0.001	0.07 × number of positive nodes

A scoring model was produced based on the regression coefficients from the final model as described previously. The total 'diagnostic' score is given by summing the individual scores. A patient with a higher score is more likely to have a 10% RAVI perometer volume increase.

This scoring model gives an AUROC of 0.77 (95% CI 0.71 to 0.82). For a cut-off score of 1.41, where a patient with a score of ≥ 1.41 is predicted to have a 10% perometer volume increase, the scoring model would give a sensitivity of 72.1% (62/86), a specificity of 72.2% (472/654), a PPV of 25.4% (62/244) and a NPV of 95.2% (472/496). The cut-off score was chosen to maximise the sum of the sensitivity and specificity, giving equal weight to both. This model has similar AUROC and would be easy to apply in NHS practice and its components would have few extra costs (i.e. FACT-B+4/lymphoedema checklist) in any NHS setting.

Model of prediction of lymphoedema (relative arm-volume increase of > 10%) from 1 month

Variables considered for the scoring model were RAVI at 1 month (categorical), BIS at 1 month (categorical), TOI at pre-surgery, FACT-B total at pre-surgery, ARM subscale at pre-surgery, lymphoedema checklist questions at pre-surgery (swelling, numbness, heaviness), B3 at pre-surgery (categorical: 0–2, considerable swelling vs. 3–4, little to no swelling), age, BMI at pre-surgery, ER status, number of positive nodes, adjuvant chemotherapy and radiotherapy.

A total of 522 patients were included in this analysis.

A scoring model was produced based on the regression coefficients from the final model as described previously (*Table 42*). The total 'diagnostic' score is given by summing the individual scores. A patient with a higher score is more likely to have a 10% RAVI perometer volume increase.

This scoring model gives an AUROC of 0.71 (95% CI 0.64 to 0.77). For a cut-off score of 0.82, where a patient with a score of ≥ 0.82 is predicted to have a 10% perometer volume increase, the scoring model would give a sensitivity of 62.9% (56/89), specificity of 70.7% (306/433), PPV of 30.6% (56/183) and NPV of 90.3% (306/339). The cut-off score was chosen to maximise the sum of the sensitivity and specificity, giving equal weight to both.

Prediction model: using sleeve as 'lymphoedema' definition after 6 months

The variables considered for the scoring model were perometer at 6 months (categorical), BIS at 6 months (categorical), TOI at 6 months, FACT-B total at 6 months, ARM subscale at 6 months, lymphoedema checklist questions at 6 months (swelling, numbness, heaviness), B3 at 6 months (categorical: 0–2, considerable swelling vs. 3–4, little to no swelling), age, BMI at 6 months, ER status, number of positive nodes, adjuvant chemotherapy and adjuvant radiotherapy (*Table 43*).

Patients with a RAVI of ≥ 10% before, or at, 6 months were excluded from the analysis.

A total of 548 patients were included in this analysis.

A scoring model was produced based on the regression coefficients from the final model as described previously. The total 'diagnostic' score is given by summing the individual scores. A patient with a higher total score is more likely to have a lymphoedema requiring a sleeve.

TABLE 42 Model of prediction of lymphoedema (RAVI of > 10%) from 1 month

Variable	OR (95% CI)	*p*-value	Score
RAVI at 1 month			
< 3%	1 (–)	< 0.001	0
≥ 3 to < 5%	2.11 (1.06 to 4.19)		0.5
≥ 5% to < 10%	4.02 (2.18 to 7.39)		1.5
≥ 10%	8.89 (2.86 to 27.64)		2
Lymphoedema checklist swelling at pre-surgery			
No	1 (–)	0.010	0
Yes	2.22 (1.21 to 4.09)		1
Number of positive nodes (per-node increase)	1.08 (1.04 to 1.12)	< 0.001	0.07 × number of positive nodes

TABLE 43 Prediction model: using sleeve as 'lymphoedema' definition after 6 months

Variable	OR (95% CI)	*p*-value	Score
RAVI at 6 months			
< 3%	1 (–)	< 0.001	0
≥ 3 to < 5%	2.69 (1.36 to 5.31)		1
≥ 5% to < 10%	5.89 (3.07 to 11.30)		2
Lymphoedema checklist swelling at 6 months			
No	1 (–)	0.003	0
Yes	2.31 (1.33 to 4.02)		1
ER status			
Negative	1 (–)	0.045	0
Positive	0.40 (0.16 to 0.98)		1
Adjuvant radiotherapy			
No	1 (–)	0.005	0
Yes	4.74 (1.61 to 13.92)		1.5

This scoring model gives an AUROC of 0.76 (95% CI 0.70 to 0.82). For a cut-off score of 4, where a patient with a score of ≥ 4 is predicted to have clinical lymphoedema or a sleeve applied, the scoring model would give a sensitivity of 48.6% (34/70), a specificity of 90.0% (430/478), a PPV of 41.5% (34/82) and a NPV of 92.3% (430/466). The cut-off score was chosen to maximise the sum of the sensitivity and specificity, giving equal weight to both.

Again, this model uses simple measures easily available in the NHS and provides good prediction of lymphoedema.

Model predicting lymphoedema (sleeve) development from 1 month post surgery

The variables considered for the scoring model were: perometer at 1 month (categorical), BIS at 1 month (categorical), TOI at pre-surgery, FACT-B total at pre-surgery, ARM subscale at pre-surgery, lymphoedema checklist questions at pre-surgery (swelling, numbness, heaviness), age, BMI at pre-surgery, ER status, number of positive nodes, adjuvant chemotherapy and adjuvant radiotherapy (*Table 44*).

TABLE 44 Lymphoedema prediction model sleeve application from 1 month post surgery

Variable	OR (95% CI)	*p*-value	Score
RAVI at 1 month			
< 3%	1 (–)	< 0.001	0
≥ 3 to < 5%	1.45 (0.88 to 2.41)		0.5
≥ 5% to < 10%	3.61 (2.33 to 5.59)		1
≥ 10%	5.70 (2.32 to 14.02)		1.5
Adjuvant radiotherapy (planned)			
No	1 (–)	0.018	0
Yes	1.93 (1.12 to 3.31)		0.5
Number of positive nodes (per-node increase)	1.05 (1.02 to 1.08)	0.001	0.05 × number of positive nodes

A total of 837 patients were included in this analysis.

A scoring model was produced based on the regression coefficients from the final model. The individual scores are the regression coefficients for binary or categorical variables rounded to the nearest 0.5 and the regression coefficients for continuous variables to two decimal places due to their per-unit increase interpretation. The total 'diagnostic' score is given by summing the individual scores. A patient with a higher total score is more likely to have a clinical lymphoedema or require a sleeve.

This scoring model gives an area under the receiver operator characteristic (AUROC) of 0.67 (95% CI 0.62 to 0.71).

Note that the ARM subscale is significant if included in the above model. However, only 558 patients would be included in the model and the area under the curve (AUC) is not improved by a large amount by its inclusion (AUC 0.67, 95% CI 0.62 to 0.73).

These models provide reasonable prediction of patients at risk of lymphoedema and those for 1 month after surgery have only three variables and are simple to apply in a clinical setting.

Models from 6 months have higher AUROC and are a better fit because patients have completed their treatments at that point.

Summary

The ability to individualise lymphoedema risk is an important step to tailor follow-up and advice to patients. The models predicting at 1 month have lower diagnostic accuracy as patients have not completed adjuvant chemotherapy or radiotherapy. Nonetheless, the main value may be in identifying women at sufficiently low risk of lymphoedema at 6 months post surgery so they can be reassured and released from further arm monitoring.

Health economics: estimation of health-related utility measures – data available for analysis

A data extract was created in July 2017 containing EuroQol-5 Dimensions, three-level version (EQ-5D-3L) data collected from 1100 BEA patients for up to 24 months.

Successful completion of all of the five dimensional questions (i.e. mobility, self-care, usual activities, pain/discomfort and anxiety/depression) required for calculation of the utility measure was disappointing, declining steadily from 82% to 62% during the 2-year period from baseline (*Table 45*). Most of the incomplete records contained no data for any of the five questions and were therefore unusable for analysis. Completed documents were more often missing for obese patients (BMI of > 30 kg/m^2: $p < 0.0001$) and current smokers ($p < 0.004$).

TABLE 45 Completion rates for the five QoL dimensions in the EQ-5D-3L patient forms

Time from baseline (preoperative)	Complete record	At least one of the five dimension ratings missing	No data provided
Baseline	904 (82.1%)	17 (1.5%)	180 (16.3%)
6 months	811 (73.7%)	13 (1.2%)	277 (25.2%)
12 months	776 (70.5%)	15 (1.4%)	310 (28.2%)
18 months	711 (64.6%)	7 (0.6%)	383 (34.8%)
24 months	681 (61.9%)	12 (1.1%)	408 (37.1%)
Overall	3883 (70.5%)	64 (1.2%)	1558 (28.3%)

The response to the EuroQol visual analogue scale (EQ VAS) question (requiring only a simple cross on a scale between 0 and 100) was similarly disappointing (*Table 46*).

Of particular interest is the number of patients supplying a continuous sequence of complete EQ-5D-3L data from baseline onwards, as this allows temporal changes in estimated health-related utility to be tracked over time, and correlated with clinical events and the development of lymphoedma. As many as possible of the EQ-5D ratings spoiled by missing dimension entries were remedied by tracing similarities in the pattern of response in earlier and later completed forms, and interpolating where the patient showed consistency of response over time. EuroQol forms with missing responses, which could not be remedied by imputation, were excluded from subsequent analyses.

Table 47 shows that a full complete EQ-5D-3L record after imputation of missing values was available for only 37% of the patient sample, and for 17% of patients no data were provided at all.

Data imputation

Most of the 40 EQ-5D ratings spoiled by missing dimension entries were remedied by tracing similarities in the pattern of response in earlier and later completed forms and interpolating where the patient showed consistency of response over time. Only four were found to be wholly or partly irredeemably flawed and excluded from subsequent analyses.

Data analysis

The objective of the analysis carried out on this data set was to identify and quantify the mean change in the EQ-5D-3L utility estimate attributable to the presence of confirmed clinical lymphoedema. Ideally, this would be carried out by using complete sequences of utility estimates over 24 months, and comparing those recorded for patients developing lymphoedema with those for patient who remained lymphoedema-free

TABLE 46 Completion rates for the EQ VAS in the EQ-5D-3L patient forms

	EQ VAS rating, *n* (%)	
Time from baseline (preoperative)	Provided	Missing
Baseline	895 (81.3)	206 (18.7)
6 months	793 (72.0)	308 (28.0)
12 months	773 (70.2)	328 (29.9)
18 months	698 (63.4)	403 (36.6)
24 months	678 (61.6)	423 (38.4)
Overall	3837 (69.7)	1668 (30.3)

TABLE 47 Distribution of patients providing useable EQ-5D-3L data over continuous periods of time

Continuous sequence of EQ-5D-3L data from baseline (preoperative)	Patients with complete useable data, *n* (%)
No EQ-5D data provided at any time point	190 (17.3)
Baseline data only	212 (19.3)
Baseline	
6 months complete	123 (11.2)
12 months complete	105 (9.5)
18 months complete	62 (5.6)
24 months complete	409 (37.2)

throughout. Unfortunately, the poor completion rates described above result in only 140 patients developing lymphoedema during the trial and also having a full valid sequence of EQ-5D-3L responses from baseline to 24 months after imputation: limiting the reliability of estimates of disutility obtained. However, alternative methods of analysis have been explored in order to obtain an approximation to the magnitude of the effect of lymphoedema on patient experience.

A search for potentially confounding patient characteristics likely to affect the estimation of patient utility values identified a prospective cohort study of lymphoedema patients at the University of Pennsylvania Lymphoedema Clinic, which described 124 patients with upper extremity cancer lymphoedema and reported EQ-5D-3L results.[42] The severity of the lymphoedema had little effect on the mean estimated utility value, but the authors reported strong associations between estimated utility and BMI, higher BMI being associated with lower utility scores.

An initial exploratory regression analysis of the BEA data confirmed a similarly strong association between patient BMI and EQ-5D-3L utility estimates in our study.

Figure 14 demonstrates that obese and very obese patients are more likely to develop lymphoedema (chi-squared test, $p = 0.023$). As patient recruitment to the BEA study was not randomised, it was necessary in any comparison between subcohorts to apply a corrective adjustment to counter baseline differences in BMI.

Another patient characteristic known to influence patient-reported utility is the age of patients. An analysis was undertaken of the relationship between the age at which patients entered the BEA study, and their propensity to develop lymphoedema in the 2 years following surgery.

Figure 15 shows that differences in the distribution of patients by age is less pronounced between those who did and did not develop lymphoedema during the study, which is confirmed by a non-significant chi-squared test result ($p = 0.39$). Correlation analysis between age and utility estimates confirmed that no significant bias is associated with variations by age. Therefore, it was concluded that no adjustment for age was necessary to standardise between the two cohorts.

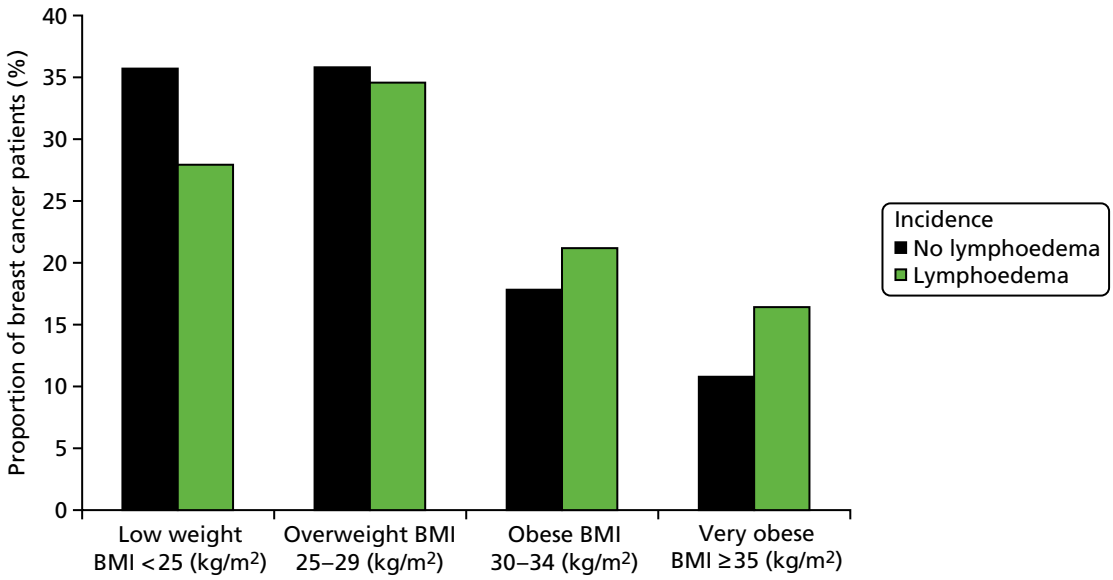


FIGURE 14 Association between the incidence of lymphoedema (assessed by perometry) and patient BMI.

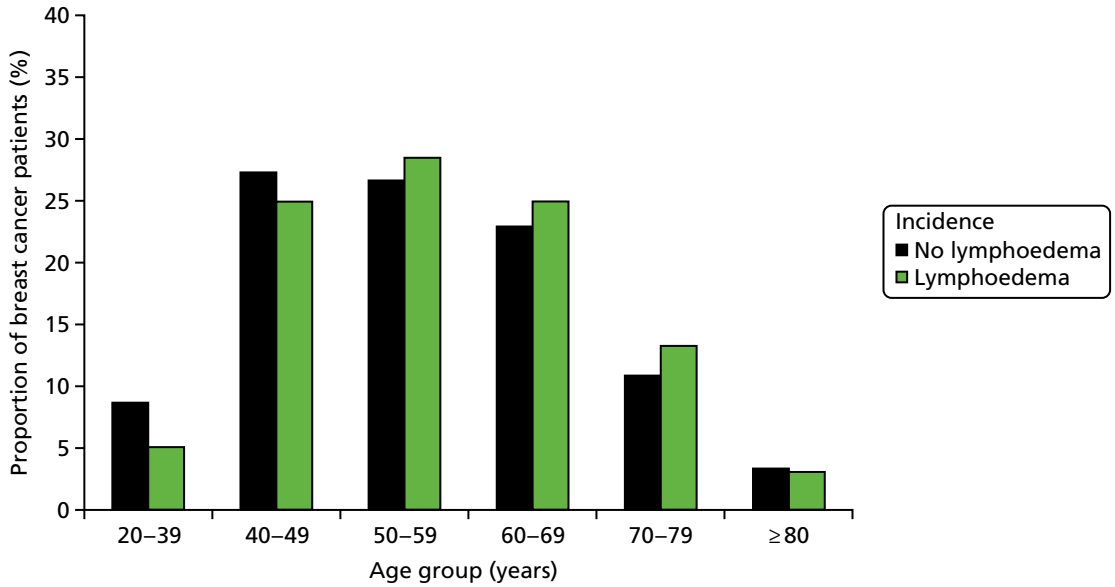


FIGURE 15 Association between the incidence of lymphoedema (assessed by perometry) and patient age.

For a total of 403 patients, full EQ-5D responses were submitted or derived by imputation across the 2-year period from baseline (i.e. five data sets at 6-monthly intervals) and a valid BMI could be calculated. Of these, 137 (34%) were identified with primary lymphoedema during the 2-year period, and 266 (66%) were lymphoedema-free throughout. The mean EQ-5D utility estimates are shown in *Figure 16*, unadjusted for BMI. Patients with lymphoedema are shown in three subgroups according to whether the diagnosis was made by perometry, by clinical assessment with fitting of a compression sleeve, or both in combination.

Figure 17 shows the same comparison following adjustment of utility estimates in the three lymphoedema subgroups to match the mean BMI in the lymphoedema-free group at individual patient level to a common BMI average (26.6 kg/m^2). It is important to note that none of the graphical differences in either chart is statistically significant, because of the small number of cases in each of the lymphoedema subgroups.

Nonetheless, it is possible to identify suggestive patterns in these data:

- There is a consistent loss of estimated patient utility at the 6-month assessment relative to the preoperative (baseline) values, consistent with the impact of recovering from surgery.
- By the 12-month assessment, there is a general recovery of at least some of the initial utility loss.
- Patients who do develop lymphoedema in the 24-month period post surgery appear to recover to similar utility levels to those recorded at baseline.
- The subgroups which featured the need for a compression sleeve to be fitted when lymphoedema was diagnosed (whether or not perometry was used to confirm the diagnosis) generally failed to recover to preoperative utility levels during follow-up.
- The very small subgroup who were found to have developed lymphoedema by perometry but were not deemed clinically to require a sleeve fitting appear to recover to preoperative utility levels (or possibly better), although this may be related to small number uncertainty.

Of particular interest in assessing the cost-effectiveness interventions aimed at reducing the incidence and/or impact of lymphoedema is the estimation of patient-reported disutility attributable to experiencing lymphoedema over an extended period of time. This involves comparing utility estimates for patients with and patients without lymphoedema from the BEA study population.

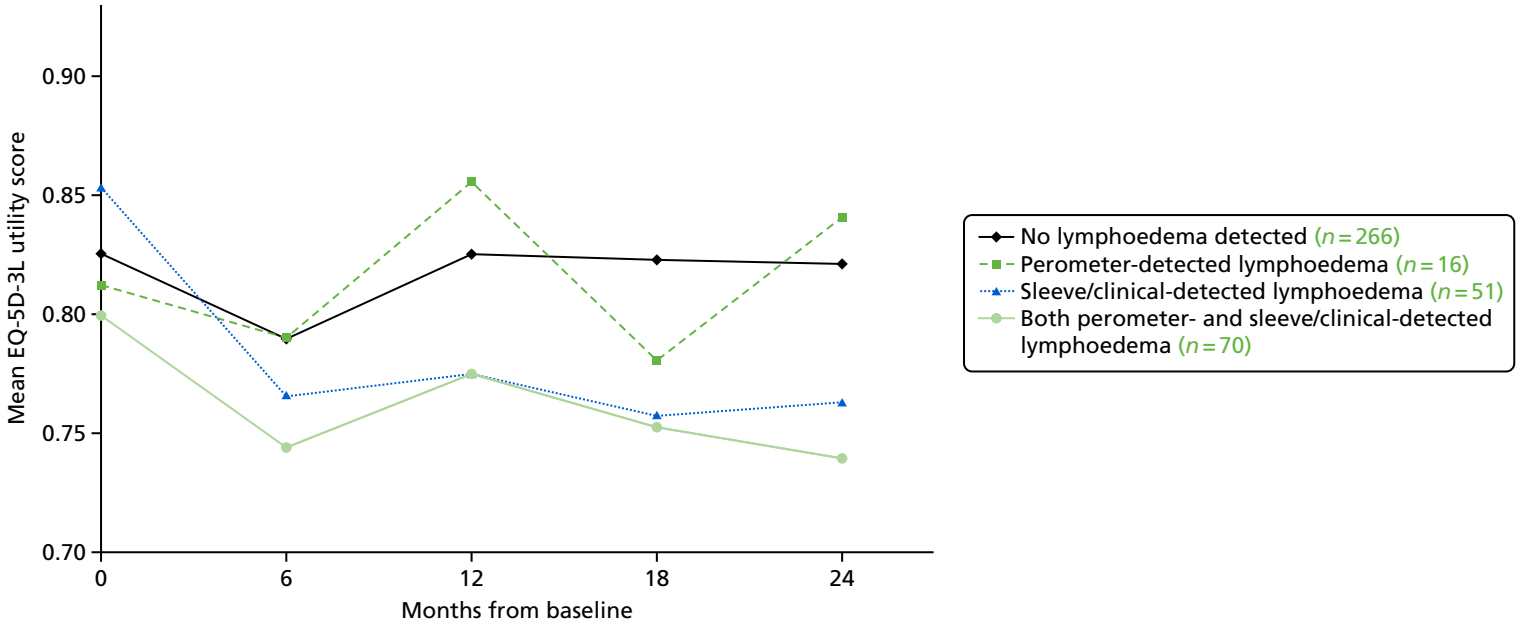


FIGURE 16 Mean utility estimates at 6-monthly intervals, by method of assessment leading to diagnosis of lymphoedema, unadjusted for BMI differences.

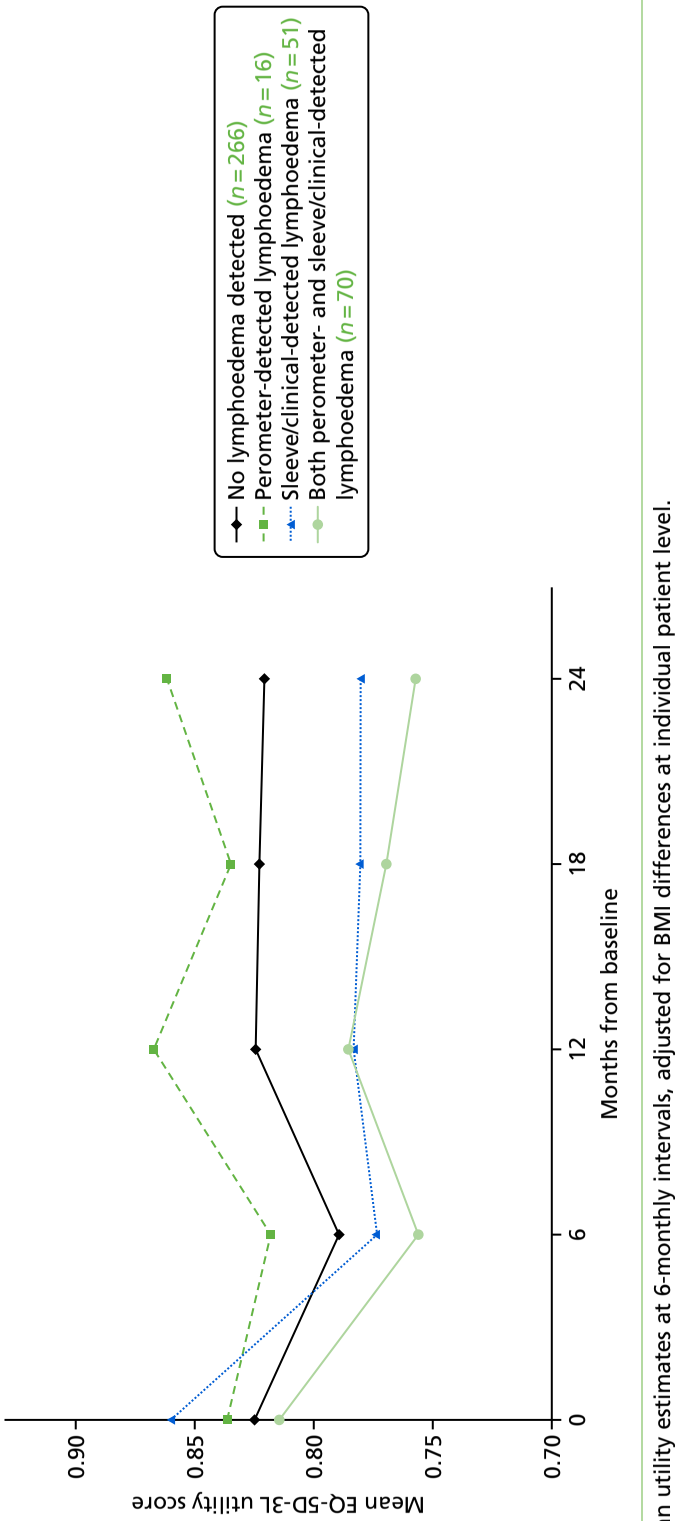


FIGURE 17 Mean utility estimates at 6-monthly intervals, adjusted for BMI differences at individual patient level.

This has been performed by identifying any patient with a diagnosis of lymphoedema by any method within the first few months after baseline, for whom a full sequence of five utility estimates are available. This limits consideration to patients with at least 6 months experience of the condition. A total of 41 patients fulfilled this criterion, and their utility values at 12, 18 and 24 months were compared with data at the same time points from patients never experiencing lymphoedema.

The results are shown in *Table 48* and indicate consistent non-zero disutility estimates at all three time points.

Averaged over this 12-month period of observation, patients with extended experience of lymphoedema recorded a mean utility score of 0.721, compared with 0.823 for patients with no recorded lymphoedema, giving an estimated mean disutility attributable to lymphoedema of –0.102 (95% CI –0.127 to –0.076). If BMI-adjusted utility values are used instead, the size of this effect would reduce to –0.073 (95% CI –0.122 to –0.023).

A search of the literature for comparable research-based estimates of the disutility associated with lymphoedema following breast surgery proved fruitless. Only one published cost-effectiveness study included an assumed value for disutility of –0.03, justified only as the 'smallest clinically important difference in utility'.[2,43] The estimates obtained using the available BEA data, although not definitive, are statistically significant and evidence-based, and should, therefore, be considered superior.

Further analysis of the BEA data will be possible and will also be performed for PLACE trial participants.

Data analysis: lymphoedema incidence

Another important statistic required to carry out a cost-effectiveness analysis is the incidence rate of the key outcome variable, in this case the proportion of patients confirmed to suffer from clinical lymphoedema, and the timing of such events.

Data on the first recorded time of confirmed lymphoedema have become available for a period exceeding 5 years from baseline. This has made a Kaplan–Meier analysis of the timing of the first recorded lymphoedema event (i.e. the duration of the initial lymphoedema-free period from baseline) possible, as displayed in *Figure 18*.

This exhibits a typical profile as seen in studies where assessments are carried out at predetermined intervals, but that the precise timing is spread over several weeks around the target time. This gives rise to periods of time between planned assessments when only a very few 'opportunistic' primary lymphoedema events are recorded, followed by multiple events occurring either side of each planned assessment time. To mitigate the bias introduced by the study design, it is necessary to identify an 'envelope' of accurate data points corresponding to the time at the end of 'step-down' phase of the prespecified assessment times. At these points all planned and opportunistic events up to that time are included. These 'envelope' data are represented in the chart by the large circles in *Figure 18*.

TABLE 48 Mean EQ-5D-3L utility for patients experiencing lymphoedema for 6 months or more, compared with patients without lymphoedema for 2 years (unadjusted for BMI)

Patient group	Mean utility			Average estimated utility
	12 months	18 months	24 months	
Patients without lymphoedema ($n = 268$)	0.825	0.823	0.821	0.823
Patients with lymphoedema for ≥ 6 months ($n = 41$)	0.755	0.680	0.729	0.721
Estimated lymphoedema disutility	–0.070	–0.143	–0.092	–0.102

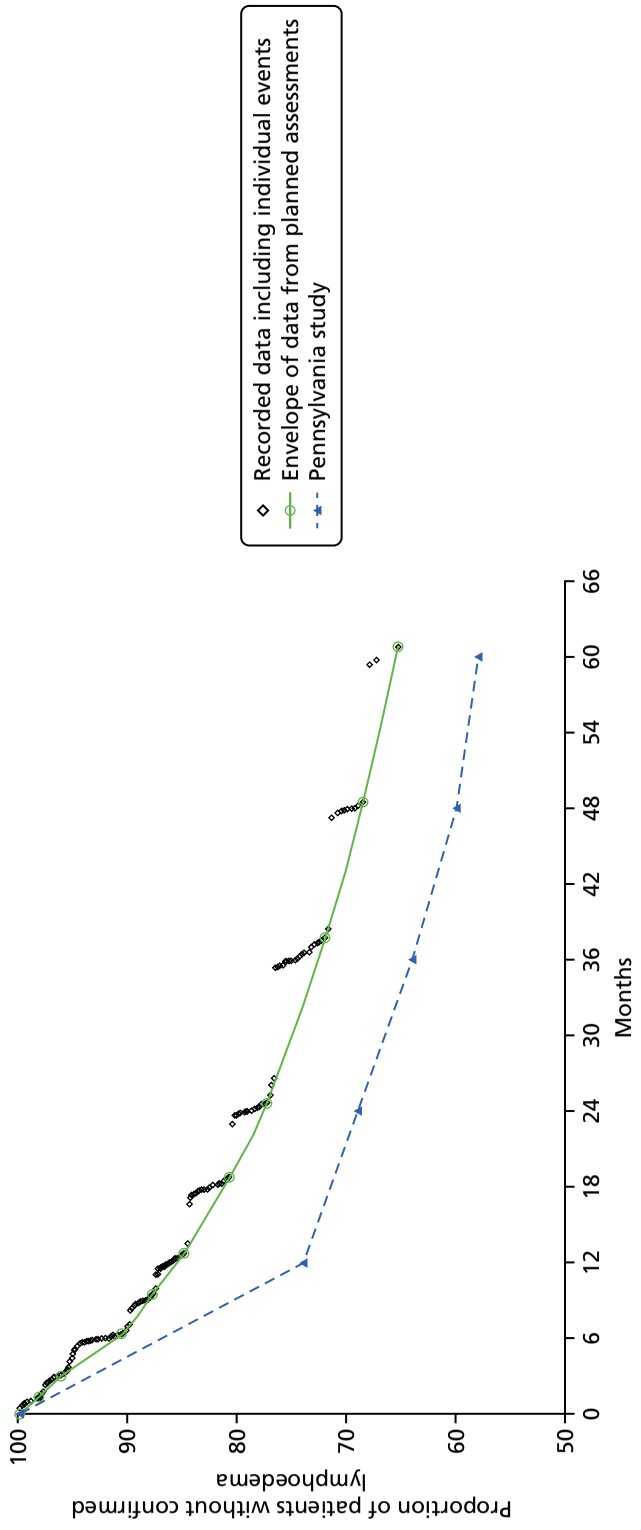


FIGURE 18 Kaplan–Meier survival analysis of primary lymphoedema incidence in BEA patients, compared with the Pennsylvania study.[44]

Using sections of the envelope data, it was possible to estimate the annual incidence rate of primary lymphoedema at different periods of time. In the first 6 months from baseline, the incidence rate was 16.4% per annum, contrasting with 9.5% between 9 and 24 months, and 4.9% between 36 and 60 months. Clearly, the risk of lymphoedema-free patients suffering a primary event decreased steadily throughout the 5-year observation period.

Figure 18 also shows comparable 5-year lymphoedema incidence from a study of 631 breast cancer patients in Philadelphia and Delaware Counties, Pennsylvania.[45] Although these patients suffered higher incidence of lymphoedema throughout, the difference between the two trends is wholly attributable to a much higher incidence in the first 12 months (74% lymphoedema-free in the Pennsylvania study, compared with 85% lymphoedema-free in the current study), but the risk of developing lymphoedema thereafter was very similar to that found in the current study.

To estimate the incidence of primary lymphoedema at future times beyond the available data set, a range of standard statistical parametric models was fitted to the envelope data. However, this proved disappointing, with poor correspondence to the trial data when some functions were tested and unrealistic estimates of the mean long-term time spent lymphoedema-free for other functions.

An alternative approach was attempted, which sought to incorporate the existence of an unknown proportion of the study population who were at zero risk of lymphoedema. This method did not generally improve the correspondence of fitted models to the study data and led to a wide variation in the estimates of the zero-risk subset of the population (between 33% and 58%). Therefore, it has been concluded that without additional evidence from other sources it is not possible to obtain reliable estimates of the number of patients suffering lymphoedema beyond the available data and the timing of incident events.

Workstream 3: graduated compression garments to prevent onset of chronic lymphoedema

Sentinel lymph node biopsy staging reduces the need for ANC, but 30% of breast cancer patients are node positive and require ANC to remove diseased nodes.[21–24]

A clinical end point of > 10% increase in ipsilateral arm volume (vs. contralateral arm) is an accepted criterion for a diagnosis of lymphoedema.[21–24] Up to 40% of women develop lymphoedema by 18 months post ANC based on this criterion. Intervention before arm swelling becomes chronic may prevent the complications of lymphoedema after ANC.

The management of patients after ANC does not routinely include prospective measurement of the ipsilateral arm. In the absence of prospective arm measurements, early changes preceding lymphoedema are difficult to detect. Consequently, patients present with marked arm swelling before being considered for treatment.[20–22] Initially when a patient presents with concerns about their arm (unless measurement confirms arm swelling equivalent to a 10% arm-volume increase, compared with the contralateral arm), advice is provided regarding arm massage, active movement (series of exercises) and limb elevation, and on avoiding injury and infection of the affected limb(s).[23,28,29]

Graduated compression garments, which decrease the amount of interstitial fluid (especially during exercise), are designed to cover the entire area of oedema and are graduated with the greatest compression at the distal end and the least compression at the proximal end. They have been shown to produce reductions in arm swelling by 4–24% in small single-centre randomised trials.[23,28,29] Once arm swelling reduces, to maintain compression on the subcutaneous tissues refitting of a tailored compression sleeve is required. Early intervention before gross arm swelling occurs will reduce the need to refit sleeves because these become looser and no longer fit the arm with the correct pressure gradient.

In the ALMANAC trial, ANC patients had a 40% incidence of lymphoedema by 18 months after surgery overall; however, for those women who developed 4–9% increases in arm volume, there was a 60% lymphoedema incidence at 18 months post surgery.[20,46]

Conventional advice is that early arm swelling does not portend chronic swelling and should be treated conservatively.[23,28,29] Arm swelling of 4–9% is usually not clinically apparent unless arm measurements have been made preoperatively, and only 15% of women in the 'ANC arm' of the ALMANAC trial complained of significant swelling at 6 and 18 months.[20,27] Early intervention (in a group of patients with 4–9% arm swelling) with a compression garment may prevent the development of chronic lymphoedema.[23] Research has shown that as arm swelling is treated and subsides, QoL significantly improves.[23,26,28] Currently, there is no evidence to support the value of compression garments in preventing lymphoedema after ANC.

There is a need to test early intervention in women after ANC, with a 50–70% risk of lymphoedema at up to 9 months after surgery. We used graduated compression sleeves to test whether prevention in women at high risk of lymphoedema is potentially better than current management and our current inability to cure the condition.

Design

The design was a randomised open controlled trial testing (1) standard care (written advice, arm elevation, exercises and massage) versus (2) the intervention, application of whole arm graduated compression garments (pressure 15–24 mmHg) to the affected arm, together with standard management for 1 year (see *Appendix 18*).

As women randomised to compression garments were given four compression garments for their wardrobe, we expected that in this group the extra training and reinforcement of the importance of preventing arm swelling will mean that they will reutilise their sleeves if necessary even if they are no longer being prescribed new sleeves at the end of the 1-year intervention to prevent substantial progression of arm swelling between clinic visits.

Primary outcome

- Time to development of lymphoedema (RAVI of > 10% assessed by perometer scanning) from randomisation.

Secondary outcome

- Time to development of moderate lymphoedema (RAVI of > 20%) from randomisation.
- Quality of life in each group (TOI and FACT-B+4 ARM subscale).
- Costs and utility measurement of individual strategies (EQ-5D-3L utility measures).
- Incidence of infection/lymphangitis.
- Incidence of lymphoedema at 5 years post surgery (NB 90% of lymphoedema develops by 3 years post ANC).

Setting

Breast outpatient clinics in teaching and district hospitals affiliated with specialist lymphoedema clinics.

Target population

Women with node-positive, early breast cancer scheduled to undergo ANC who consent to preoperative arm measurements with a perometer and subsequently develop a 4–9% increase in arm volume at 1, 3 or 6 months post surgery.

Inclusion criteria

- Women aged 18–90 years.
- Early breast cancer (no metastasis), scheduled to undergo ANC.
- Consented to prior (pre-surgical) arm measurements who develop arm-volume increases of 4–9% within 6 months after surgery.
- Written informed consent.

Exclusion criteria

- Any patients with no pre-surgical baseline measurements.
- Known distant metastasis.
- Inoperable breast cancer (T4 category or distant metastasis).
- Node negative not undergoing axillary clearance.
- Previous axillary radiotherapy or clearance.
- Past history of breast/chest wall radiotherapy prior to commencement of monitoring.
- Bilateral axillary clearance.

Results

One hundred and forty-three patients have been randomised (74 to no sleeve standard care and 69 to compression sleeves plus standard care) between 1 October 2010 and November 2015. On account of slow recruitment, the number of centres was increased from 7 to 21 by November 2013 and a qualitative study commenced to understand the reasons behind the poor recruitment compared with that expected.

Qualitative nested study of recruitment

The qualitative study is more fully reported in *Appendix 19*.

In-depth interviews were conducted with 38 purposively sampled patients and 16 purposively sampled recruiting staff, from five purposively selected trial sites and two PLACE trial management staff. Recruiting staff were initially invited to participate in focus groups using vignette techniques to explore issues in the recruitment of patients to the trial and were then interviewed one to one. Interviews were audio-recorded, transcribed verbatim and subject to analysis using framework analysis themes. This included *patient motivators* with patients identifying participating because of altruistic reasons as well as belief that they would receive 'better care' due to closer monitoring from the breast cancer research nurses and access to a specialised team.[47] On the other hand there were also *patient barriers* and a major reason cited was 'inappropriate timing' of the trial for their individual circumstances and not wanting to burden themselves with further commitments. One older patient (aged 87 years) considered herself 'to be too old' to be bothered with taking part. Some patients declined if their preference for their preferred allocated study arm was not met. Patients also reported withdrawing from the study as they found wearing the study sleeve uncomfortable or stigmatising. Most patients commented on the professional and caring attitude of recruitment staff and this was identified as an *organisational facilitator*. However, there were also a number of *organisational barriers* related to *procedures/protocol* not being followed correctly or *misunderstood*, *lack of training/confidence* in explaining the RCT, *auditing and trial management* issues, as well as *staffing issues*.

Procedural issues

It became apparent that recruitment staff did not always follow the PLACE trial protocol or study procedures correctly and eligible patients were not always invited to participate. Recruiting staff held variable interpretations of who was eligible for the trial, and there was evidence of a 'wait and see' culture, whereby they assumed that they could wait to see if patients were still eligible at later check-up appointments. In some sites this appeared to be the norm, but it had the effect that patients 'timed out' at 9 months and thus became de facto ineligible. Most recruiting staff were nurses and they experienced *role conflict* between their professional roles as clinician and patient advocate and recruiter. These recruiters acted as *gatekeepers* and often appeared to have assumed that taking part in the RCT would be burdensome, or not beneficial to, for example, patients undergoing chemotherapy. In addition, some patients presenting with reports of distressing symptoms (swelling, heaviness, etc.) or arm swelling towards the upper limit of eligibility for the PLACE trial would be referred directly to the lymphoedema service instead of being entered into the trial.

There were also problems with *lack of understanding of the rationale for the trial* (misunderstanding of equipoise), *explaining the RCT incorrectly* to patients, and presenting the randomisation process in ways that may have been off-putting to patients. One recruiter reported that she could not see the benefit of taking part in the PLACE trial, which may have reduced recruitment. A number of patients were interviewed specifically because, according to screening logs, they had been approached and had declined to participate. Some reported no recollection of being approached, and it is not clear if they had been explicitly approached to participate and had forgotten, or if the approach had been rather informal and 'throw-away' and not recognised as a request to participate by the patient, or if they had indeed not

actually been asked to take part, but that the recruiter had logged this incorrectly, either intentionally or inadvertently.

Although *screening logs* were completed across recruiting sites, these *could not be verified*. Staff were not accountable to the research team as they were employed by NIHR Clinical Research Network and had competing trials to recruit to. High *turnover of recruitment staff* was cited as having a detrimental impact on recruitment. As staff were managed by the network rather than the trial, the trial *management* team were not made aware of staff changes, and were thus not in a position to ensure training to new staff outside the regular site visits and updates.

In overview, staff struggled with role conflict, problems in understanding and explaining the trial and did not always prioritise this trial. Indeed, nurses reportedly felt that they should use clinical judgement to assess patients' eligibility to the trial rather than simply base it on arm swelling criteria. They tended to adopt a 'wait and see' approach, which resulted in eligible patients timing-out, and/or were overprotective and referred directly to specialist services rather than entering the patient into the trial. As the IDMC closed recruitment before we could feed back results from the qualitative work, we do not know if any of the changes to recruitment procedures that would have followed from our qualitative work could have improved recruitment. These findings concur with other reports in the literature (e.g. Quintet Recruitment Intervention) and suggest that qualitative work of this sort should become an integral part of trials from the outset, to provide insight into recruitment and facilitate improved recruitment rates.

Qualitative study conclusion

Assumptions made by recruitment staff that taking part in the RCT may be burdensome for patients had a significant impact on recruitment behaviour, which in turn led to poor recruitment rates. During recruitment encounters, staff acted as gatekeepers by only suggesting taking part in the PLACE trial with those patients who were deemed suitable for the trial, rather than with all patients who met the inclusion eligibility criteria. Making a clinical judgement not to recruit patients in this way is perceived as paternalistic. For example, PLACE trial recruiters were making decisions on their patients' behalf with the view that, as clinicians, they knew what was best for patients. Certain recruiters generally described their focus was on protecting and caring for patients' needs rather than sharing knowledge and information about the RCT.

Current position of the PLACE trial

The IDMC in March 2016 recommended that the trial close to further recruitment as it was unlikely to reach 270 patients in any reasonable time frame and no further centres had been identified. Moreover, BEA had reached 1100 patients and it appeared that around 25% developed an arm-volume increase of 4–9% and were eligible for the PLACE trial. The trial remained open to BEA recruits who had been offered PLACE trial entry if they developed arm-volume increases of 4–9%. Recruitment ceased in late November 2016 and follow-up of participants continued until November 2018.

In general, groups were well matched in BMI, age, dominant arm, side of operation, smoking history, type of surgery and radiotherapy treatments. The median follow-up was 22 months (*Table 49*).

The overall lymphoedema rate is 40% with a 33% Kaplan–Meier lymphoedema rate by 24 months currently. The final results from this trial will not be available until all patients have a minimum 2-year follow-up (November 2018).

After March 2016, when the CTU statistician retired, closer consideration of the PLACE trial data by Julie Morris (trial statistician, appointed May 2016) indicated the overall lymphoedema rate to be 40% and, with longer follow-up, it remains possible that an outcome from the trial will be found, particularly

TABLE 49 Characteristics of participants in the two arms of the PLACE trial

Characteristic	Trial arm	
	No sleeve ($N = 74$)	Sleeve ($N = 69$)
BMI (kg/m^2) (preoperatively)	27.8 (95% CI 17.2 to 45.3)	28.7 (95% CI 16.9 to 60.9)
BMI (kg/m^2) (at PLACE trial entry)	26.9 (95% CI 18.0 to 47.0)	28.4 (95% CI 20.7 to 58.4)
Difference between arms in % change (at PLACE trial entry)	5.9 (95% CI 4.1 to 8.9)	6.4 (95% CI 4.0 to 8.5)
Follow-up (months from randomisation)	23 (95% CI 0 to 59)	21 (95% CI 0 to 61)
Age (years) at randomisation	55.5 (95% CI 33.5 to 89.9)	55.8 (95% CI 32.0 to 86.9)
Tumour site (*n*)		
UO	34	37
UI	9	7
LO	9	2
LI	6	2
Central areolar	5	10
Other	11	11
Side (*n*)		
Right	38	28
Left	36	41
Dominant hand (*n*)		
Right	69	64
Left	5	5
Smoking history (*n*)		
Never	49	35
Ex	20	25
Current	5	9
Type of surgery (*n*)		
ANC	13	15
WLE + ANC	23	17
Mastectomy + ANC	36	34
Other	2	3
Post-surgery radiotherapy: yes (*n*)	59	58
Dose (cagy)	(*n* = 59) 4005 (95% CI 3960 to 5605)	(*n* = 58) 4005 (95% CI 1068 to 6010)
Number of fractions	15 (95% CI 15 to 25)	15 (95% CI 4 to 30)
Site of radiotherapy (*n*)		
Breast	28	25
Breast + SCF	18	21
Breast + axilla	3	2
Breast + SCF + axilla	3	2
Other	7	8

LI, lower inner; LO, lower outer; UI, upper inner; UO, upper outer.

combining the data in a meta-analysis with those from a similar trial being conducted in Boston, MA, USA (principal investigator, A Taghian). The PLACE trial remains the largest multicentre external compression garment trial to prevent lymphoedema, as the previous four trials of compression garments recruited only 85 patients in total and were all single centre. The results from this trial will be crucial to inform the future direction of lymphoedema management and the value of external compression garments to prevent lymphoedema. It appears that baseline and regular arm measurements combined with information leaflets, advice and exercises such as simple lymphatic drainage may reduce rates of lymphoedema development and are valuable in a high-risk population. Although rates of axillary clearance surgery in breast cancer are reducing for low node-positive breast patients (fewer than three nodes involved), clearance surgery remains the treatment for node-positive breast and melanoma patients with involved nodes. Key findings from the PLACE trial are thus likely to be generalisable and applicable in the future.

Patient and public involvement

Patient and public involvement (PPI) occurred during the life of this project from its inception right through to its end. Patient representatives sat on the management committee, giving a patient perspective on how the project was undertaken. Their input of was invaluable in ensuring that the patient point of view was never lost in how the WS were conducted.

Workstream 1

The consumer panels of three cancer research networks were consulted in the development of the research protocol for WS1. The response was positive, supportive and constructive in all cases. For example, one panel wrote, 'This is a most excellent study that is badly needed'. Recommendations from the panels were integrated into the design of the study.

Similarly, the suggestions of patient representatives on the cancer research networks were followed for training research staff. Patient representatives consented to carry out training interviews with research staff giving them feedback on their interview technique. This proved particularly useful to provide insight into and experience of interacting with supportive 'patients' themselves. Recommendations about the design from both WS1 and WS2/3 panels were integrated into the design and helped with the Trial Management Group.

Workstream 2

A group of 10 people with lymphoedema from University Hospital of South Manchester were involved in helping us to develop better treatments for lymphoedema, primarily with regard to different designs of compression sleeves. We involved them in the design of this trial and the quality-of-life measures. They commented that they would have preferred to have had earlier intervention with external compression garments than to have undergone manual lymphatic drainage and compression therapy once they had developed lymphoedema.

Two patients who developed lymphoedema within 2 years of ANC surgery agreed to sit on the patient management group and were both initially involved with this project. Unfortunately, both died during the first 3 years of the project, and two further patient representatives were subsequently involved. A qualitative study consulted patients to understand the poor recruitment in the PLACE trial.

We involved the PPI forum within University Hospital of South Manchester to ensure that patients and the public were formally involved in plans to carry out research, monitor progress, implement findings and monitor the impact on services. We have liaised with charities that have a role in patient support, including BCC and Breakthrough Breast Cancer, to involve the public and patients in this research.

Discussion

Over 2000 NHS patients took part in these studies in nearly 50 NHS breast units and we appreciate the contributions of all the patients, doctors and nursing staff, without whom these studies would not have been possible. Although WS1 commenced on time, delays in opening WS2 and WS3 because of delays in site approval of the BIS device, and the subsequent need to extend the number of centres from 7 to 21 to improve recruitment for the PLACE trial, delayed data collection and follow-up. However, there is now a network of sites for lymphoedema studies developed, which could be built on for further studies.

The studies of preference reveal that in about half of consultations both the patient and the surgeon chose the same person as making the surgical decision, but the actual agreement between surgeons and patients is low. In univariate analyses, increasing age predicts not undergoing surgery from the age of 75 years, compared with those aged 70–74 years. Adjusting for health measures and choice, only women aged > 85 years have reduced odds of surgery. Patient role in treatment decisions makes 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. The qualitative study of women who did not receive primary surgery revealed three approaches: 'patient declined', 'patient considered' and 'surgeon decided'.

These reductions in surgical rates with increasing age are in broad agreement with previous studies, although previous work reports unadjusted odds.[3,7] Once patient health and choice were adjusted for, both the location and the size of effect changed, and only the oldest women aged > 85 years retained significantly reduced odds of surgery. Moreover, neither patient health nor choice accounts for the lack of surgery for the oldest women aged > 85 years, and this reduction in effect size for 75- to 84-year-olds appears to be largely driven by adjustment for measures of health rather than by patient choice. On the basis of responses to the CPS, there is no evidence that there was any real active choice to not have surgery among those who did not have surgery. These findings suggest that the lack of surgery for the oldest patients is not because they actively opt out of having this treatment. A likely explanation for this is that the option of not having surgery is offered/discussed only if there are concerns about the patient undergoing surgery.

There is some evidence that surgical rates are improving for older women with breast cancer in the UK and our results tend to confirm this. It seems likely that improved surgical rates reflect changes in practice following publication of guidelines and reorganisation of cancer services over the past decade. Nonetheless, although the situation appears to be improving, the lack of surgery for women aged > 85 years persists and, as defined by national policy,[1,17] 'inappropriate undertreatment' is still occurring for this oldest age group. Older age does not predict complications and 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.[9,15] The number of observed cancer deaths exceeded those expected for participants whose tumours were of higher grade or stage and steroid receptor negative, but 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. Given these findings, it is hard to see on what basis surgery should be withheld from older women who are fit for surgery.

Following surgery, many older women do not receive chemotherapy and radiotherapy, even though they may have benefited from these therapies.[15,16,48] Can this lack of chemotherapy and radiotherapy be explained by patient choice or health? We demonstrated that women aged ≥ 75 years have lower chemotherapy and radiotherapy rates than women aged 65–69 years. After adjusting for tumour characteristics, health measures and choice, women aged ≥ 75 years still have reduced odds of receiving chemotherapy, whereas age has no impact on the radiotherapy rates of older women. Thus, lower chemotherapy rates in older women cannot be explained by health or patient choice.

Overall, although over the past decade there have been improvements in the access older women have to breast cancer services, there are still substantial gains to be made by ensuring that treatment decisions are

based on 'fitness' and ability to benefit rather than on age per se. The endemic ageism of the past may have gone, but there remains room for improvement.

Assessing lymphoedema objectively depends on an agreed international definition.[22–24] We found arm volume measurement (RAVI) to be the optimal choice for assessment of arm swelling, and that BIS, although reasonably specific (85–92%), had a lower sensitivity and only modest correlation with arm volume. It would have led to significantly more patients receiving compression sleeves that were applied inappropriately. If compared with sleeve application as treatment (excluding patients randomised to sleeve in the PLACE trial), BIS missed some patients with lymphoedema and misdiagnosed (false-positive) others. BIS increases of < 10% at 6 months did not aid prediction of lymphoedema, whereas patients with a RAVI of 5–9% had a 35% risk of lymphoedema at 18 months. Moreover, RAVI of > 9% and/or 'considerable' arm swelling predicted the clinical benefit of sleeve application.

Some studies have suggested that self-reported symptoms predict lymphoedema,[4] whereas others have shown that factors such as being overweight, axillary radiation and chemotherapy are more predictive of lymphoedema after breast cancer surgery.[25] The results indicate that self-report on ARM subscale (particularly B3, 'considerable swelling') and the lymphoedema checklist are good predictors of lymphoedema that indicate that patient subjective concerns (probably coupled with anxiety) drive sleeve application, to at least as great an extent as objective measures such as RAVI.

There is, however, some debate over whether gain in weight is a reliable predictor of lymphoedema after surgery for breast cancer, with some conflicting evidence as to whether BMI is significantly related to lymphoedema,[26] or not.[27] BMI at surgery was an independent predictor of both QoL and risk of lymphoedema. In our data, substantial change in BMI after surgery was rare, but encouraging interventions to reduce BMI will reduce lymphoedema occurrence and, potentially, improve QoL.

We found that 25% of patients reported symptoms of swelling and/or numbness, and/or heaviness in the limb on their at risk side even before their surgery.[23] These data support the need for a rigorous preoperative baseline assessment and subsequent measurements to determine arm swelling changes. Screening for breast cancer-related lymphoedema would benefit patients by enabling early intervention.[29] Stout Gergich *et al.*[28] found that in a group of 43 patients with a 3% arm-volume increase, the group wearing compression garments showed a greater decrease in arm-volume than an age-matched control group with a mean follow-up time for the intervention of 4.8 months.[29] The findings support a threshold for intervention of > 4–9% RAVI to prevent progression to lymphoedema, provided that the intervention is demonstrably effective.

The measurement and diagnosis of lymphoedema are inconsistent,[22–24] highlighting a need for preoperative baseline measurements against which to monitor early changes in arm volume. The importance of consistent, objective and robust measurement techniques remains and the reliance on symptoms alone to diagnose lymphoedema is insufficient. Perometer has been shown to be the easiest and most objective tool to measure arm swelling given that definitions of lymphoedema are based on arm-volume increases (whether 200 ml, or a RAVI of > 5 or > 10%). Nonetheless, treatment decisions to apply compression sleeves are more subjective and based on patient symptoms such as heaviness and swelling of the arm. Indeed, some staging classifications describe a prodromal or latent phase of lymphoedema characterised by arm heaviness or swelling in the absence of a RAVI of > 10%. We identified a composite definition based on a RAVI of > 5% and B3 of > 2, which identified 99% of patients who would not develop lymphoedema and could be reassured. Composite definition of lymphoedema (utilising a RAVI of > 9% and a B3 score of < 2) produced a diagnostic accuracy of 94–95% for sleeve application.

Patient concerns and anxiety about developing lymphoedema has led to external compression garments described as 'prophylactic' with a lower arm compression (10–15 mmHg) being prescribed in the absence of any evidence for either the intervention or the compression pressure (as opposed to therapy garments 15–24 mmHg). The modelling of sleeve application indicates that in a multicentre study, sites used

symptoms combined with QoL deficits to justify application of garments despite the absence of objective arm swelling evidence indicating a need for better definitions of lymphoedema which are a composite of RAVI and self-reported symptoms. In particular in the absence of RAVI > 9% and/or self-reported 'considerable' arm swelling (B3 scores) little benefit in QoL was seen following sleeve application. Lymphoedema Practitioners need to be clear with their patients who sleeves are not a solution for numbness, painful arm movement or heaviness in the absence of 'considerable' arm-volume increases. Such objectivity would reduce NHS costs.

The PLACE trial will help determine the validity of early intervention with external compression garments and their effects on arm-volume increases which affect subjective symptoms and QoL.

The prevalence of lymphoedema at 12 and 24 months varies by the assessment criterion with 25% RAVI of > 10% and 66% having symptoms by 24 months yet only approximately 24% have external compression garments fitted by 24 months. Understanding which factors trigger decisions to apply sleeve therapy is crucial to developing an evidence base for lymphoedema treatment.

Although there are several risk factors commonly associated with the development of lymphoedema, there is still a need to determine some of the underlying pathological and genetic factors associated with the development of secondary lymphoedema after axillary surgery. Specht *et al.* found that even in patients who underwent sentinel node biopsy, 10–15% still developed lymphoedema, and a RAVI increase of 5–9% also predicted lymphoedema development in sentinel node biopsy patients.[45] The exact threshold for early intervention to prevent progression to lymphoedema postulated at > 4–9% needs confirmation to allow close monitoring or intervention for patients who present with these arm-volume changes. Although there is some correlation between perometer and BIS measurements during the first 6 months after surgery, longer-term data are required to determine their equivalence in predicting and diagnosing lymphoedema.

In addition, identifying genetic markers of lymphoedema would be important, and within the BEA and PLACE study we have 619 patients who have provided paxgene blood samples to investigate this question at a future date.

The study of QoL is the largest in node-positive patients. Fleissig *et al.*[26] studied QoL in the ALMANAC trial of ANC versus sentinel node biopsy, but the majority (74%) were node negative. In the ANC group they found a TOI reduction of six in the first 6 months corrected to baseline by 12 months and a similar change for FACT-B+4. No attempt to compare effects of Lymphoedema on QoL was made. Likewise, a TOI reduction of five was found by 3 months in the BEA study and in patients who developed Lymphoedema by 6 months the TOI score remained significantly lower even at 18 and 24 months. FACT-B+4 fell by seven points at 6 months but returned to baseline by 12 months. Thus Lymphoedema reduces QoL for sufferers.

A RAVI of > 10% showed greater falls in TOI QoL (fall of –5) than BEA > 10 (fall of –3), suggesting that RAVI of > 10% is a better marker for QoL effects. We will undertake more detailed analysis of FACT-B outcomes from the PLACE trial once full follow-up data on all participants are available. Importantly, understanding the relationship between RAVI increases with symptoms, patient anxiety and QoL reductions may suggest other approaches, such as cognitive–behavioural therapy, to reduce the need for sleeve intervention, as labelling a patient with a lymphoedema diagnosis by applying a sleeve implies the need for interventions for the remainder of a patient's life.

What was and was not successful in the Programme Grant

The programme of work in elderly breast cancer involving multicentre studies successfully recruited and provided important work on the management of elderly breast cancer. Workstream 2 recruited well after ANC and has produced clear results about the value of arm volume measurements and the use of, and indications for, compression arm sleeves. A health economics analysis was less successful because patients who were acutely affected by their cancer diagnosis and morbidity were reluctant to fill in QoL questionnaires. The trial of compression garments in patients developing early arm swelling failed to recruit

sufficient patients because of lack of equipoise among lymphoedema nurses and clinicians. Thus, results of the PLACE trial are still awaited.

Implications for practice

Our findings suggest that older women should be offered surgery, which can be performed under local anaesthetic block if there are concerns over fitness, and surgeons need to make clear the advantages of surgical excision of the cancer on breast cancer survival. The lymphoedema prediction index described will aid communication and individualisation of monitoring of patients after ANC surgery. The use of the Lymphoedema Checklist in women after ANC surgery will aid early recognition of arm problems, particularly if it proves as good a marker of need for intervention as arm measurements. BIS does not reach the expected sensitivity or specificity compared with perometry and the Lymphoedema Checklist to justify its cost and introduction to NHS practice [this was the subject of a recent NICE Medical Technologies Evaluation Programme review www.valueinhealthjournal.com/article/S1098-3015(17)3246-9/fulltext]. Sleeves are not effective in the absence of RAVI of > 9% or 'considerable' self-reported arm swelling.

Future work

Understanding the drivers for, and producing more objective measures to understand, sleeve application/prescription in the NHS is required, which we intend to investigate further once source data are further verified. Developing an evidence base for lymphoedema treatment is essential, and ensuring equality of access to a high-quality service throughout the NHS requires a robust understanding of indications for intervention and the benefits of those interventions applied. Trials investigating the value of diet and exercise to prevent or treat lymphoedema in overweight patients are required. Research to understand how self-reported symptoms of lymphoedema (such as heaviness and arm swelling) can be alleviated without the need for sleeve application, by cognitive–behavioural therapy, diet and or various arm or weight-reducing exercise regimes, is required.

Acknowledgements

We are grateful to all of the patients who took part in these studies, the clinicians who enrolled their patients, research nurses and the lymphoedema nurses who helped with the study. We appreciate the work of the interviewers, data managers at the CTU and the trial co-ordinators who worked on this Programme Grant.

Katrina Lavelle aided Chris Todd in leading and writing the WS1 elderly breast cancer patient studies. Katrina Lavelle was also involved in designing, conducting, analysing and writing up the qualitative study of patient choice. Jane Griffiths designed, conducted, analysed and wrote up the qualitative study of recruitment.

Three individuals provided trial co-ordination, Charlotte Stockton, Sarah Ashton and Donna Watterson, and we are grateful for all of their help in arranging the trial management group and liaison with all of the investigators.

The success of this programme is the result of hard work and dedication from a large number of research staff. In WS1 this included research assistants Noshaba Anwar, Lorie Dickinson, Kirsty Ewing, Nisha Patel, Georgina Pennington-Smith, Emma Rhodes and Bernhard Wagner; and administrator Rosie Perry.

Steering Group members included Nigel Bundred, Linda Ashcroft, Katrina Lavelle, Katie Riches, Chris Todd, Vaughan Keeley, Charlotte Stockton, Elizabeth Stein, Maria Bramley, Ash Kothari, Sari, Catherine Fellows, Arnie Purushotham, Janet Walls, Alison Myatt, Amy Cavanagh, Tracy Hodgkiss, Adrian Bagust, Vernie Ramalingam, Norma Hewitt and Sarah Ashton.

We appreciate the work of the IDMC, which was chaired by Professor Mike Bennett with Professor Robert Mansel and Roger Hearn, the IDMC statistician.

The Manchester Academic Health Science Centre – Clinical Trials Unit was responsible for data management, data collection and in the first 3 years the statistical analyses.

Contributions of authors

Nigel Bundred (Professor of Surgical Oncology and Consultant Breast Surgeon) was responsible for writing the report conclusions and recommendations; was responsible for recruitment organising centres and liaising with the CTU for data collection for the BEA in place at trials; and assessed the QoL results, wrote the text and summarised the findings.

Chris Todd (Professor of Primary Care and Community Health) was responsible for writing the report conclusions and recommendations; led and was responsible for writing the WS1 elderly breast cancer patient studies; assessed the QoL results, wrote the text and summarised the findings; designed, conducted, analysed and wrote up the qualitative study of patient choice; and designed, conducted, analysed and wrote up the qualitative study of recruitment.

Julie Morris (Head of Medical Statistics) was responsible for the modelling of the lymphoedema risk and the final statistical analyses presented; and assessed the QoL results, wrote the text and summarised the findings.

Vaughan Keeley was responsible for recruitment organising centres and liaising with the CTU for data collection for the BEA in place at trials.

Arnie Purushotham (Professor of Breast Cancer and Consultant Surgeon) was involved with patient recruitment and reviewed the manuscript.

Adrian Bagust was responsible for the health economics text and summary.

Philip Foden (Medical Statistician) was responsible for the modelling of the lymphoedema risk and the final statistical analyses presented; and assessed the QoL results, wrote the text and summarised the findings.

Maria Bramley (Consultant Breast Surgeon) was involved with patient recruitment and reviewed the manuscript.

Katie Riches was responsible for recruitment organising centres and liaising with the CTU for data collection for the BEA in place at trials.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Please note exclusive use will be retained until the publication of major outputs. Access to anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

References

1. Department of Health and Social Care. *Cancer Reform Strategy*. London: Department of Health and Social Care; 2007.
2. Nichol MD, Epstein J. Separating gains and losses in health when calculating the minimum important difference for mapped utility measures. *Qual Life Res* 2008;**17**:955–61. https://doi.org/10.1007/s11136-008-9369-7
3. Lavelle K, Moran A, Howell A, Bundred N, Campbell M, Todd C. Older women with operable breast cancer are less likely to have surgery. *Br J Surg* 2007;**94**:1209–15. https://doi.org/10.1002/bjs.5834
4. Møller H, Sandin F, Bray F, Klint A, Linklater KM, Purushotham A, *et al.* Breast cancer survival in England, Norway and Sweden: a population-based comparison. *Int J Cancer* 2010;**127**:2630–8. https://doi.org/10.1002/ijc.25264
5. Lavelle K, Sowerbutts AM, Bundred N, Pilling M, Degner L, Stockton C, Todd C. Is lack of surgery for older breast cancer patients in the UK explained by patient choice or poor health? A prospective cohort study. *Br J Cancer* 2014;**110**:573–83. https://doi.org/10.1038/bjc.2013.734
6. Degner LF, Sloan JA, Venkatesh P. The Control Preferences Scale. *Can J Nurs Res* 1997;**29**:21–43.
7. Beaver K, Luker KA, Owens RG, Leinster SJ, Degner LF, Sloan JA. Treatment decision making in women newly diagnosed with breast cancer. *Cancer Nurs* 1996;**19**:8–19. https://doi.org/10.1097/00002820-199602000-00002
8. Degner LF, Kristjanson LJ, Bowman D, Sloan JA, Carriere KC, O'Neil J, *et al.* Information needs and decisional preferences in women with breast cancer. *JAMA* 1997;**277**:1485–92. https://doi.org/10.1001/jama.1997.03540420081039
9. Janz NK, Wren PA, Copeland LA, Lowery JC, Goldfarb SL, Wilkins EG. Patient–physician concordance: preferences, perceptions, and factors influencing the breast cancer surgical decision. *J Clin Oncol* 2004;**22**:3091–8. https://doi.org/10.1200/JCO.2004.09.069
10. Sowerbutts AM, Griffiths, J, Todd C, Lavelle K. Why are older women not having surgery for breast cancer? *Psychooncology* 2015;**24**:1036–42. https://doi.org/10.1002/pon.3764
11. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;**33**:159–74. https://doi.org/10.2307/2529310
12. Audisio RA, Ramesh H, Gennari R, Corsini G, Maffezzini M, Hoekstra HJ, *et al.* Can preoperative assessment of cancer in the elderly (PACE) predict 30-days postoperative outcomes? *J Clin Oncol* 2006;**24**(Suppl. 18):8537.
13. Ring A, Reed M, Leonard R, Kunkler I, Muss H, Wildiers H, *et al.* The treatment of early breast cancer in women over the age of 70. *Br J Cancer* 2011;**105**:189–93. https://doi.org/10.1038/bjc.2011.234
14. Sturgis P, Thomas R, Purdon S, Bridgwood A, Dodd T. *Comparative Review and Assessment of Key Health State Measures of the General Population*. London: Department of Health and Social Care; 2001. URL: https://eprints.soton.ac.uk/80196/1/2001_Comparative_review_of_key_health_state_measures.pdf (accessed 7 May 2019).
15. Haywood K, Garratt A, Schmidt L, Mackintosh A, Fitzpatrick R. *Health Status and Quality of Life in Older People: A Structured Review of Patient-assessed Health Instruments Reported from the Patient Assessed Health Instruments Group to the Department of Health*. London: Department of Health and Social Care; 2004.

16. Hind D, Wyld L, Reed MW. Surgery, with or without tamoxifen, vs tamoxifen alone for older women with operable breast cancer: Cochrane review. *Br J Cancer* 2007;**96**:1025–9. https://doi.org/10.1038/sj.bjc.6603600

17. Harnett A, Smallwood J, Titshall V, Champion A, Guideline Development Group. Diagnosis and treatment of early breast cancer, including locally advanced disease – summary of NICE guidance. *BMJ* 2009;**338**:b438. https://doi.org/10.1136/bmj.b438

18. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. *Health Econ* 2005;**14**:487–96. https://doi.org/10.1002/hec.944

19. Office for National Statistics (ONS). *Cancer Survival Rates, Cancer Survival in England: Patients Diagnosed 2007–2011 and Followed up to 2012*. Newport: ONS. URL: www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-320365 (accessed 9 January 2016).

20. Brennan MJ. Lymphedema following the surgical treatment of breast cancer: a review of pathophysiology and treatment. *J Pain Symptom Manage* 1992;**7**:110–16. https://doi.org/10.1016/0885-3924(92)90122-X

21. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. *Lancet Oncol* 2013;**14**:500–15. https://doi.org/10.1016/S1470-2045(13)70076-7

22. Shaitelman SF, Cromwell KD, Rasmussen JC, Stout NL, Armer JM, Lasinski BB, Cormier JN. Recent progress in the treatment and prevention of cancer-related lymphedema. *CA Cancer J Clin* 2015;**65**:55–81. https://doi.org/10.3322/caac.21253

23. Armer J, Stewart BR. A comparison of four diagnostic criteria for lymphedema in a post breast cancer population. *Lymphatic Res Biol* 2005;**3**:208–17. https://doi.org/10.1089/lrb.2005.3.208

24. Agency for Health Research and Quality, 14 January 2011. URL: www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id66aTA.pdf (accessed 7 May 2019).

25. Engel J, Kerr J, Schlesinger-Raab A, Sauer H, Hölzel D. Axilla surgery severely affects quality of life: results of a 5-year prospective study in breast cancer patients. *Breast Cancer Res Treat* 2003;**79**:47–57. https://doi.org/10.1023/A:1023330206021

26. Fleissig A, Fallowfield LJ, Langridge CI, Johnson L, Newcombe RG, Dixon JM, *et al.* Post-operative arm morbidity and quality of life. Results of the ALMANAC randomised trial comparing sentinel node biopsy with standard axillary treatment in the management of patients with early breast cancer. *Breast Cancer Res Treat* 2006;**95**:279–93. https://doi.org/10.1007/s10549-005-9025-7

27. Moseley AL, Carati CJ, Piller NB. A systematic review of common conservative therapies for arm lymphoedema secondary to breast cancer treatment. *Ann Oncol* 2007;**18**:639–46. https://doi.org/10.1093/annonc/mdl182

28. Stout Gergich NL, Pfalzer LA, McGarvey C, Springer B, Gerber LH, Soballe P. Preoperative assessment enables the early diagnosis and successful treatment of lymphedema. *Cancer* 2008;**112**:2809–19. https://doi.org/10.1002/cncr.23494

29. Cornish BH, Ward LC, Thomas BJ, Bunce IH. Quantification of lymphoedema using multi-frequency bioimpedance. *Appl Radiat Isot* 1998;**49**:651–2. https://doi.org/10.1016/S0969-8043(97)00266-2

30. Ward LC. Bioelectrical impedance analysis: proven utility in lymphedema risk assessment and therapeutic monitoring. *Lymphat Res Biol* 2006;**4**:51–6. https://doi.org/10.1089/lrb.2006.4.51

31. Armer JM, Radine ES, Porock D, Culbertson SD. Predicting breast cancer-related lymphedema using self-reported symptoms. *Nurs Res* 2003;**52**:370–9. https://doi.org/10.1097/00006199-200311000-00004

32. National Institute for Health and Care Excellence (NICE). *L-Dex U400 for Lymphoedema After Breast Cancer Treatment. Medtech Innovation Briefing (MIB111)*. London: NICE; 2017. URL: www.nice.org.uk/guidance/mib111 (accessed 8 May 2019).

33. Bundred NJ, Stockton C, Keeley V, Riches K, Ashcroft L, Evans A, Skene A, *et al.* Comparison of multi-frequency bioimpedance with perometry for the early detection and intervention of lymphoedema after axillary node clearance for breast cancer. *Breast Cancer Res Treat* 2015;**151**:121–9.

34. Bundred N, Todd C, Morris J, Keeley V, Purushotham A, Bagust A, *et al. Clinical Trial Protocol: Multi-frequency Bioimpedance in the Early Detection of Lymphoedema after Axillary Surgery*. National Institute for Health Research and Cancer Research UK; 2015. URL: www.journalslibrary.nihr.ac.uk/programmes/pgfar/RP-PG-0608-10168/#/ (accessed 7 May 2019).

35. Bland M, Altman M. *An Introduction to Medical Statistics*. 3rd edn. Oxford: Oxford University Press; 2005.

36. Deltombe T, Jamart J, Recloux S, Legrand C, Vandenbroeck N, Theys S, Hanson P. Reliability and limits of agreement of circumferential, water displacement, and optoelectronic volumetry in the measurement of upper limb lymphedema. *Lymphology* 2007;**40**:26–34.

37. Paskett ED, Naughton MJ, McCoy TP, Case DL, Abbott J. The epidemiology of arm and hand swelling in premenopausal breast cancer survivors. *Cancer Epidem Biomarkers* 2007;**16**:775–82. https://doi.org/10.1158/1055-9965.EPI-06-0168

38. Hui SL, Zhou XH. Evaluation of diagnostic tests without gold standards. *Stat Methods Med Res* 1998;**7**:354–70. https://doi.org/10.1177/096228029800700404

39. Rutjes AW, Reitsma JB, Coomarasamy A, Khan KS, Bossuyt PM. Evaluation of diagnostic tests when there is no gold standard. A review of methods. *Health Technol Assess* 2007;**11**(50). https://doi.org/10.3310/hta11500

40. Naaktgeboren CA, Bertens LC, van Smeden M, de Groot JA, Moons KG, Reitsma JB. Value of composite reference standards in diagnostic research. *BMJ* 2013;**347**:f5605. https://doi.org/10.1136/bmj.f5605

41. Ritchie J, Spencer L. Qualitative Data Analysis for Applied Policy Research. In Bryman A, Burgess RG, editors. *Analysing Qualitative Data*. London: Routledge; 1994. pp. 172–94. https://doi.org/10.4324/9780203413081_chapter_9

42. Verry H, Lord SJ, Martin A, Gill G, Lee CK, Howard K, *et al.* Effectiveness and cost-effectiveness of sentinel lymph node biopsy compared with axillary node dissection in patients with early-stage breast cancer: a decision model analysis. *Br J Cancer* 2013;**106**:1045–52. https://doi.org/10.1038/bjc.2012.62

43. Norman SA, Localio AR, Potashnik SL, Simoes Torpey HA, Kallan MJ, Weber AL, *et al.* Lymphedema in breast cancer survivors: incidence, degree, time course, treatment, and symptoms. *J Clin Oncol* 2009;**27**:390–7. https://doi.org/10.1200/JCO.2008.17.9291

44. Office for National Statistics (ONS). *Cancer Statistics Registrations: Registrations of Cancer Diagnosed in 2011, England*. Series MB1 No. 42. Newport: ONS; 2011. URL: https://webarchive.nationalarchives.gov.uk/20151014092800/www.ons.gov.uk/ons/rel/vsob1/cancer-statistics-registrations–england–series-mb1-/no–42–2011/index.html (accessed 7 May 2019).

45. Specht MC, Miller CL, Russell TA, Horick N, Skolny MN, O'Toole JA, *et al.* Defining a threshold for intervention in breast cancer-related lymphedema: what level of arm volume increase predicts progression? *Breast Cancer Res Treat* 2013;**140**:485–94. https://doi.org/10.1007/s10549-013-2655-2

46. Mansel RE, Fallowfield L, Kissin M, Goyal A, Newcombe RG, Dixon JM, *et al.* Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. *J Natl Cancer Inst* 2006;**98**:599–609. https://doi.org/10.1093/jnci/djj158

47. Cheville AL, Almoza M, Courmier JN, Basford JR. A prospective cohort study defining utilities using time trade-offs and the Euroqol-5D to assess the impact of cancer-related lymphedema. *Cancer* 2010;**116**:3722–31. https://doi.org/10.1002/cncr.25068

48. Bouchardy C, Rapiti E, Blagojevic S, Vlastos AT, Vlastos G. Older female cancer patients: importance, causes, and consequences of under treatment. *J Clin Oncol* 2007;**25**:1858–69. https://doi.org/10.1200/JCO.2006.10.4208

49. Lavelle K, Sowerbutts AM, Bundred N, Pilling M, Todd C. Pretreatment health measures and complications after surgical management of elderly women with breast cancer. *Br J Surg* 2015;**102**:653–67. https://doi.org/10.1002/bjs.9796

50. Wade J, Donovan JL, Lane JA, Neal DE, Hamdy FC. It's not just what you say, it's also how you say it: opening the 'black box' of informed consent appointments in randomised controlled trials. *Soc Sci Med* 2009;**68**:2018–28. https://doi.org/10.1016/j.socscimed.2009.02.023

51. Fletcher B, Gheorghe A, Moore D, Wilson S, Damery S. Improving the recruitment activity of clinicians in randomised controlled trials: a systematic review. *BMJ Open* 2012;**2**:e000496. https://doi.org/10.1136/bmjopen-2011-000496

52. Department of Health and Social Care. *Best Research for Best Health – A New National Health Research Strategy*. London: Department of Health and Social Care; 2006.

53. UK Clinical Trials Gateway. *Public and Patient Survey*. Southampton: NIHR; 2012. URL: www.nihr.ac.uk/documents/about-NIHR/NIHR- Publications/UKCTG-Report-Public-and-Patient-Survey-Report-2012.pdf (accessed 19 April 2018).

54. Adams M, Caffrey L, McKevitt C. Barriers and opportunities for enhancing patient recruitment and retention in clinical research: findings from an interview study in an NHS academic health science centre. *Health Res Policy Syst* 2015;**13**:8 https://doi.org/10.1186/1478-4505-13-8

55. Donovan JL, Paramasivan S, de Salis I, Toerien M. Clear obstacles and hidden challenges: understanding recruiter perspectives in six pragmatic randomised controlled trials. *Trials* 2014;**15**:5. https://doi.org/10.1186/1745-6215-15-5

56. Mills N, Donovan J, Wade J, Hamdy F, Neal D, Lane JA. Exploring treatment preferences facilitated recruitment to randomized controlled trials. *J Clin Epidemiol* 2011;**64**:1127–36. https://doi.org/10.1016/j.jclinepi.2010.12.017

57. Brown R, Butow PN, Butt DG, Moore AR, Tattersall MH. Developing ethical strategies to assist oncologists in seeking informed consent to cancer clinical trials. *Soc Sci Med* 2004;**58**:379–90. https://doi.org/10.1016/S0277-9536(03)00204-1

58. Tomlin Z, deSalis I, Toerien M, Donovan JL. Patient advocacy and patient centredness in participant recruitment to randomized-controlled trials: implications for informed consent. *Health Expect* 2012;**17**:670–82. https://doi.org/10.1111/j.1369-7625.2012.00792.x

59. Bower P, Brueton V, Gamble C, Treweek S, Smith CT, Young B, Williamson P. Interventions to improve recruitment and retention in clinical trials: a survey and workshop to assess current practice and future priorities. *Trials* 2014;**15**:399. https://doi.org/10.1186/1745-6215-15-399

60. Townsend D, Mills N, Savović J, Donovan JL. A systematic review of training programmes for recruiters to randomised controlled trials. *Trials* 2015;**16**:432. https://doi.org/10.1186/s13063-015-0908-6

61. Srivastava A, Thomson SB. Framework analysis: a qualitative methodology for applied policy research. *J Adm Govern* 2009;**4**:72–9.

62. Sugarman J, McCrory DC, Hubal RC. Getting meaningful informed consent from older adults: a structured literature review of empirical research. *J Am Geriatr Soc* 1998;**46**:517–24. https://doi.org/10.1111/j.1532-5415.1998.tb02477.x

Appendix 1 Consolidated Standards of Reporting Trials flow diagrams for workstream 1

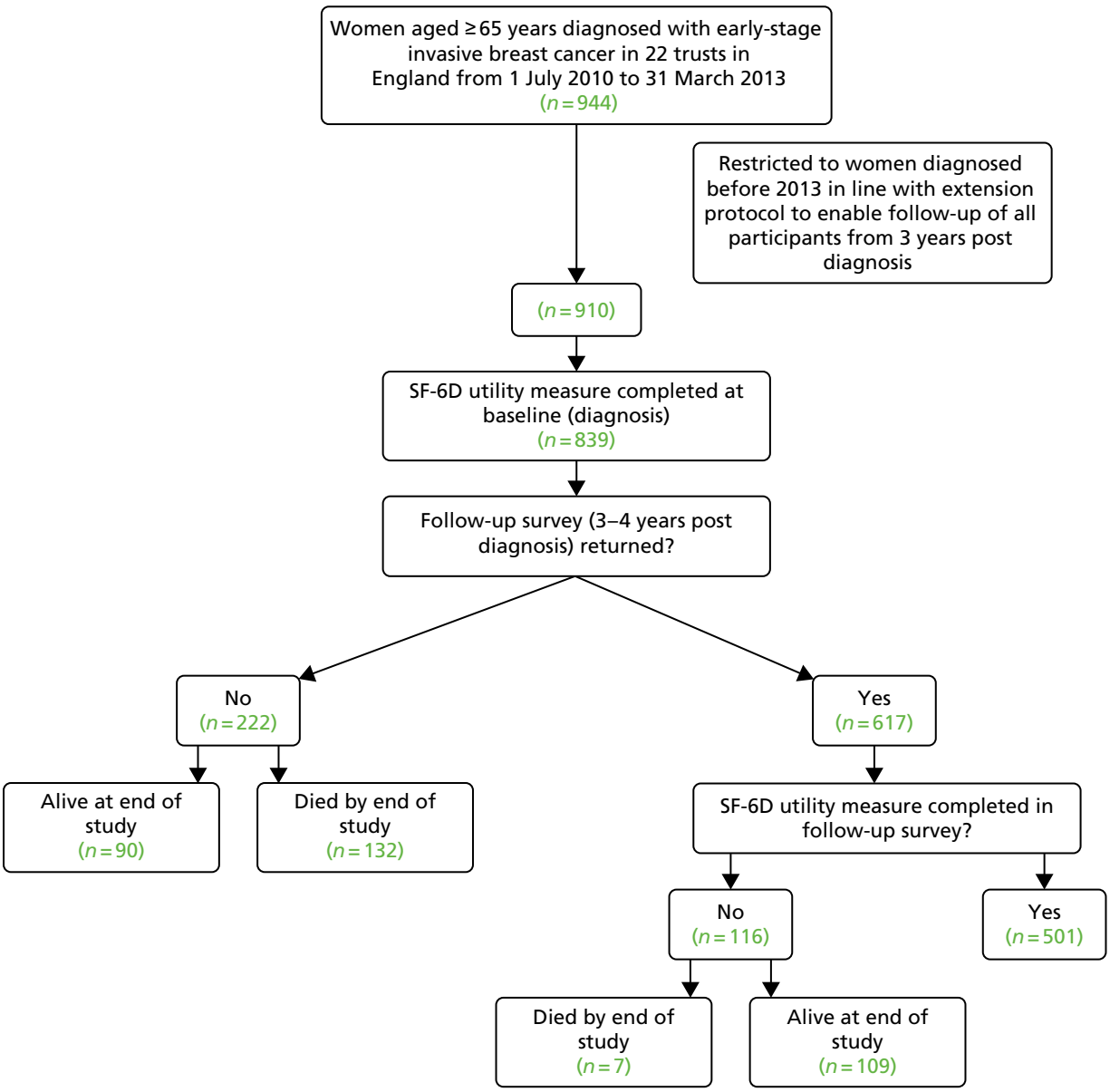


FIGURE 19 Flow diagram of participants in analyses of aim A: impact of primary surgery on survival and HRQoL. Participants included in analyses of breast cancer-specific survival to study end on 5 February 2016 ($n = 910$). Participants included in analyses of difference in HRQoL by primary surgery ($n = 501$). SF-6D set at 0 and included in the analysis of QALYs with participants returning the SF-6D ($n = 501 + 132 + 7 = 640$).

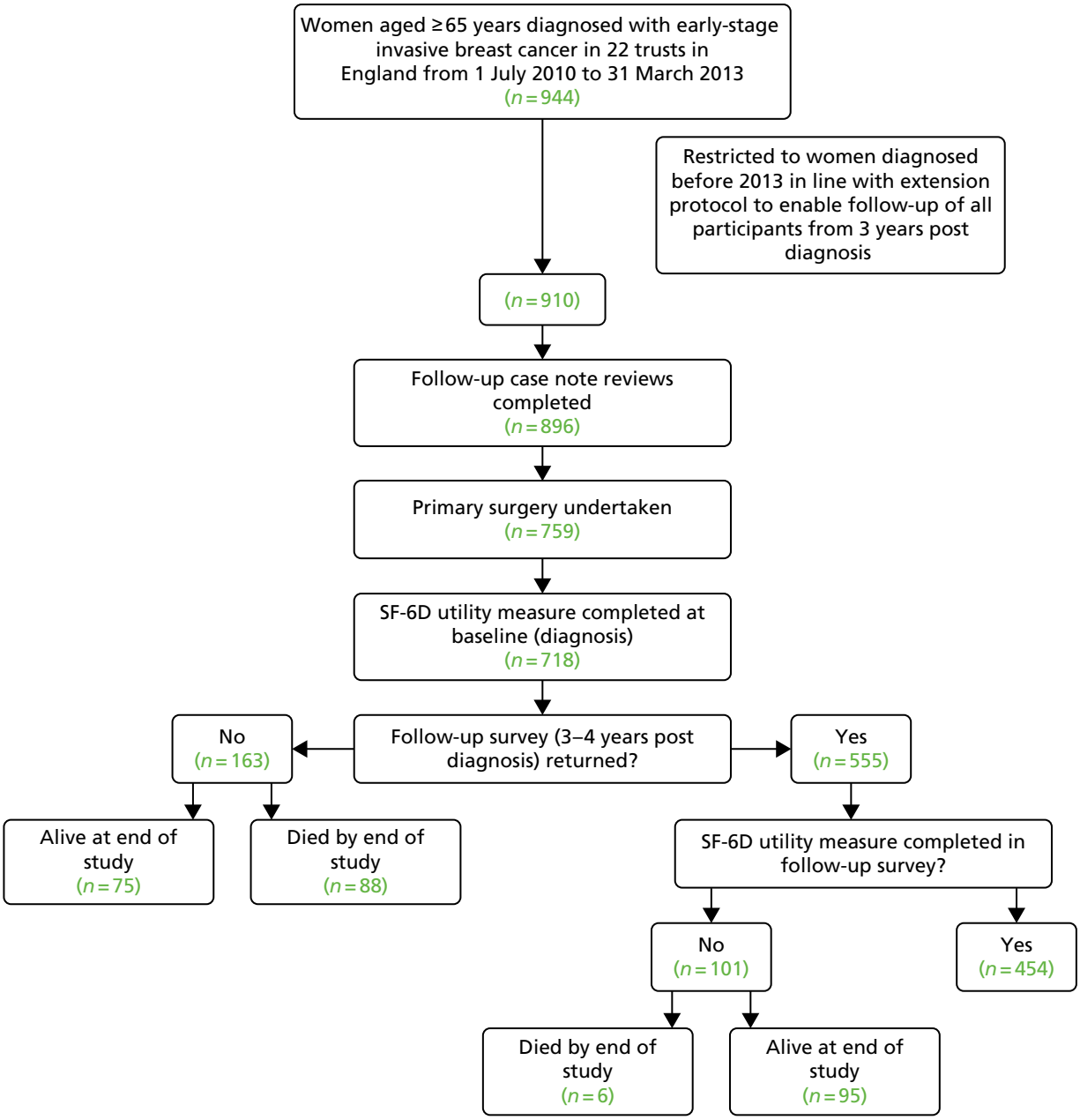


FIGURE 20 Flow diagram of participants in analyses of aim Bi: impact of adjuvant therapy on survival and HRQoL. Participants included in analyses of impact of adjuvant therapy on survival to study end on 5 February 2016 ($n = 910$). Participants included in analyses of difference in HRQoL by adjuvant treatment ($n = 454$). SF-6D set at 0 and included in the analysis of QALYs with participants returning the SF-6D ($n = 454 + 88 + 6 = 548$).

TABLE 50 Extension summary: current cohort = 910 women aged ≥ 65 years diagnosed with early-stage breast cancer at 22 English breast units between 1 July 2010 and 31 December 2012

Aim: to investigate	Outcome(s)	Explanatory variables	Method	Sample
A. The extent to which primary surgery for older women with early-stage breast cancer increases survival and HRQoL and is cost-effective	Survival (to 3 years post diagnosis) Difference in HRQoL (at diagnosis, 3–4 years later) QALYs	Treatment received (i.e. primary surgery < 3 months of diagnosis) Pre-treatment health Pre-treatment health measures, tumour characteristics and sociodemographics	We have collected extensive data on health at diagnosis and surgical treatments received < 3 months of diagnosis via interview and case note review, respectively We have set up mortality flagging and investigate effect of surgery on survival at 3 years In addition, we have undertaken a further case note reviews at 3 years and survey at 3–4 years to also measure/investigate outcomes of cost-effectiveness and HRQoL, respectively	All 910 women in cohort 910 for survival outcome 501 for HRQoL and 640 for QALY outcomes See *Figure 2* and submitted paper
Bi. The extent to which adjuvant treatment (chemo-/radiotherapy with surgery) increases survival and HRQoL and is cost-effective		Treatments received (i.e. radiotherapy < 12 months of diagnosis) Chemotherapy commenced < 12 months of diagnosis Pre-treatment health measures, tumour characteristics and sociodemographics		759 women in cohort who had surgery 759 for survival outcome 454 for HRQoL and 548 for QALY outcomes See *Figure 3*
Bii. The extent to which lack of adjuvant treatment can be explained by patient health and choice	Radiotherapy < 12 months of diagnosis Chemotherapy commenced < 12 months of diagnosis	Pre-treatment health measures, patient choice, tumour characteristics and sociodemographics	The effect of pre-treatment health/choice on whether or not patients had surgery has already been investigated.[49] We repeat this analyses investigating access to adjuvant treatment by undertaking a further case note review at 3 years and survey at 3–4 years	688 retained in cohort who had surgery and did not die or move away < 12 months of diagnosis See *Appendix 3*

Appendix 2 Surgical management of older breast cancer patients: which pre-treatment health measures predict 30-day complications?

Figure 21 and *Tables 51–56* in this section are based on Lavelle *et al.*[49]

Abstract

Introduction

Older breast cancer patients are less likely to have surgery; in part due to co-morbidities and reduced functional ability. However, there is little consensus on how best to assess surgical risk for this patient group.

Methods

We investigated the ability of pre-treatment health measures to predict complications in a prospective, cohort study of a consecutive series of 664 women aged ≥70 years undergoing surgery for operable (stage 1-3a) breast cancer at 22 English breast units (2010-2013). Data on treatment, surgical complications, health measures and tumour characteristics were collected by case note review and/or patient interview. Outcome measures: All complications and serious complications within 30days of surgery.

Results

41% experienced ≥1 complications, predominantly seroma or primary/minor infections. 6.5% had serious complications. More extensive surgery predicted a higher number of complications but not serious complications. Older age did not predict complications. Several health measures were associated with complications univariately and included in multivariable analyses, adjusting for type/extent of surgery and tumour characteristics. In the final models pain predicted a higher count of complications (OR 1.006, 95% CI:1.002-1.011). Fatigue (IRR 1.019, 95% CI:1.006-1.033), low platelets (OR 4.189, 95% CI:1.025-17.123) and pulse rate (OR 0.957, 95% CI:0.926-0.990) predicted serious complications.

Conclusion

Predictors of surgical risk were identified in multivariable models, but effects were weak with 95% confidence intervals close to unity. The search for more robust predictors continues. However, risk of serious complications is low. In line with national guidance, older women should be given the same consideration for breast cancer surgery as younger patients.

Introduction

Breast cancer is predominantly a disease of old age: incidence doubles from 215 per 100,000 for women aged 45–49 to 442 per 100,000 for those aged ≥85 years (England 2011). One third of all new cases in England are diagnosed in women aged ≥70 years[1]. Within an ageing population, both the number and proportion of older patients requiring treatment at breast units is rising and set to continue to do so for the next 50 years[2].

Primary surgery (mastectomy or wide local excision of the tumour) is the recommended initial treatment for early stage breast cancer[3;4]. However, the percentage of women having surgery for breast cancer in England decreases with older age; from as low as 40% of patients aged ≥80 years to around 90% of younger age groups[5;6].

UK treatment guidelines state that 'significant co-morbidity' may preclude surgery for patients with early stage breast cancer[3;4]. As co-morbidity increases with older age this may account for the lower surgical rates amongst elderly patients. However, although co-morbidity does explain some of the decline in surgical rates with age, older women are still less likely to have surgery once co-morbidity is adjusted for[5]. Our recent study suggests that adjusting for wider measures of health, such as functional decline/frailty, may explain lack of breast surgery for older women up to, but not beyond, the age of 85 years[7]; providing evidence that, at least up to the age of 85 years, patient health is the primary consideration when assessing surgical risk, rather than age.

However, there is little consensus on how best to assess surgical risk for older breast cancer patients. Precluded from earlier trials, the evidence base on older patients' risks and benefits of treatment is poor[8;9]. A more recent older age specific trial comparing surgery with endocrine therapy vs. endocrine therapy alone for patients aged ≥70 years closed due to slow recruitment[9]. Patients largely opted not to take part in this trial in which they had a 50% chance of not having surgery; possibly because surgery is now such an accepted mainstay of treatment for early stage breast cancer. In this context cohort studies can help bridge the knowledge gap by identifying pre-treatment health measures which predict surgical complications.

One such large cohort investigating surgical risk assessment, for all ages/types of surgery, combines measures used within pre-operative assessment such as co-morbidity and body mass index into predictive models. The US-based National Surgical Quality Improvement Program (NSQIP) has developed a universal measure of surgical risk based on all surgical procedures at 393 enrolled hospitals[10]. Multivariate models of mortality and morbidity are based on 21 pre-operative measures recorded on the dataset. Model discrimination is good (AUC >0.8) presenting a considerable step forward in risk stratification for surgical patients in general. Limitations of this risk tool include restriction to pre-operative measures recorded on the dataset and lack of disease and procedure specific pre-operative measures such as type/extent of surgery[11]. Underestimation of complications rates in the NSQIP dataset has also been reported due to non-inclusion of procedure specific complications and limitation to academic hospitals enrolled in this quality improvement programme; which have better surgical outcomes

compared to the rest of the US[11;12]. Generalisability to the UK is also questionable given the difference in health care systems. The lack of a British version of NSQIP is likely to increase interest in risk stratification in the UK[12].

Surgical risk assessment specifically for older cancer patients has been developed to also incorporate measures of functional decline/frailty. The Comprehensive Geriatric Assessment (CGA) is a battery of varying health status and functional tests recommended by the International Society for Geriatric Oncology as essential to treatment decision making with older cancer patients. However, there is a lack of consensus on which health measures best predict risk and therefore should be included in a CGA[13]. Functional status and fatigue have been found to predicted surgical complications amongst generic cancer patients[14]. However, as risk varies considerably for different types of surgery there is a need to identify health measures which predict surgical risk within specific cancer groups[15].

As part of a wider research programme we undertook a prospective, cohort study investigating the extent to which the lack of surgery for older breast cancer patients is explained by patient choice or poor health[7]. Here we report on the study's secondary aim of investigating the ability of a range of pre-treatment health measures to predict 30 day surgical complications amongst a subset of 664 patients aged ≥70 years who received surgery.

Methods

Study design

This is a prospective, cohort study of a consecutive series of women aged ≥70 years undergoing surgery for operable (stage 1-3a) breast cancer at 22 breast units, predominantly in Northwest England, over a period of 33 months (2010-2013). Data on treatment, surgical complications, a range of pre-operative health measures and tumour characteristics were collected by case note review and/or patient interview[7].

Primary outcome measure: Complications within 30 days of primary surgery (mastectomy or Wide Local Excision, WLE) for operable (stage 1-3a) breast cancer. All patients were followed up for 90 days post diagnosis. Patients not having primary surgery within 90 days of diagnosis were not included in this study. As initial WLE may be followed by mastectomy, patients were classified as receiving mastectomy or WLE based on the most extensive primary surgery. Similarly axillary node procedure was based on the most extensive dissection. Two measures of complications are used: a count of all complications and having serious complications (vs. not). All complications occurring within 30 days of the last primary surgery were recorded; non infections based on a checklist developed from the East Anglian Hip Fracture Audit[16] and the Pre-operative Assessment of Cancer in the Elderly Project[14], with breast surgery specific items[17;18] and infectious complications based on the national prevalence survey of hospital acquired infections[19]. Complications occurring after the commencement of adjuvant radiotherapy or chemotherapy were not included. Patients were classified as having serious complications if they had complications (other than a seroma or primary/minor infection) which warranted readmission as an inpatient, delayed discharge or other procedure. Delayed discharge was defined by being in excess of median length of stay[20] and the maximum time limits reported as 'usual' in national NHS patient information sources[21] i.e. more than one day for WLE and five or more days for mastectomy. Other procedures included as indicating a serious complication were return to theatre, treatment for confirmed hospital acquired MRSA infection, stroke or pulmonary embolism, extensive wound repair (i.e. excising of necrotic tissue/ applying sutures/wound packing) and blood transfusions.

Explanatory variables: Age, measures of health, tumour characteristics, demographics and hospital resources.

Measures of health: A range of health measures were recorded both from self-report at a patient interview (undertaken within 2 weeks of diagnosis and before surgery) or from pre-operative assessment as recorded in the case notes. Measures included are listed in Box 1, and represent patients' functional/health status and Health Related Quality of Life (HRQoL), in addition to co-morbidity and other clinical measures recorded at the pre-operative health assessment. Self-report measures were primarily selected based on ease of administration, validity, reliability, acceptability to older people[22;23], and prediction of treatment received[24;25] and/or treatment outcomes[13-15]. Clinical measures recorded at pre-operative assessment were also considered if data were available for at least 85% of sample. Classification for blood results was based on the National Pathology Harmonisation Standardisation project[26;27].

Tumour characteristics: Pre-treatment assessments of tumour characteristics, tumour size, stage, nodal and steroid receptor status were recorded based on clinical, imaging and fine needle/core biopsy assessments (cTNM[28]).

Socio–demographics: Socio-economic class is measured using the Office of National Statistics Socio-Economic Classification[29] and based on main occupation pre-retirement if retired and the highest classification if the participant was married or living with a partner. Ethnicity was recorded based on UK census classification categories[30]. Of the 22 breast units in the study 19 were in the North West of England, two in London and one in the Midlands.

Inclusion criteria

Women: Men were not included as <1% of all invasive breast cancer occurs in men[1] and surgical management may differ[3;4].

Aged ≥70 years: Women aged 70-74 years are included as a reference group.

Having primary surgery within 90 days of diagnosis of a new episode of operable invasive breast cancer (stage 1-3a): Carcinoma in situ, stage 3b, metastatic and recurrent breast cancers are not included as the standards for operable breast cancer do not apply[3;4].

Screening/Accrual

Screening and accrual processes are reported elsewhere[7]. Of the 800 patients aged ≥70 years, recruited into the main study investigating the extent to which patient health and choice explain lack of surgery, 664 (83%) had primary surgery within the follow up period of 90 days and therefore are included in the analyses of prediction of surgical complications reported here.

Data Collection.

Patients who agreed to take part were interviewed within 30 days of diagnosis, before surgery took place. The interview comprised demographic variables and measures of health detailed above. The case notes of each patient were reviewed up to 3 months post-diagnosis, using a proforma developed to collect data on tumour characteristics at diagnosis, treatments undertaken, co-morbidity and complications. Inter-rater agreement levels for the proforma items satisfied the Kappa >0.6 criterion indicating substantial to perfect agreement[31]. Three percent of case note review proformas and 8% of patient interviews were tested for data input errors. Error rates per data item inputted were <0.5% so no further data-checking was warranted. The proformas of patients having complications were initially assessed by AMS and KL independently against the above criteria for serious complications devised with NB and CT. Disagreements were resolved by consensus with any final outstanding decisions made by NB or CT.

Analyses

Explanatory variables were investigated in univariable analysis using Pearson's χ^2 test, Fisher's exact test, χ^2 test for trend and univariable regression analyses (two tailed with $\alpha = 0.05$). The distribution of continuous variables was assessed for Normality using the Shapiro–Wilk W test. Associations between non-Normal variables and categorical data were investigated using the non-parametric two sample Wilcoxon rank sum (Mann Whitney test) and Kruskal-Wallis equality-of-populations rank test. Associations for parametric variables were investigated using the two sample t-test. Due to the large number of health measures tested for univariate associations with complications, significance was considered after a Bonferroni adjustment for multiple testing was calculated.

Independent variables found to be significantly associated with outcomes in univariable analyses were used as independent variables in the subsequent multiple regressions (forward stepwise). Models were built in line with our Data Analysis Plan agreed *a priori* with the project's Independent Data Monitoring Committee modifying an approach suggested by Hosmer and Lemeshow (2000)[32]. Type of surgery (mastectomy vs. WLE) and extent of axillary node surgery formed the base models based on clinical relevance and previous literature[11;33]. Remaining variables were initially tested against the null model and retained based on (1) the difference between the model with the additional variable and the previous model using the Likelihood Ratio Test (a.k.a. analysis of deviance) or (2) producing a significant coefficient in the model (both at a 5% significance level). Explanatory variables were considered in three groups and added into the model in order of importance to the secondary aim of the study i.e. health measures, socio-demographics and then tumour characteristics. Within each group the order in which variables were added into the model was determined by minimising Bayesian Information Criterion (BIC) values of each variable added into the model individually. Those variables with lower BIC values were added in sequentially starting with the variable giving the lowest value. At each step an individual variable's contribution to the model was assessed using the above two criteria. In order to reduce the likelihood of multicollinearity, and ensure the number of cases in the model could sustain the potentially high number of health measures, they were only retained in the model if they produced both a significant coefficient and likelihood ratio test. Tumour characteristics and socio demographic variables were retained if they had a significant likelihood ratio test only.

Once each group of variables had been added VIFs (Variance Inflation Factors) were checked and variables exhibiting factors above 10 investigated to prevent multicolinearity[34]. Logistic regression models were tested for goodness of fit (Hosmer & Lemeshow) and discrimination (area under Receiver Operating Characteristic curve). Variables included in the final models were tested for two way interactions.

A sensitivity analysis was conducted by additionally performing backwards stepwise regression, and this approach led to comparable final models and therefore suggested robust results.

Data were analysed using STATA version 12.1[35].

Sample size

The sample size was determined *apriori* by the study's primary aim as reported elsewhere[7]. In order to test the study's aim reported in this paper, the recommended sample size is determined by the number of explanatory variables included in the multivariate models predicting the two complications outcome measures. However, the given sample size of 664 should also be sufficient to support negative binomial (predicting count of complications) as the sample size ≥ 50 + 8p and ≥ 104 + p (where p is the number of explanatory variables)[36]. Logistic regression (predicting serious complications) should have around 10 cases for each explanatory variable for both categories of the dependent variable[37;38], although in other scenarios it has been shown that 5 cases for each explanatory variable is sufficient[39]. In order to help meet this guidance health measures with non-significant coefficients (at 5% level) were dropped from the model once the total number of variables exceeded this limit during the model building process. In practice only one health measure was lost from the model for this reason and the resultant final logistic regression model included five explanatory variables (i.e. 8 events per variable).

Results

Sample characteristics

Six hundred and sixty four women were included, all of whom had primary surgery within 90 days of diagnosis. Half (49.5%, n = 329), had a mastectomy and half (50.5%, n = 335) Wide Local Excision (WLE); 39% were aged 70-74 years, 30% 75- 79 years, 19% 80-84 years and 12% aged ≥85 years (Table 1). The sample was predominantly of professional/ intermediate social class and white ethnic group. Over half were treated at a district general hospital rather than a university teaching hospital. Over 40% of the sample were recorded with stage I disease at diagnosis, 55.9% were stage II or IIIa hence regarded as having early operable breast cancer[40]. Over two thirds of the sample (70.3%) had no nodal involvement recorded at diagnosis and over half the sample had small tumours of ≤20mm (56.3%). The vast majority of participants were steroid receptor positive for either oestrogen or progesterone receptors (83.6%).

Complications rates

Of the 664 women in the sample, 41.0% (272) had some form of complication within 30 days of surgery (95% CI: 37.2-44.7%) (Figure 1). However, only 21.8% (145) had complications other than seroma (95% CI: 18.7-25.0%), predominantly related to wound infection of the surgical site. The number of complications experience by women varied from 0 to 5 (mean 0.58, SD 0.85) (Table 2). For 6.5% (43) of the sample, complications warranted delayed discharge, readmission to hospital or further procedure and they were thereby classified as having serious complications (95% CI: 4.6-8.4%).

Univariable analyses

Participants who underwent mastectomy had a higher mean number of complications (P<0.001), but were no more likely to have serious complications (P = 0.139), compared to those having WLE (Table 1). Similarly those undergoing more extensive axillary node procedures had a higher number of complications (P<0.001) but were not significantly more likely to experience serious complications (P = 0.087). No association was found between number of complications and patient age group (P = 0.512). Similarly the number of complications did not significantly increase with each year of age (IRR 1.02, 95%CI: 1.00-1.04, P = 0.109). Although the proportion experiencing serious complications increased from 4.3% for 70-74 year olds to 10.1% for women aged ≥85 years, this effect failed to reach statistical significance at 5% level; regardless of whether age was measure in groups (P_{Trend} = 0.061) or continuously (two sample t test with equal variances P = 0.060). Participants presenting with larger (P = 0.009), later stage (P = 0.001) tumours and nodal involvement (P < 0.001) had a higher number of complications. However, no tumour characteristics were associated with serious complications.

Health measures

Of the 46 separate health measures tested (Box1), 14 were found to be univariately associated with number of complications and 19 with serious complications (Tables 3 & 4) at the 5% level. Bonferroni's adjustment[41] applied (at $\alpha/n = 0.05/46 = 0.001$) is also considered.

Amongst the categorical measures of health (Table 3), smoking status, blood pressure and cognitive impairment (6CIT) had no association with post-surgical complications. At the 5% significance level a BMI indicative of obesity or underweight was associated with a higher count of all complications, but not serious, complications. A dependent ECOG Performance Status and abnormal haemoglobin were associated with both total and serious complications. Co-morbidity (Charlson Index), a high ASA risk score and low platelets were associated with serious complications only. However, none of these measures retained significance once Bonferroni's adjustment was applied at 0.1%.

Of the continuous measures of health (Table 4) lack of functional ability to undertake both basic Activities of Daily Living (e.g. self-care/hygiene) and more advanced 'Instrumental' activities (e.g. shopping/cooking) predicted increased count of all, and odds of serious, complications at the 5% level. However, only Instrumental ADL's prediction of complication count retained significance at the 1% level. Similarly, better physical health status, as measured by the SF-12 PCS, predicted a lower complication count at the 0.1% (Bonferroni adjusted) level but only predicted lower odds of serious complications at the 5% level. Of the 15 EORTC HRQoL domains 10 were associated with complications at the 5% level. However, for most of the domains, the 95% CIs were close to unity (indicating a weak effect) and only 4 domains were significant at the 0.1% level i.e. better physical and role function predicted a lower count of all and serious complications, and increased pain and fatigue predicted having serious and a higher count of complications respectively.

However strongly pre-operative health measures are associated with complications univariately, multivariate analyses are needed to establish the extent to which the health measures continue to predict complications once the effects of potential confounding variables are adjusted for. Therefore, all health measures that significantly predicted complications at the 5% level were considered for inclusion in multivariate analyses adjusting for a range of variables (including extent of surgery, socio-demographics and tumour characteristics) as per the strategy detailed in methods.

In the multivariate analyses a higher count of complications was predicted for women undergoing a mastectomy vs. WLE (IRR 1.64, 95% CI: 1.28-2.12) and more extensive axillary node surgery as opposed to sentinel node biopsy (IRR 1.43, 95% CI: 1.13-1.82) (Table 5). Of the health measures only increased pain predicted outcome, with the total number of complications increasing by 1.006 (95% CI: 1.002-1.011) for each point increase (indicating worsening pain) on the EORTC C30 pain scale.

Neither type of primary surgery nor extent of axillary node procedure predicted odds of serious complications in the multivariate logistic regression analysis (Table 6). Three health measures retained in the model significantly predicted serious complications. Patients with abnormally low platelets had over four times the odds of serious complications compared to patients with normal/high platelets (OR 4.19, 95% CI: 1.03-17.12). The odds of serious complications decreased with higher pulse rate (OR 0.957, 95% CI: 0.926-0.990) and increased by 1.02 (95% CI: 1.006-1.033) times for each point increase (indicating worsening fatigue) on the EORTC C30 fatigue domain. There was no significant difference between the observed and final model predicted values (goodness of fit test χ^2 (Hosmer–Lemeshow) = 7.34: d.f. = 8; P=0.500) and model discrimination (AUC=0.745) is considered 'acceptable'[32]. However, even when the models probability cut point (0.5 by default) was set to 0.063, maximising sensitivity/specificity, these were still low (71.9%) and the false positive/negative rates high (28.1%). In addition, the 95% confidence intervals for all four health measures predicting complications in both final models are close to unity indicating weak effects.

Discussion

Summary

Although a large proportion (41.0%) of the older women in this study experienced one or more complications these were predominantly seroma or minor infections. A relatively low percentage (6.5%) experienced serious complications which necessitated delayed discharge, readmission or further procedures. More extensive primary and axillary node surgery were associated with a higher number of all complications but not serious complications. Older age did not predict increase in risk of complications. Several health measures were associated with complications univariately. In the multivariate analyses self-reported pain predicted a higher count of all complications whilst fatigue, along with low platelets and pulse rate predicted serious complications.

Complication rates

Previous studies report a wide range of overall rates of breast surgery complications from 2 – 50%[11;42;123]. Although at the higher end of this range our estimates are similar to previous reported studies of older breast cancer patients[17;43;44]; Chat *et al* (2011) for example report overall and major complication rate of 37.1% and 5.7% respectively[43]. Although other studies of older breast cancer patients report somewhat lower overall complication rates (e.g. between 18-26%[45-47]) considerable variation across studies is to be expected depending on co-morbid conditions, time period of data collection/patient follow up, completeness of data sources used as well as the definition and assessment of complications. Rocco *et al* (2013) for example highlight that their estimate of 18.2% among breast cancer patients age ≥65years may be low due to the use of retrospective records from 1997-2012[47]. However, attempts to benchmark breast surgery complication rates have been reported elsewhere[33;43].The aim of the study reported here is to investigate predictors of surgical risk amongst older breast cancer patients.

Extent of surgery

Consistent with previous studies[11;33;43;45], we found that more extensive surgery, both in terms of type of primary surgery (mastectomy vs. WLE) and axillary node dissection, strongly predicted a higher count of all complications. Conversely the extent of surgery did not predict serious complications. This appears contradictory to Chatzidaki *et al*'s (2011) study in which greater extent of surgery predicted major complications. However, the small number of patients experiencing major complications (8/140 participants) limits the generalisability of Chatzidaki *et al*'s findings. In addition, the effect of extent of surgery on all complications may be largely driven by wound complications which have been found to be strongly associated with extent of surgery [11;33]. Wound complications make up a large proportion of complications overall[42] but are underrepresented in our measure of serious complications, which only includes secondary/major wound infections.

Age

Older age predicted neither number nor seriousness of complications. Although older age has been found to predict breast surgery complications in earlier[48;49] and smaller scale studies[47], many other studies have found no assoication[11;17;33;44;46]. Notably, in the US-based National Surgical Quality Improvement Program's cohort, older age did not predict wound complications after breast surgery in either the of 3,107 breast cancer patients treated from 2001-2004[33] nor in the follow up study of 26,988 treated from 2005 – 2007[11]. The authors argue that employing multivariate analyses and, controlling for a variety of potentially confounding pre-operative factors, enabled them to demonstrate this in a large and diverse cohort of patients[11]. However, de Glas *et al*[45], in their cohort of 3179 patients diagnosed with breast cancer from 1997-2004, found that women aged ≥85 years had 1.58 the odds of one or more complication following breast surgery compared to 65-69 year olds study (95% CI: 1.14-2.16) after adjusting for comorbidities , surgery type and tumour stage. Hence an increased surgical risk for older breast cancer patients cannot be ruled out; albeit one of a small magnitude limited to the oldest patients.

Health measures

Several pre-operative health measures predicted complications in the univariate analyses. As in previous studies co-morbidity[43;45;47], BMI[11;33;43], ASA risk score[14;43] and functional status[14] (as measured by ADL and ECOG Performance Status) demonstrated some association with surgical risk at the 5% level. These findings are far from consistent, with other studies finding no association between surgical risk and co-morbidity[14;46], BMI[45;47], ASA[11] and functional status[33]. Smoking status showed no association with surgical complications in our study. Although the weight of literature indicates that smoking predicts surgical complications from breast surgery[11;45;47;50] this finding is not universal[17;33]. For example, El-Tamer *et al*[33] investigated the influence of a range of patient variables amongst their cohort of 3,107 breast cancer patients and found that smoking had no significant association with post-operative wound complications.

Predictors of surgical risk, identified from studies testing large numbers of pre-operative measures, may only reach statistical significance because of the increased chance of finding an association the greater the number of variables tested. Raising the significance level in line with the total number of variables tested can adjust for this effect (e.g. Bonferroni's adjustment)[41]. Although there are examples in the literature of previous studies investigating risk prediction of large numbers of pre-operative measures for breast surgery[33;43;45], none of the papers cited made either Bonferonni, or similar adjustments. Once Bonferroni's adjustment is applied only 6 of the 22 pre-operative measures which significantly predicted surgical complications at the original 5% level remain significant at the reassigned 1% level. Consistent with a previous study investigating surgical risk of solid tumours[14], increasing dependence in instrumental IADL (e.g. shopping, housework) predicted complications along with the SF-12 measure of physical health status and four domains of the EORTC-C30 (pain, fatigue, physical/role function). These measures were originally selected into the main study on ability to predict treatment[7;25], and/or their high validity/reliability particularly in older populations[22], yet they displayed stronger associations with

surgical complications than many of the traditional preoperative health measures. Moreover pain and fatigue predicted complications in the final multivariate models although many health measures failed to do so.

Few previous studies have undertaken similar multivariate analyses specifically predicting risk of breast surgery[11;33;45]. However, similar to our study, Audisio *et al*[14] found that moderate/severe self-reported fatigue increased the risk of complications from surgery for solid tumours amongst patients aged ≥70 years, adjusting for type/ stage of tumour, operative severity and patient age/gender. Generalised neuropathic pre-operative pain has been found to be predictive of postoperative pain after surgery for breast cancer[51] but not previously investigated regarding other complications. Conceivably self-reported pain may be acting as a proxy indicator of poorly managed/symptomatic co-morbidities. Contradictory to our results, El-Tamer *et al*[33] found no association between platelets and wound complications after breast surgery adjusting for a range of tumour characteristics, socio-demographics and other pre-operative health measures. This inconsistency may be due to the difference in outcome measures as primary/minor wound infections were not included in our measure of serious complications. Lower preoperative pulse rate, as a continuous measure, predicted serious complications, suggesting that the underlying conditions indicated by bradycardia (e.g. Ischaemic Heart Disease) may be increasing surgical risk. However when preoperative pulse rate was instead categorised as bradycardia/normal/tachycardia, this became borderline non-significant (P=0.062), possibly because of the low numbers of patients with abnormal pulse rates.

Although the pre-operative measures retained in the final model accounted for the variation in complications more strongly than the eliminated health measures in the modelling process, it should be noted that their effects in the final model are still weak; with 95% CIs around estimates close to unity. Moreover, although discrimination of the final model predicting serious complications (AUC = 0.745) is classified as statistically 'acceptable'[32], sensitivity and specificity only just exceed 70% and false positives/negatives are far from clinically acceptable; with this model failing to predict complications, and incorrectly predicting complications, in almost 30% of cases. Further research is clearly needed to identify/confirm strong predictors of surgical risk for older patients, which demonstrate clinically acceptable levels of discrimination.

A large number of initially significant health measures were narrowed down to relatively few predictors in the final model. Although somewhat disappointing, we would argue that this is due to the thorough statistical process that should be employed particularly when developing tools for clinical use. As potential users of such risk prediction tools, clinicians should be wary and ensure that the claimed prediction of such assessments are not due to multiple testing, without correction for the increase chance of finding a significant effect (such as Bonferonni), that multivariate analyses (adjusting for potential confounders) were undertaken and sensitivity/ specificity as well as overall discrimination are reported. No located previous literature investigating prediction of complications from breast surgery met all these criteria. As part of the US-based National Surgery Quality Improvement Programme, El-Tamer *et al*[33], comes closest; reporting a similar reduction in variables in the final model and model discrimination just slightly lower than our model (AUC 0.709 vs. 0.745).

Conclusions

This paper reports results of a large prospective cohort investigating surgical complications for older breast cancer patients treated the UK, testing prediction of an unprecedented range of pre-operative health measures and adjusting for extent of surgery, tumour characteristics and socio-demographics in multivariate analyses. In the final models self-reported pain predicted a higher count of all complications while fatigue, along with low platelets and pulse rate, predicted serious complications. However, the effects were weak: with 95% confidence intervals close to unity and low sensitivity and specificity.

This analysis was a secondary aim for our study and as such was limited to the sample size, geographical area and pre-operative health measures included in the main study. Other limitations of the main study are discussed elsewhere[7]. Of most relevance to the analysis reported here is the under-representation of women aged ≥85 years; limiting the generalisability of these findings to the oldest age group. However, under-representation of the oldest patients in any study requiring patient consent is likely as capacity for informed consent decreases with older age[52]. Future studies need to either focus on the oldest age group with ethical approval for vulnerable adults/ consent by proxy or examine a few pre-operative health measures that most strongly predict risk within routine/large clinical datasets collected for all patients.

Although universal models for surgical risk prediction based on large clinical data sets have been developed in the US[10] the search for robust predictors of surgical risk for older breast cancer patients in the UK continues. However, focusing on surgery for solid tumours with greater surgical risk[14] may be of greater utility. Clinicians need to ensure that risk prediction of proposed health assessments is not due to multiple testing, that potential confounders are adjusted for and that sensitivity/specificity is clinically sufficient.

Allowing for the potential selection bias due to the need to consent older patients and the reduced proportion of patients aged ≥85 years, the risk of serious complications from breast surgery for older patients in this sample is relatively low and did not increase significantly with age. This supports national guidance which asserts that older age in itself should not be a consideration when planning surgical treatment with older breast cancer patients[4].

Acknowledgements

This paper presented independent research funded by the Breast Cancer Campaign (2008NOVPR35), a National Institute for Health Research (NIHR) Programme Grant for Applied Research (RP-PG-0608-10168) and research arising from a Post Doctoral Fellowship supported by the NIHR (PDF/01/2008/027). The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health. Ethical approval was granted by the National Research Ethics Service (10/H1014/32 & 33).

Tables and figures

BOX 1: Independent variables

Type of surgery i.e. Wide Local Excision vs. Mastectomy

Extent of axillary node procedures i.e. Sentinel Node Biopsy vs. Axillary Node Surgery

Health measures at pre-operative assessment

- Blood pressure (low, normal, high)
- Body Mass Index (underweight, normal, overweight, obese)[a]
- Smoking status (current, non-smoker)[a]
- Blood tests (9 both continuous and categorical)[b]
- Pulse (beats per minute)
- Co-morbidity (Charlson Index)[53]
- American Society of Anaesthesiologists (ASA) physical status classification[54]

Health measures self-reported/assessed at pre-operative interview

- Functional status:

Eastern Co-operative Oncology Group Performance Status (ECOG-PS)[55]

Elderly Population Health Survey – Activities of Daily Living (ELPHS ADL) Basic/ Instrumental[56]

- Health status (Short Form-12: Physical & Mental Component Summaries)[57]
- Health Related Quality of Life (EORTC C30 = 15 separate scales)[58]
- 6 item Cognitive Impairment Test (6CIT)[59]

Tumour Characteristics (pre-operative)[28]

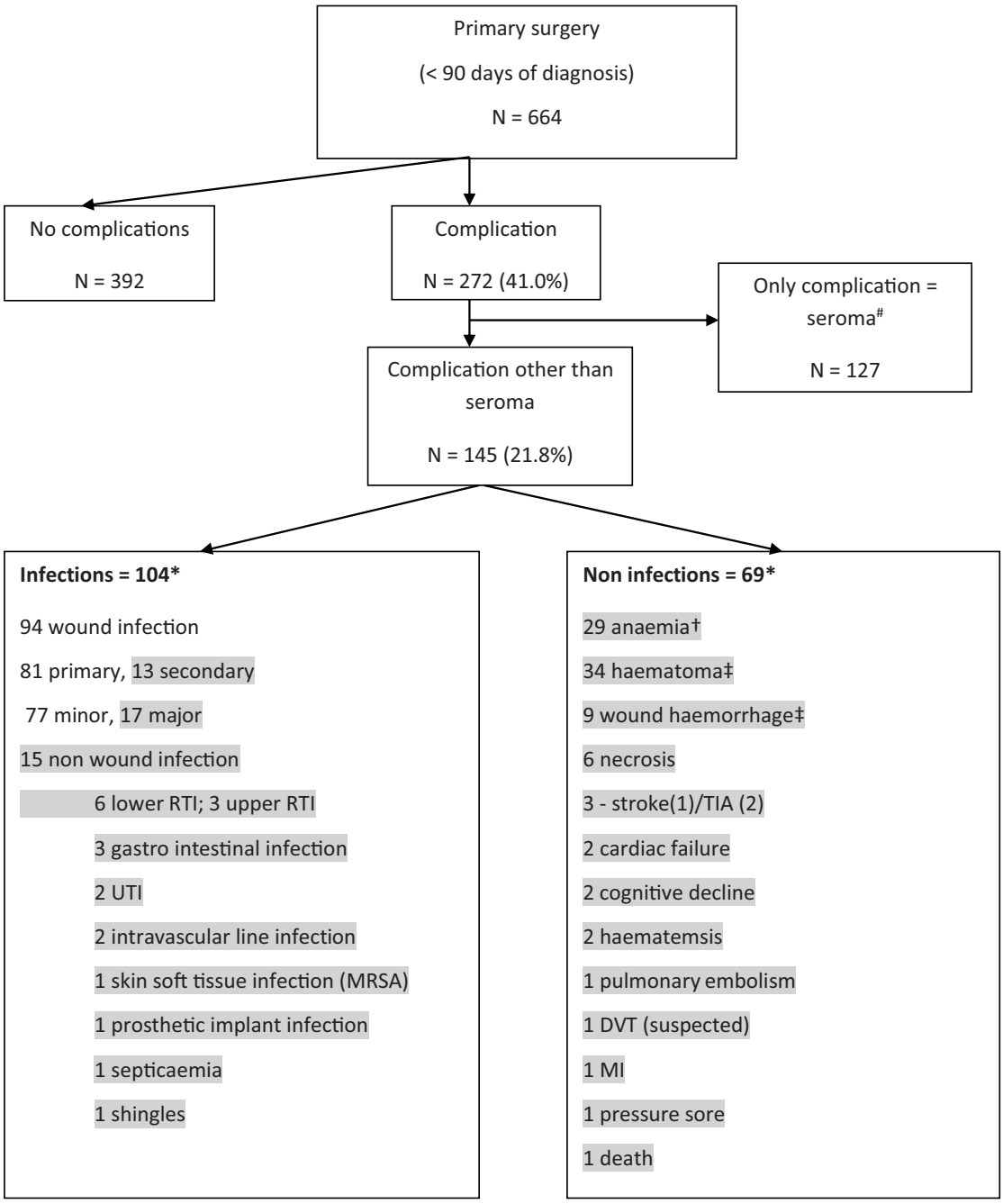
- Tumour size (mm)
- Stage
- Nodal involvement
- Grade
- Steroid Receptor Status (Oestrogen & Progesterone receptor positive or negative)

Socio-demographics

- Age
- Socio – Economic Classification[29]
- Type of hospital treated at i.e. university/teaching vs. district

a. Taken from self-report at interview if pre-operative measures not reported in case notes
b. Test Included if recorded at pre-operative assessment for at least 85% of total sample

FIGURE 21: Flow diagram of complications within 30 days of breast surgery



Classified as serious complications if warranted re admission, further procedures or delayed discharge

Only drained seromas recorded.

*Totals not summative. Infections based on the national prevalence survey of hospital acquired infections[19]. Non infections based on a checklist developed from the East Anglian Hip Fracture Audit[16] & Pre-operative Assessment of Cancer in the Elderly Project[14].

† Patients with low haemoglobin (<11.8g/L) pre-operatively were not included unless post-operative blood transfusion. ‡ 6 cases recorded as both hematoma and wound haemorrhage counted as one complication as insufficient information recorded in case notes to distinguish.

TABLE 51: Surgery, socio demographics and tumour characteristics by 30 day surgical complications

Variable	Category	n	Percent	All complications - Count		Serious complications - ≥1		
				Mean (SD)	P*	n	Percent	P*
Primary surgery	Mastectomy	329	49.5	0.80 (0.95)		26	7.9	
	WLE	335	50.5	0.38 (0.68)	**<0.001**[e]	17	5.1	0.139[b]
Axillary Node Procedure†	SNB only	397	59.8	0.45 (0.74)		19	4.8	
	ANS	262	39.5	0.80 (0.97)		24	9.2	
	No ANP	5	0.8	0.20 (0.45)	**<0.001**[e]	0	0.0	0.087[c]
Age group (years)	70-74	257	38.7	0.55 (0.81)		11	4.3	
	75-79	201	30.3	0.57 (0.83)		15	7.5	
	80-84	127	19.1	0.65 (0.83)		9	7.1	
	85+	79	11.9	0.65 (1.04)	0.512[e]	8	10.1	0.061[a]
Socio-economic classification	Professional	358	53.9	0.60 (0.85)		24	6.7	
	Intermediate	169	25.5	0.56 (0.84)		8	4.7	
	Manual	131	19.7	0.55 (0.79)	0.792[e]	9	6.9	0.664[c]
	Missing	6	0.9	1.00 (2.00)	0.922[e]	2	33.3	0.093[c]
Ethnicity	White	643	96.8	0.58 (0.84)		41	6.4	
	Other	14	2.1	0.71 (0.73)	0.281[e]	0	0.0	1.000[c]
	Missing	7	1.1	1.14 (1.86)	0.496[e]	2	28.6	0.093[c]
Hospital type	Teaching/Uni	287	43.2	0.55 (0.86)		17	5.9	
	District	377	56.8	0.61 (0.85)	0.189[e]	26	6.9	0.614[b]
Tumour stage	I	293	44.1	0.48 (0.78)		22	7.5	
	II & IIIa[d]	371	55.9	0.67 (0.90)	**0.001**[e]	21	5.7	0.337[b]
Nodes involved	Yes	197	29.7	0.72 (0.87)		13	6.6	
	No/NR	467	70.3	0.53 (0.84)	**<0.001**[e]	30	6.4	0.933[b]
Tumour size	≤20mm	374	56.3	0.52 (0.81)		27	7.2	
	>20≤50mm	260	39.2	0.66 (0.89)		13	5.0	
	>50mm	15	2.3	1.07 (1.10)	**0.009**[e]	2	13.3	0.203[c]
	Missing	15	2.3	0.40 (0.51)	**0.021**[e]	1	6.7	0.302[c]
Grade	1	112	16.9	0.58 (0.89)		8	7.1	
	2	347	52.3	0.57 (0.88)		25	7.2	
	3	146	22.0	0.59 (0.73)	0.541[e]	7	4.8	0.414[a]
	Missing	59	8.9	0.64 (0.92)	0.656[e]	3	5.1	0.781[c]
ER or PR Positive	Yes	555	83.6	0.59 (0.87)		35	6.3	
	No	68	10.2	0.62 (0.83)	0.585[e]	6	8.8	0.435[c]
	Missing	41	6.17	0.51 (0.71)	0.824[e]	2	4.9	0.684[c]
Total		**664**	**100%**			**43**	**6.5%**	

WLE Wide Local Excision.
SNB Sentinel Node Biopsy only. ANS Axillary Node Surgery.
ER Oestrogen Receptor. PR Progesterone Receptor
† Most extensive ANP Axillary Node Procedure.
* P values for each variable for complete data reported first followed by data including missings if relevant.
Bold p values significant at 5% level.
a. Chi squared test for trend: b. Chi squared Person: c. Fisher's exact test
d. Includes 14 patients with stage IIIa: e. Kruskal–Wallis $\chi 2$ adjusted for ties

TABLE 52: Distribution of 30 day surgical complications

Count of complications	Frequency	%
0	392	59.0
1	188	28.3
2	62	9.3
3	14	2.1
4	6	0.9
5	2	0.3
Total	**664**	**100.0**

Mean number of complications = 0.58, SD = 0.85, Variance = 0.73.
Count of complications does not follow a Poisson distribution as mean ≠ variance.

TABLE 53: Pre-operative health measures (categorical) by 30 day surgical complications

Variable	Category	n	Percent	All complications - Count		Serious complications - ≥1		
				Mean (SD)	P*	*n*	Percent	P*
Charlson Co-morbidity	0	371	55.9	0.53 (0.79)		20	5.4	
	1	179	27.0	0.59 (0.86)		9	5.0	
	2+	114	17.2	0.75 (1.02)	0.195[e]	14	12.3	**0.028**[f]
Body Mass Index	<18.5	9	1.4	0.89 (0.93)		2	22.2	
	18.5 – 24.9	201	30.3	0.48 (0.78)		11	5.5	
	25-29.9	238	35.8	0.55 (0.86)		15	6.3	
	30+	216	32.5	0.70 (0.89)	**0.019**[e]	15	6.9	0.253[c]
Smoker	No	612	92.2	0.58 (0.84)		39	6.4	
	Yes	52	7.8	0.65 (0.95)	0.761[e]	4	7.7	0.766[c]
Blood pressure (mmHg)[a]	Normal	186	28.0	0.56 (0.78)		11	5.9	
	High >140/90	411	61.9	0.59 (0.84)		25	6.1	
	Low <90/60	41	6.2	0.63 (1.07)	0.978[e]	5	12.2	0.305[c]
	Missing	26	3.9	0.65 (1.13)	0.994[e]	2	7.7	0.395[c]
Pulse (beats/min)	Normal	538	81.0	0.58 (0.85)		35	6.5	
	High ≥100	32	4.8	0.41 (0.56)		0	0.0	
	Low <60	45	6.8	0.76 (0.93)	0.226[e]	6	13.3	0.062[c]
	Missing	49	7.4	0.59 (0.91)	0.395[e]	2	4.1	0.120[c]
ECOG PS	0-1	476	71.7	0.52 (0.80)		21	4.4	
	2-4	170	25.6	0.78 (0.97)	**0.001**[e]	19	11.2	**0.002**[b]
	Missing	18	2.7	0.50 (0.62)	**0.004**[e]	3	16.7	**0.002**[c]
ASA	1-2	411	61.9	0.57 (0.82)		23	5.6	
	3-4	155	23.3	0.70 (0.95)	0.097[e]	18	11.6	**0.014**[b]
	Missing	98	14.8	0.47 (0.80)	0.054[e]	2	2.0	**0.007**[c]
6CIT cog impairment	≤ 7 none	518	78.0	0.58 (0.85)		35	6.8	
	>7 mild/mod	76	11.5	0.61 (0.87)	0.812[e]	1	1.3	0.071[c]
	Missing	70	10.5	0.59 (0.88)	0.971[e]	7	10.0	0.061[c]
Blood results[d]								
Haemoglobin	Low	75	11.3	0.75 (0.97)		9	12.0	
	Normal	482	72.6	0.52 (0.80)		21	4.4	
	High	43	6.5	0.72 (0.77)	**0.016**[e]	5	11.6	**0.008**[c]
	Missing	64	9.6	0.78 (1.05)	**0.014**[e]	8	12.5	**0.003**[c]
Platelets	Low	13	2.0	0.85 (1.07)		3	23.1	
	Normal	555	83.6	0.56 (0.82)		32	5.8	
	High	21	3.2	0.24 (0.54)	0.094[e]	0	0.0	**0.042**[c]
	Missing	75	11.3	0.80 (1.07)	0.055[e]	8	10.7	**0.032**[c]
Total		**664**	**100%**	**0.59 (0.88)**		**43**	**6.5%**	

ECOG-PS Eastern Co-operative Oncology Group – Performance Status 0-5 categories indicating decreasing functional status. ASA American Society of Anaesthesiologists physical status classification system. 6CIT 6 Item Cognitive Impairment Test (scale 0-28: increase indicated worse cognitive impairment 0-7 indicates normal)

a. blood pressure classed as high or low based on limits for hypertension[60] and hypotension[61]

b. Chi squared Person: c. Fisher's exact test

d. 9 blood results investigated. Only reported if significantly associated with complications P<0.05. Neutrophils, Lymphocytes, Sodium, Potassium, Urea, Creatinine and White blood cells therefore not reported. Classification for blood results were based on the National Pathology Harmonisation Standardisation project[26;27]

e. Kruskal–Wallis $\chi 2$ adjusted for ties:

f. Chi squared test for trend

*P values for each variable for complete data reported first followed by data including missings if relevant. Bold p values significant at 5% level. No variables retained significance once Bonferroni's correction applied at α/number of tests = 0.05/46 = 0.001.

TABLE 54: Pre-operative health measures (continuous) by 30 day surgical complications*

Variable	n	All complications - Count			Serious complications - ≥1		
		IRR[a]	95% CI	P	OR[b]	95% CI	P
ELPHS ADL Functional Status 1-4 increase = worse							
Basic ADLs	661	1.37	1.12 - 1.68	0.002	2.08	1.25 - 3.47	0.005
Instrumental ADLs	648	1.26	1.11 - 1.43	<0.001	1.65	1.15 - 2.36	0.006
SF12 PCS, 1-100 inc = better	648	0.98	0.98-0.99	<0.001	0.97	0.94 - 0.99	0.006
EORTC C30 Function Scales, 1-100, increase = better							
Global QoL	638	0.99	0.99 - 1.00	0.002	0.98	0.97 - 0.99	0.001
Physical	656	0.99	0.99 - 1.00	<0.001	0.98	0.97 - 0.99	<0.001
Role	652	0.99	0.99 - 1.00	<0.001	0.98	0.97 - 0.99	<0.001
Cognitive	652	0.99	0.99 - 1.00	0.028	-	-	-
Social	643	0.99	0.99 - 1.00	0.001	-	-	-
EORTC C30 Symptom Scales, 1-100, increase = worse							
Fatigue	652	1.01	1.00 - 1.01	0.001	1.02	1.01 - 1.04	<0.001
Pain	655	1.01	1.00 - 1.01	<0.001	1.01	1.00 - 1.02	0.025
Dyspnoea	655	1.01	1.00 - 1.01	0.003	1.01	1.00 - 1.02	0.027
Constipation	652	-	-	-	1.01	1.00 - 1.02	0.026
Appetite Loss	654	-	-	-	1.01	1.00 - 1.02	0.044
Pulse (beats/minute)	615	-	-	-	0.96	0.93 - 0.98	0.002
Blood results							
Sodium (mmol/l)	613	-	-	-	0.89	0.82 - 0.98	0.012
Potassium(mmol/l)	608	-	-	-	2.53	1.20 - 5.34	0.015

a. Incident Rate Ratios generated by univariable negative binomial regression.
b. Odds Ratios generated by univariable logistic regression.
ELPHS ADL, Elderly Population Health Status Survey's Activity of Daily Living (scale 1–4: increase indicates worse functional status). Basic ADLs include basic self-care and mobility. Instrumental ADLs include more advanced activities such as housework and shopping; SF-12, Short Form 12 Physical Component Summary (scale 1–100: increase indicates better health); EORTC QLQ-C30, European Organization for Research on Treatment of Cancer Quality of Life Questionnaire (version 3) Global Quality of Life scale 1–100: increase indicates better health.
* Health measures only reported if significantly associated with complications P<0.05. Following measures therefore not reported above; EORTC QLQ-C30 Emotional Functioning, Insomnia, Financial Problems, Nausea/Vomiting and Diarrhoea; SF-12, Short Form 12 Mental Component Summary; Blood results: Urea, Creatinine, Haemoglobin, Platelets, White Blood Cells, Neutrophils, Lymphocytes
Underlined P values indicate that significance retained once Bonferroni's correction applied at α/number of tests = 0.05/46 = 0.001.

TABLE 55: Multivariable negative binomial regression model predicting count of all 30 day surgical complications (n = 622)

Variable*		Adjusted IRR‡	SE	P**	95% CI	
					Lower	Upper
Primary Surgery	WLE	(ref)	-	-	-	-
	Mastectomy	**1.642**	**0.212**	**<0.001**	**1.274**	**2.115**
Axillary Node Procedure†	SNB only	(ref)				
	ANS	**1.433**	**0.173**	**0.003**	**1.131**	**1.816**
	No ANP	0.460	0.477	0.454	0.060	3.504
EORTC Global QoL, 1-100, inc = better		0.996	0.003	0.207	0.991	1.002
EORTC Pain, 1-100, inc = worse		**1.006**	**0.002**	**0.004**	**1.002**	**1.011**
Tumour size (mm)		1.004	0.004	0.340	0.996	1.013
Constant		0.367	0.093	<0.001	0.223	0.604
Alpha		0.188	0.112		0.059	0.602

IRR Incidence Rate Ratio. SE Standard Error. CI Confidence Interval. WLE Wide Local Excision
† Most extensive ANP Axillary Node Procedure. SNB Sentinel Node Biopsy only. ANS Axillary Node Surgery.
‡Adjusted for all other variables in the table
* Health measures BMI, ECOG performance status, Haemoglobin, ELPHS ADL functional status, SF-12 Physical Component Summary, EORTC C30 scales (Physical, Role, Cognitive & Social Functions, Fatigue & Dyspnoea) not included as no significant effect in initial multivariable model. Tumour stage & nodal status were removed as they did not significantly improve fit of model. **P-values <0.05 are shown in bold.

TABLE 56: Multivariable logistic regression model predicting ≥ 1 serious complication at 30 days post-surgery (n = 537)

Variable*		Adjusted OR‡	SE	P**	95% CI	
					Lower	Upper
Primary Surgery	WLE	(ref)				
	Mastectomy	1.041	0.425	0.922	0.467	2.317
Axillary Node Procedure†	SNB only	(ref)				
	ANS	1.748	0.697	0.162	0.800	3.820
Platelets	Normal/high#	(ref)				
	Low	**4.189**	**3.009**	**0.046**	**1.025**	**17.123**
Pulse (beats/minute)		**0.957**	**0.016**	**0.010**	**0.926**	**0.990**
EORTC Fatigue (1-100, inc= worse)		**1.019**	**0.007**	**0.004**	**1.006**	**1.033**
Constant		0.635	0.810	0.722	0.052	7.753

OR Odds Ratio. SE Standard Error. CI Confidence Interval.
† Most extensive ANP Axillary Node Procedure. SNB Sentinel Node Biopsy only. ANS Axillary Node Surgery. None of the 5 patients having no ANP retained in the final model
‡Adjusted for all other variables in the table
Retained 19 cases with high platelets amalgamated with 555 cases with normal platelets as high category omitted due to lack of events
* Charlson Co-morbidity, ECOG performance status, Haemoglobin, ELPHS ADL functional status, ASA, Potassium, SF-12 Physical Component Summary and EORTC C30 scales (Global QoL, Physical Function, Role Function, Pain, Dyspnoea, Constipation, Appetite Loss) not included as no significant effect in initial multivariable model. Sodium removed from model as it produced VIFs >100.
**P-values <0.05 are shown in bold.
Goodness of fit test χ^2 Hosmer-Lemeshow = 7.34: d.f. = 8; P = 0.500
Area under Receiver Operator Characteristics curve = 0.745
Sensitivity & Specificity 71.9%, False positive & negative rate 28.1% (probability cutpoint set to 0.062742)

References

(1) Office of National Statistics. Cancer statistics registrations: Registrations of cancer diagnosed in 2011, England. Series MB1 No. 42. www.statistics.gov.uk . 2011.

(2) Moody H. Aging: Concepts and controversies. Thousand Oaks, California: Pine Forge Press; 2009.

(3) Association of Breast Surgeons at British Association of Surgical Oncologists. Surgical guidelines for the management of breast cancer. European Journal of Surgical Oncology.35 Suppl 1:1-22. 2009.

(4) National Institute for Clinical Excellence. Early and locally advanced breast cancer: diagnosis and treatment. 2009. London.

(5) Lavelle K, Downing A, Thomas JD, Lawrence G, Forman D, Oliver SE. Are lover rates of surgery amongst older women with breast cancer in the UK explained by co-morbidity? *British Journal of Cancer* 2012; **107**:1175-1180.

(6) Lawrence G, Kearins O, Lagord C, Cheung S, Sidhu J, Sagar C. The Second All Breast Cancer Report. 2011. National Cancer Intelligence Network.

(7) Lavelle K, Sowerbutts A, Bundred N, Pilling M, Degner L, Stockton C *et al*. Is lack of surgery for older breast cancer patients in the UK explained by patient choice or poor health? A prospective cohort study. *British Journal of Cancer* 2014; **110**:573-583.

(8) Balducci L, Extermann M, Carreca I. Management of breast cancer in the older woman. *Cancer Control* 2001; **8**:431-441.

(9) Ring A, Reed M, Leonard R, Kunkler I, Muss H, Wildiers H *et al*. The treatment of early breast cancer in women over the age of 70. *British Journal of Cancer* 2011; **105**(2):189-193.

(10) Bilimoria KY, Liu Y, Paruch JL, Zhou L, Kmiecik TE, Ko CY *et al*. Development and evaluation of the universal ACS NSQIP surgical risk calculator: a decision aid and informed consent tool for patients and surgeons. *Journal of the American College of Surgeons* 2013; **217**(5):833-842.

(11) de Blacam C, Ogunleye A, Momoh A, Colakoglu S, Tobias A, Sharma R *et al*. High body mass index and smoking predict morbidity in breast cancer surgery: a multivariate analysis of 26,988 patients from the national surgical quality improvement program database. *Annals of Surgery* 2012; **225**(3):551-555

(12) Shah N, Hamilton M. Clinical review: Can we predict which patients are at risk of complications following surgery? *Critical Care* 2013; **17**(226).

(13) Biganzoli L, Wildiers H, Oakman C, Marotti L, Loibl S, Kunkler I *et al*. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). [Review]. *Lancet Oncology* 2012; **13**(4):e148-e160.

(14) Audisio RA, Pope D, Ramesh HS, Gennari R, van Leeuwen BL, West C *et al*. Shall we operate? Preoperative assessment in elderly cancer patients (PACE) can help. A SIOG surgical task force prospective study. *Critical Reviews in Oncology-Hematology* 2008; **65**(2):156-163.

(15) Audisio RA, Zbar AP, Jaklitsch MT. Surgical management of oncogeriatric patients. [Review] [73 refs]. *Journal of Clinical Oncology* 2007; **25**(14):1924-1929.

(16) Todd CJ, Freeman CJ, Camilleri-Ferrante C, Palmer CR, Hyder A, Laxton CE *et al*. Differences in mortality after fracture of hip: the east Anglian audit. *BMJ* 1995; **310**(6984):904-908.

(17) Forouhi P, Dixon JM, Leonard RC, Chetty U. Prospective randomized study of surgical morbidity following primary systemic therapy for breast cancer. *British Journal of Surgery* 1995; **82**(1):79-82.

(18) O'Brien W, Hasselgren PO, Hummel RP, Coith R, Hyams D, Kurtzman L *et al*. Comparison of postoperative wound complications and early cancer recurrence between patients undergoing mastectomy with or without immediate breast reconstruction. *American Journal of Surgery* 1993; **166**(1):1-5.

(19) Steering Group of the Second National Prevalence Survey. National prevalence survey of hospital acquired infections: definitions. A preliminary report of the Steering Group of the Second National Prevalence Survey. *Journal of Hospital Infection* 1993; **24**(1):69-76.

(20) Marla S, McMillan DC, Stallard S. Factors influencing postoperative length of hospital stay after breast cancer surgery. *Breast* 2013; **22**(3):289-294.

(21) Department of Health. Matectomy Recovery. NHS Choices. 2012. Available from: URL:http://www.nhs.uk/Conditions/Mastectomy/Pages/Recovery.aspx

(22) Haywood K, Garratt A, Schmidt L, Mackintosh A, Fitzpatrick R. Health status and quality of life in older people: A structured reiew of patient-assessed health instruments. 200. London, Department of Health.

(23) Sturgis P, Thomas R, Purdon S, Bridgewood A, Dodd T. Comparative Review and Assessment of Key Health State Measures of the General Population. 2001. London, Department of Health.

(24) Lavelle K, Moran A, Howell A, Bundred N, Campbell M, Todd C. Older women with operable breast cancer are less likely to have surgery. *British Journal of Surgery* 2007; **94**(10):1209-1215.

(25) Mandelblatt JS, Hadley J, Kerner JF, Schulman KA, Gold K, Dunmore-Griffith J *et al*. Patterns of breast carcinoma treatment in older women: patient preference and clinical and physician influences. *Cancer* 2000; **89**(3):561-573.

(26) Berg J. The approach to pathology harmony in the UK. *The Clinical Biochemist Reviews* 2012; **33**(3):89-93.

(27) Clinical Laboratory Medicine RL&BUHHT. Blood Sciences. 2014. Available from: URL:http://pathlabs.rlbuht.nhs.uk/home.htm

(28) UICC. TNM Classification of Malignant Tumours, 7th Edition. Oxford: Wiley-Blackwell; 2009.

(29) Office of National Statistics. The National Statistics Socio-Economic Classification (NS-SEC rebased on the SOC2010). [2013 Available from: URL:http://www.ons.gov.uk/ons/guide-method/classifications/current-standard-classifications/soc2010/soc2010-volume-3-ns-sec--rebased-on-soc2010--user-manual/index.html

(30) Office of National Statistics. Ethnic group (2001 Census). 2010. Available from: URL:http://data.gov.uk/dataset/ethnic_group_2001_census

(31) Landis J, Koch G. The measurement of observer agreement for categorical data , **33,** 159-174. *Biometrics* 1977; **33**:159-174.

(32) Hosmer and Lemeshow. Applied Logistic Regression. 2nd ed. New York: John Wiley; 2000.

(33) El-Tamer MB, Ward BM, Schifftner T, Neumayer L, Khuri S, Henderson W. Morbidity and mortality following breast cancer surgery in women: national benchmarks for standards of care. *Annals of Surgery* 2007; **245**(5):665-671.

(34) Kutner M, Nachtsheim C, Neter J. Applied Linear Regression Models, 4th edition. 4th Edition ed. New York: McGraw-Hill Irwin; 2004.

(35) StataCorp. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP.; 2011.

(36) Tabachnick B, Fidell L. Using Multivariate Statistics (Fourth Edition). 2001.

(37) Bland M. An introduction to medical statistics. 3rd Edition. Oxford: Oxford University Press; 2005.

(38) Peduzzi P, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *Journal of Clinical Epidemiology* 1996; **49**(12):1373-1379.

(39) Vittinghoff E, McCulloch C. Relaxing the rule of ten events per variable in logistic and Cox regression. *Am J Epidemiol* 2007; **165**:710-718.

(40) SIGN. Breast cancer in women: a national clinical guideline recommended for use in Scotland. 1998. Edinburgh, Royal College of Physicians.

(41) Bland JM, Altman DG. Multiple significance tests: the Bonferroni method. *BMJ* 1995; **310**(6973):170.

(42) Vitug AF, Newman LA. Complications in breast surgery. [Review] [94 refs]. *Surgical Clinics of North America* /20; **87**(2):431-451.

(43) Chatzidaki P, Mellos C, Briese V, Mylonas I. Perioperative complications of breast cancer surgery in elderly women (>80 years). *Annals of Surgical Oncology* 2011; **18**(4):923-931.

(44) Wyld L, Garg D, Kumar I, Brown H, Reed M. Stage and treatment variation with age in postmenopausal women with breast caner: compliance with guidelines. *British Journal of Cancer* 2004; **90**:1486-1491.

(45) de Glas NA, Kiderlen M, Bastiaannet E, de Craen AJ, van de Water W, van de Velde CJ *et al*. Postoperative complications and survival of elderly breast cancer patients: a FOCUS study analysis. *Breast Cancer Research & Treatment* 2013; **138**(2):561-569.

(46) Houterman S, Janssen-Heijnen ML, Verheij CD, Louwman WJ, Vreugdenhil G, van der Sangen MJ *et al*. Comorbidity has negligible impact on treatment and complications but influences survival in breast cancer patients. *British Journal of Cancer* 2004; **90**(12):2332-2337.

(47) Rocco N, Rispoli C, Pagano G, Rengo G, Compagna R, Danzi M *et al*. Breast cancer surgery in elderly patients: postoperative complications and survival. *BMC Surgery* 2013; **13**(Suppl 2):S25.

(48) Nieto A, Lozano M, Moro MT, Keller J, Carralafuente C. Determinants of wound infections after surgery for breast cancer. *Zentralblatt fur Gynakologie* 2002; **124**(8-9):429-433.

(49) Vinton AL, Traverso LW, Jolly PC. Wound complications after modified radical mastectomy compared with tylectomy with axillary lymph node dissection. *American Journal of Surgery* 1991; **161**(5):584-588.

(50) Sorensen LT, Horby J, Friis E, Pilsgaard B, Jorgensen T. Smoking as a risk factor for wound healing and infection in breast cancer surgery.[Erratum appears in Eur J Surg Oncol. 2003 Jun;29(5):482]. *European Journal of Surgical Oncology* 2002; **28**(8):815-820.

(51) Bruce J, Thornton AJ, Scott NW, Marfizo S, Powell R, Johnston M *et al*. Chronic preoperative pain and psychological robustness predict acute postoperative pain outcomes after surgery for breast cancer. *British Journal of Cancer* 2012; **107**(6):937-946.

(52) Sugarman J, McCrory DC, Hubal RC. Getting meaningful informed consent from older adults: a structured literature review of empirical research. [Review] [118 refs]. *Journal of the American Geriatrics Society* 1998; **46**(4):517-524.

(53) Charlson M, Pompei P, Ales K, MacKenzie C. A new method of classifying prognostic co-morbidity in longitudinal studies: development and validation. *Journal of Chronic Disease* 1987; **40**(5):373-383.

(54) American Society of Anesthesiologists. ASA Physical Status Classification System. 2014. Available from: URL:http://www.asahq.org/For-Members/Clinical-Information/ASA-Physical-Status-Classification-System.aspx

(55) Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET *et al*. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *American Journal of Clinical Oncology* 1982; **5**(6):649-655.

(56) Sharples LD, Todd CJ, Caine N, Tait S. Measurement properties of the Nottingham Health Profile and Short Form 36 health status measures in a population sample of elderly people living at home: results from ELPHS. *British Journal of Health Psychology* 2000; **5**:217-233.

(57) Ware J, Konsinski M, Turner-Bowker D, Gandek B. How to Score Version 2 of the SF-12(R) Health Survey (with a Supplement Documenting Version 1). QualityMetric Incorporated; 2002.

(58) Osoba D, Aaronson N, Zee B, Sprangers M, te VA. Modification of the EORTC QLQ-C30 (version 2.0) based on content validity and reliability testing in large samples of patients with cancer. The Study Group on Quality of Life of the EORTC and the Symptom Control and Quality of Life Committees of the NCI of Canada Clinical Trials Group. *Quality of Life Research* 1997; **6**(2):103-108.

(59) Brooke P, Bullock R. Validation of a 6 item cognitive impairment test with a view to primary care usage. *International Journal of Geriatric Psychiatry* 1999; **14**(11):936-940.

(60) National Institute for Clinical Excellence. Hypertension: Clinical managment of primary hypertension in adults. 2011. London.

(61) NHS Choices. Low blood pressure (hypotention). 2013. Available from: URL:http://www.nhs.uk/conditions/blood-pressure-(low)/Pages/Introduction.aspx

Appendix 3 The impact of health and patient choice on receipt of surgery, radiotherapy or chemotherapy in breast cancer patients on short-term survival of older breast cancer patients in the UK: a prospective cohort study

Abstract

Introduction: Lack of surgery for older breast cancer patients may reduce breast cancer survival. Few previous studies adjust for comorbidity and tumour characteristics which also effect survival.

Methods: As part of a wider programme investigating older breast cancer patients' treatment, analyses of short-term survival (mean 3.8 years) was undertaken for 910 breast cancer patients aged ≥65 years diagnosed at 22 English hospitals from 1/7/10-31/12/12. Primary outcome is breast cancer specific survival (at 5/2/16). Independent variables include surgery, comorbidity, functional status and tumour characteristics recorded from patient interview (at diagnosis) and case note review (90 days post-diagnosis). Data analyses included Cox's multiple regression.

Results: Patients who had primary surgery (vs. those who did not) had 0.36 times the hazard of dying of breast cancer (95% CI: 0.20-0.66, p=0.001) adjusting for other factors. In univariate analysis women aged ≥85 years had an increased hazard of breast cancer death compared to 65-69 year olds (HR 4.02, 95% CI: 1.61-10.01, p=0.003). However when adjusted for surgery, tumour characteristics and general health this was only borderline significant at 5% level (p=0.053).

Conclusions: Surgery for older breast cancer patients reduces the hazard of breast cancer death by a third, independent of age, comorbidity and tumour characteristics.

Introduction

Older women in the UK are less likely to have primary surgery for early operable breast cancer compared to younger postmenopausal women[1;2]. Previous studies demonstrate reduced odds of surgery from the age of 70 years and older[3;4]. The King's Fund reports that improved management of older cancer patients could reduce overall cancer mortality in England[5]. The impact of lack of surgery on older patients' survival needs to be investigated. There is good evidence that poor survival is a particular problem for older breast cancer patients in the UK. Moller *et al* (2010) found that the 5 year relative survival for women aged ≥80 years is 61% in UK compared to 74% in Norway & Sweden. Moreover the excess death rate for British breast cancer patients increases dramatically with age group compared to those in Norway and Sweden, particularly in the first year after diagnosis[6]. They conclude that this 'leads to important questions about the adequacy of care provided for the oldest patients.' However, Moller *et al* did not investigate the effect of access to treatment on survival. Moreover, the proportion of patients with co-morbidities or frailty, and later stage breast cancer increase with age and both of these factors may also effect survival.

Guidelines state that adjuvant therapy should be considered for all patients with early invasive breast cancer (NICE, 2009: 1.65). Radiotherapy is strongly recommended following breast conserving surgery and should be offered to patients after mastectomy who are at high risk of recurrence (NICE, 2009: 1.11.1 & 1.11.3). Although recommendations for chemotherapy are less clear cut, it is advised that the decision should be based on prognostic and predictive factors and the potential benefits and side effects of treatment (NICE, 2009: 1.6.6). Guidelines converge in stating that treatment of breast cancer patients should be based on tumour characteristics, patient health and choice. The role of age in considering treatment options is more contested; NICE guidelines (2009) state that breast cancer treatments should be offered to patients with early stage cancer irrespective of age whereas European Society for Medical Oncology guidelines (2015) recommend taking age into account along with other factors in breast cancer treatment planning. EMSO states breast cancer treatment "should be based on the tumour burden/location (size and location of primary tumour, number of lesions, extent of lymph node involvement) and biology (pathology, including biomarkers and gene expression), as well as the age and general health status of the patient.

This study aims to investigate the impact of primary surgery, or lack thereof, on survival of women aged ≥65 years diagnosed with breast cancer in the UK, adjusting for pre-treatment measures of health and tumour characteristics.

Method

Study Design. This study followed an established cohort of patients aged ≥65 years to three years after diagnosis. At diagnosis all patients had early stage (stage 1 to IIIa) invasive breast cancer and were recruited from 22 Trusts in England between 01/07/2010 to 31/03/2013; more details of methods, inclusion and exclusion criteria can be found elsewhere (Lavelle *et al*, 2014). The primary outcomes were curative adjuvant treatment, either radiotherapy or chemotherapy within 12 months of diagnosis, adjusting for health measures, type of primary surgery, tumour characteristics demographics and patient choice.

For more details on explanatory variables see Lavelle *et al* (2014), but in brief measures of health were Charleson Index of Co-morbidity (Charlson *et al,* 1987), Elderly Population Health Status Survey's (ELPHS), ADL (Sharpes *et al,* 2002) functional status measure and Eastern Co-operative Oncology Group-Performance Status (Oken *et al*, 1982). Primary surgery was classed either

mastectomy or wide local excision within 3 months of diagnosis. Tumour characteristics, based on biopsy, imaging and clinical assessment, were pre-surgical assessment of stage, grade, nodal and steroid receptor status (oestrogen and progesterone). ((cTNM (UICC, 2009)). Socioeconomic classification was measured using the Office of National Statistics Socio-Economic Classification (ONS, Office of National Statistics, 2013).

Patient choice: Patient choice was measured using Degner *et al* (2007) control preferences scale (CPS). This is a five point scale where the patient identifies if they were active, collaborative or passive in the treatment decision. The patient has 2 options if they considered themselves active in the decision; I made the final decision about which treatment I would receive or I made the final decision about my treatment after seriously considering my doctor's opinion. They have 1 choice for collaborative; my doctor and I shared responsibility for deciding which treatment was best for me. If the patient thinks the doctor made the treatment decision and they were passive they have 2 choices; my doctor made the final decision about which treatment would be used but seriously considered my opinion or my doctor made the final decision about which treatment I would receive.. Choice was measured for both the chemotherapy and radiotherapy treatment decision. The CPS can only be used if a treatment decision was discussed and therefore patients were given the option of indicating they were given no choice as chemotherapy or radiotherapy treatment was not discussed with them.

Data collection: A case note review was carried out 3 years post-diagnosis using a proforma developed for the project. Data was extracted on radiotherapy and chemotherapy, which treatments were received. Patients were classed as receiving curative adjuvant treatment if they initially underwent primary surgery (within 3 months of diagnosis) and were treated with radiotherapy and/or chemotherapy (within 12 months of diagnosis) and they did not have metastatic disease or a recurrence of breast cancer. Inter-rater agreement was checked for 10% of the pro-formas and satisfied Kappa > 0.6 showing substantial to perfect agreement (Landis and Koch, 1977).

Surviving patients who were not precluded from further contact (e.g. due to cognitive impairment) were surveyed for role in the adjuvant treatment decision using the CPS (Degner *et al,* 1997). Surveys

and a freepost envelope for survey return were posted where possible at 3 years post diagnosis (-/+ 2 weeks). However, due to timing of the receipt of project funding 39% patients were surveyed at 3-4 years post diagnosis. If a patient did not reply within 2 weeks a further survey was posted out. If again no reply was received in 2 weeks the patient was contacted by telephone and offered the option of completing the survey by telephone at a convenient time. If patients did not want to complete the questionnaire and did not want any further contact, they were offered the option of returning the blank survey in the freepost envelope. Postal surveys were sent out to 628 of the sample (91.3%) and returned by 513 (81.7% return rate). Ten per cent of case note review proformas and 10% of patient surveys were checked for data input errors. Data input errors were less than 0.3% and therefore no further checking was necessary.

Sample size. As this study was following up an existing cohort, the sample size was circumscribed to the patients that were originally recruited. Initially 944 patients were recruited from 01/07/2010 to 31/03/2013. For this project patients recruited after 31/12/12 were excluded in order that all patients would have at least 3 years follow up at case note review. Other reasons for exclusion were that the case notes were not available (34 patients), patients died (16) or moved away (55 patients) within 12 months. This study was concerned with adjuvant treatment in addition to primary surgery so all patients who were not treated with surgery were removed from the sample. Following these exclusions, the final sample was 688 patients (figure 1).

Analyses: Explanatory variables were investigated in univariable analysis using Pearson's χ^2 test, Fisher's exact test, and χ^2 test for trend. Logistic regression analyses of receipt of adjuvant chemotherapy and radiotherapy, adjusted for health measures, patient preference, tumour characteristics and demographic variables. Tumour characteristics include those used to determine chemotherapy status in clinical guidelines (tumour stage, grade, nodal and steroid receptor status). As clinical guidelines indicate that radiotherapy is necessary after lumpectomy but not always following mastectomy (NICE, 2009), multivariate logistic regression predicting receipt of radiotherapy was also

limited to the number of patients in the cohort receiving lumpectomy. Logistic regression models should have around ten patients for each explanatory variable for both categories of the dependent variable (Bland, 2005; Peduzzi, 1996), although in other scenarios it has been shown that five patients for each explanatory variable is sufficient (Vittinghoff, 2007). To help meet this guidance, variables in the multivariate models were limited to those essential to the core research question and with significant coefficients (at the 5 per cent level) in the univariate analyses. Both the main and nested models were tested for goodness of fit (Hosmer & Lemeshow, 2000), variance inflation factors and discrimination (area under receiver operating characteristic curve). Data were analysed using STATA version 12.

Survival analysis is based on 910 members of the cohort with a diagnosis date up to 31/12/12 in order that all participants had > 3 years survival at the time of analysis. As breast cancer mortality in the UK rises sharply from the age of 70 years, 65-69 year olds are included here as a reference group[4,7]. Data on surgical treatment, pre-operative health measures and tumour characteristics were collected by patient interview (at diagnosis/ before surgery if undertaken) and/or case note review (at 3 months post diagnosis)[1]. Surgery rates did not differ significantly between breast units[1]. The core variables used in this survival analysis were collected for the entire sample, including 136 eligible participants aged 65-69 years. All participants were followed up to a census date of 5/2/16 i.e. 37 months from the last participant entering the study. The primary end point is breast cancer specific mortality, which was defined as time from diagnosis to death due to breast cancer based on underlying cause of death provided by the Health and Social Care Information Centre. Participants dying from other causes were censored at their date of death.

Independent variables include undergoing primary surgery (mastectomy or wide local excision) within 90 days of diagnosis, age group, socio-economic status[8], co-morbidity (Charlson Index 0, 1, 2+)[9] and functional status group (ELPHS ADL 1-2 vs. 3-4)[10]. Pre-treatment assessment of steroid receptor status, grade and tumour stage (1 vs. 2-3a) based on clinical, imaging and fine needle/core biopsy assessments were recorded[11]. Expected and observed deaths were compared using the log rank test (α <0.05). Cox's proportional hazards regression was used to examine the effect of surgery on survival adjusting for age, tumour stage, grade, steroid receptor status, co-morbidity and functional status. Data were analysed using Stata version 12.1[12]. Ethical approval was granted by the UK NHS National Research Ethics Service (10/H1014/32 & 33).

Results

Adjuvant Therapy. To analyses adjuvant therapy 688 patients were included all of whom had primary surgery (45.1% mastectomy and 54.9% wide local excision). Of those who had primary surgery, 90 (13.1% 95% CI: 10.7-15.8) also had chemotherapy and 453 (65.8% 95% CI: 62.2-69.4) radiotherapy. The mean age of the patients in the sample was 75.7 years (95% CI: 75.2-76.1) (table 1). Just over half the patients had a Charlson Co-morbidity score of 0, 90% had independent functional status and 74.3% had a performance status of 0-1. The stage of disease in 48.8% of patients was 1 and 51.2% patients had stage 2-3a disease. The majority of patients (83.7%) had an oestrogen or progesterone positive tumour and most had grade 2 disease (53.2%).

Chemotherapy : The univariable analysis showed unsurprisingly that significantly more patients in the 65-69 year age group had chemotherapy compared patients aged 85 years and older, 25.4% compared to 1.6% (P<0.001) (Table1). Chemotherapy rates were also significantly higher for patients with stage 2 or 3a disease (18.5%) compared to stage 1 (7.4%) (P <0.001) and oestrogen or progesterone negative tumours (36.9%) compared to oestrogen and progesterone positive tumours (10.9%) (P<0.001). The proportion of patients receiving chemotherapy was 18% more in patients with a grade 3 tumour compared to patients with a grade 2 tumour, and over 27% compared to patients with a grade 1 tumour (P<0.001). Patients were significantly less likely to receive chemotherapy if they perceived that the choice of having or not having chemotherapy was not discussed with them (2.8%) compared to patients who stated they were given a choice but did not indicate the role they took (37.5%) or those active (43.8%) or passive (50.0%) in the treatment decision (P<0.001). In the univariate analysis, measures of health and functional status were not significantly associated with receiving chemotherapy.

TABLE 57 Baseline characteristics and adjuvant treatment (n = 688)

Baseline Characteristics				Adjuvant Treatment					
				Chemotherapy			Radiotherapy		
Variable	**Category**	**n**	**%**	**n**	**%**	**P***	**n**	**%**	**P***
Age group (Years)	65-69	118	17.2	30	25.4		88	74.6	
	70-74	233	33.9	45	19.3		176	75.5	
	75-79	175	25.4	12	6.9		107	61.1	
	80-84	99	14.4	2	2.0		55	55.6	
	85+	63	9.2	1	1.6	**<0.001**[c]	27	42.9	**<0.001**[c]
Co-morbidity (Charlson)	0	383	55.7	54	14.1		258	67.4	
	1+	305	44.3	36	11.8	0.375[d]	195	63.9	0.346[d]
Functional status	Independent (1-2)	619	90.0	86	13.9		422	68.2	
	Dependent (3-4)	67	9.7	4	6.0	0.068[d]	29	43.3	**<0.001**[d]
	Missing	2	0.3	0	0	0.137[e]	2	100	**<0.001**[e]
Performance status	0-1	511	74.3	72	14.1		357	69.9	
	2+	163	23.7	14	8.6	0.067[d]	86	52.8	**<0.001**[d]
	Missing	14	2.0	4	28.6	**0.033**[e]	10	71.4	**<0.001**[d]
Surgery[a]	Mastectomy	310	45.1	50	16.1		100	32.3	
	Wide Local Excision	378	54.9	40	10.6	**0.032**[d]	353	93.4	**<0.001**[d]
Stage	1	336	48.8	25	7.4		245	72.9	
	2 & 3a	352	51.2	65	18.5	**<0.001**[d]	208	59.1	**<0.001**[d]
Nodal involvement	No/not recorded	501	72.8	32	9.5		226	67.3	
	Yes	187	27.2	39	31.2	**<0.001**[d]	87	69.6	0.633
ER or PR positive	Yes	576	83.7	63	10.9		380	66.0	
	No	65	9.5	24	36.9	**<0.001**[d]	44	67.7	0.781[d]
	Missing	47	6.8	3	6.4	**<0.001**[e]	29	61.7	0.794[d]
Grade	1	131	19.0	3	2.3		94	71.8	
	2	366	53.2	42	11.5		245	66.9	
	3	133	19.3	40	30.1	**<0.001**[e]	87	65.4	0.497[d]
	Missing	58	8.4	5	8.6	**<0.001**[e]	27	46.6	**0.008**[d]
Socioeconomic classification	Professional	379	55.1	56	14.8		251	66.2	
	Intermediate	180	26.2	23	12.8		113	62.8	
	Manual	125	18.2	11	8.8	0.227[d]	85	68.0	0.600[d]
	Missing	4	0.6	0.0	0.0	0.349[e]	4	100	0.453[e]
Chemotherapy choice	Active/collaborative	80	11.6	35	43.8				
	Passive	48	7.0	24	50.0				
	No choice	325	47.2	9	2.8				
	Choice[b]	8	1.2	3	37.5	**<0.001**[e]			
	Missing/Died	227	33.0	19	8.37	**<0.001**[e]			
Radiotherapy choice	Active/collaborative	200	29.1				162	81.0	
	Passive	108	15.7				98	90.7	
	No choice	156	22.7				61	39.1	
	Choice[b]	28	4.1				22	78.6	**<0.001**[d]
	Missing/Died	196	28.5				110	56.1	**<0.001**[d]
Total		688	100	90			453		

Abbreviations: NR = Not recorded

[a]Most extensive surgery [b]Patient indicated they had a choice but did not select a role [c]χ^2 test for trend for age [d] χ^2 Pearson [e]Fisher's exact test *P values <0.05 are shown in bold

TABLE 58. Multivariable logistic regression of receiving chemotherapy (vs. not receiving chemotherapy) (unadjusted odds n = 688, adjusted odds n = 686)[a]

Variable	Category	Unadjusted odds ratio	95% CI	P value*	Adjusted odds ratio[c]	95% CI	P value*
Age	65-69	(ref)	-	-	(ref)	-	-
	70-74	0.70	0.41-1.19	0.188	0.43	0.21-0.89	**0.021**
	75-79	0.22	0.11-0.44	**<0.001**	0.06	0.02-0.16	**<0.001**
	80-84	0.06	0.01-0.26	**<0.001**	0.03	0.00-0.14	**<0.001**
	85+	0.05	0.01-0.36	**0.003**	0.02	0.00-0.15	**<0.001**
Co-morbidity	0	(ref)	-	-			
	1+	0.82	0.52-1.28	0.376			
Functional Status	Independent (1-2)	(ref)	-	-	(ref)	-	-
	Dependent (3-4)	0.39	0.14-1.11	0.078	0.28	0.08-1.07	0.058
Performance Status	0-1	(ref)		-			
	2+	0.57	0.31-1.05	0.070			
	Missing	2.44	0.74-7.98	0.141			
Surgery	Mastectomy	(ref)	-	-	(ref)	-	-
	WLE	0.62	0.39-0.96	**0.033**	0.81	0.43-1.55	0.530
Stage	1	(ref)	-	-	(ref)		
	2 & 3a	2.82	1.73-4.59	**<0.001**	2.89	1.49-5.62	**0.002**
Nodal involvement	No/NR	(ref)	-	-			
	Yes	3.2	2.04-5.06	**<0.001**			
ER & PR Positive	Yes	(ref)	-	-	(ref)		
	No	4.77	2.70-8.41	**<0.001**	1.4	0.62-3.06	0.432
	Missing	0.56	0.17-1.84	0.336	0.49	0.10-2.43	0.380
Grade	1	(ref)	-	-	(ref)		
	2	5.53	1.68-18.16	**0.005**	2.57	0.69-9.55	0.160
	3	18.35	5.51-61.13	**<0.001**	14.82	3.80-57.79	**<0.001**
	Missing	4.03	0.93-17.45	0.063	6.09	1.09-33.93	**0.039**
SEC[a]	Professional	(ref)	-	-			
	Intermediate	0.84	0.50-1.42	0.527			
	Manual	0.56	0.28-1.10	0.092			
Choice	Active/collaborative	(ref)	-	-	(ref)		
	Passive	1.29	0.63-2.64	0.493	1.44	0.61-3.41	0.408
	No choice	0.04	0.02-0.81	**<0.001**	0.05	0.02-0.14	**<0.001**
	Choice[b]	0.77	0.17-3.45	0.734	1.72	0.22-13.20	0.603
	Missing/Died	0.12	0.06-0.22	**<0.001**	0.15	0.07-0.32	**<0.001**

Abbreviations: SEC = Socioeconomic classification, ER = Oestrogen receptor positive PR = Progesterone receptor positive, WLE = Wide local excision, CI = Confidence interval, NR = Not reported

[a] SEC Missings are omitted from the model

[b] Patients indicated they were given a choice, but did not select a role

[c] Adjusted for all other variables in the column. Variables significant at 5% in univariable analyses entered into the multivariable model (axillary nodes represented within tumour stage and functional status included as representative/ most complete health measure -essential to research question). All variance inflation factors < 10. Goodness of fit test χ^2 Hosmer-Lemeshow = 5.11 d.f. = 8 P=0.746. Area under receiver operator characteristics curve= 0.922 *P values <0.05 are shown in bold

TABLE 59. Multivariable logistic regression of receiving radiotherapy (vs. not receiving radiotherapy) (unadjusted odds n = 688, adjusted odds n = 686)[a]

Variable	Category	Unadjusted odds ratio	95% CI	P value*	Adjusted odds ratio[c]	95% CI	P value*
Age	65-69	(ref)	-	-	(ref)	-	-
	70-74	1.05	0.63-1.75	0.844	1.37	0.67-2.83	0.389
	75-79	0.54	0.32-0.90	**0.018**	0.88	0.43-1.82	0.733
	80-84	0.43	0.24-0.76	**0.004**	0.98	0.43-2.23	0.962
	85+	0.26	0.13-0.49	**<0.001**	0.65	0.26-1.60	0.352
Co-morbidity	0	(ref)	-	-			
	1+	0.86	0.63-1.18	0.346			
Functional Status[a]	Independent (1-2)	(ref)	-	-	(ref)	-	-
	Dependent (3-4)	0.36	0.21-0.59	**<0.001**	0.39	0.16-0.92	**0.031**
Performance Status	0-1	(ref)	-	-	(ref)	-	-
	2+	0.48	0.34-0.69	**<0.001**	0.82	0.46-1.45	0.492
	Missing	1.08	0.33-3.49	0.900	1.27	0.24-6.68	0.777
Surgery	Mastectomy	(ref)	-	-	(ref)	-	-
	WLE	29.7	18.53-47.46	**<0.001**	38.03	20.92-69.13	**<0.001**
Stage	1	(ref)	-	-	(ref)	-	-
	2 & 3a	0.54	0.39-0.74	**<0.001**	2.24	1.30-3.83	**0.003**
Nodal Involvement	No/NR	(ref)					
	Yes	0.96	0.68-1.4	0.839			
ER & PR Positive	Yes	(ref)	-	-			
	No	1.08	0.62-1.87	0.781			
	Missing	0.83	0.45-1.53	0.554			
Grade	1	(ref)	-	-	(ref)	-	-
	2	0.80	0.51-1.24	0.310	1.00	0.52-1.92	0.999
	3	0.74	0.44-1.25	0.268	1.46	0.69-3.08	0.321
	Missing	0.34	0.18-0.65	**0.001**	0.50	0.19-1.33	0.164
SEC[a]	Professional	(ref)	-	-			
	Intermediate	0.86	0.59-1.24	0.424			
	Manual	1.08	0.70-1.67	0.715			
Choice	Active/collaborative	(ref)	-	-	(ref)	-	-
	Passive	2.30	1.10-4.82	**0.028**	2.22	0.92-5.34	0.076
	No choice	0.15	0.09-0.24	**<0.001**	0.23	0.12-0.43	**<0.001**
	Choice[b]	0.86	0.33-2.27	0.761	2.37	0.73-7.63	0.149
	Missing/Died	0.30	0.19-0.47	**<0.001**	0.51	0.28-0.92	**0.026**

Abbreviations: SEC = Socioeconomic classification, ER = Oestrogen receptor positive PR = Progesterone receptor positive, CI = Confidence interval, NR = Not Recorded

[a] Missings are omitted from the model. See table 1.

[b]Patients indicated they were given a choice, but did not select a role

[c]Adjusted for all other variables in the column. Variables entered into the multivariable model if significant at the 5% level in the univarible analyses. All variance inflation factors < 10. Goodness of fit test χ^2 Hosmer-Lemeshow = 4.18 d.f. = 8 P = 0.840. Area under receiver operator characteristics curve= 0.907

*P values <0.05 are shown in bold

TABLE 60 Multivariable logistic regression of receiving radiotherapy (vs. not receiving radiotherapy) for patients who were treated with wide local excision. (unadjusted odds n = 378, adjusted odds n = 376)

Variable[a]	Category	Unadjusted odds ratio	95% CI	P value*	Adjusted odds ratio[c]	95% CI	P value*
Age	65-69	(ref)			(ref)	-	-
	70-74	2.32	0.69-7.85	0.176	2.35	0.69-8.09	0.174
	75-79	0.90	0.29-2.81	0.860	0.92	0.29-2.91	0.884
	80-84	0.99	0.23-4.17	0.985	1.12	0.25-4.94	0.883
	85+	0.34	0.09-1.34	0.123	0.60	0.13-2.69	0.504
Functional Status[d]	Independent (1-2)	(ref)			(ref)	-	-
	Dependent (3-4)	0.27	0.09-0.78	**0.016**	0.30	0.09-0.98	**0.046**
Choice	Active/collaborative	(ref)					
	Passive	2.15	0.44-10.59	0.348			
	No choice	0.28	0.10-0.79	**0.016**			
	Choice	0.69	0.08-6.05	0.737			
	Missing/Died	0.71	0.23-2.18	0.546			
Choice	Choice[b]	(ref)			(ref)	-	-
	No choice	0.23	0.9-0.60	0.003	0.26	0.09-0.70	**0.008**
	Missing/Died	0.59	0.21-1.68	0.322	0.63	0.22-1.84	0.403

[a]Tumour characteristics omitted from model as not significant

[b]Patients perceived they had been given a choice

[c]Adjusted for all other variables in the column. All variance inflation factors < 10. Goodness of fit test χ^2 Hosmer-Lemeshow = 1.33 d.f. = 5 P=0.932. Area under receiver operator characteristics curve= 0.737

[d] Missings not included in model (n = 2)

*P values <0.05 are shown in bold

In the multivariable analysis the odds of having chemotherapy were significantly greater for those having stage 2 & 3a compared to stage 1 tumours (OR 2.89, 95% CI: 1.49-5.62) and grade 3 compared to grade 1 tumours (OR14.83, 95% CI: 3.80-57.79) (Table 2). All participants aged 70 years and older had decreased odds of chemotherapy compared to 65-69 year olds and these odds decrease with age with those aged over 85 having 0.02 times the odds of chemotherapy compared to 65-69 year olds (95% CI: 0.00-0.15). Chance of chemotherapy was not significantly different if the patients were passive in the decision compared if they were actively involved in deciding to have the treatment (P = 0.408). However, if the patient perceived that the choice of having versus not having chemotherapy was not discussed with them, the odds of having chemotherapy significantly reduced to 0.05 (95% CI: 0.02-0.14). The reduction in odds of chemotherapy for those with dependent functional status failed to reach significance at the 5% level (P = 0.063)

The model was robust; all variance inflation factors were under 10, the goodness of fit test χ^2 showed no significant difference between observed and expected values (Hosmer-Lemeshow = 5.11 d.f. = 8 P=0.746) and the area under the receiver operator characteristics was 0.92 showing excellent discrimination (Hosmer and Lemeshow, 2000).

Radiotherapy

The analysis of whether or not patients received radiotherapy was first carried out on the whole sample of 688; this included patients treated with mastectomy as well as wide local excision. In the univariate analysis, older age, dependent functional status, a performance status of 2+, and not been offered a choice significantly reduced the chance that patients would be given radiotherapy (table1). Seventy four percent of patients aged 65 to 69 years had radiotherapy compared to 42.9% of patients aged 85 years and older (P<0.001). Patients with poorer measures of health had significantly reduced chance of having radiotherapy compared to those who were healthier; dependent functional status 43.3% of patients with dependent functional status had radiotherapy compared to 68.2% independent functional status patients (P<0.001) and 52.8% of patients with performance status 2+ had

radiotherapy compared to 69.9% with a performance status of 0-1 (P<0.001). Having primary surgery of wide local excision significantly increased the chance of having radiotherapy (93.4%) compared to 32.3% for patients whose primary surgery was a mastectomy (P<0.001).

In the multivariate analysis, adjusting for health, tumour characteristics, sociodemographics and choice, age was no longer a significant factor in receiving radiotherapy (table 3). However, patients with poorer health – a dependent functional status - had less chance of receiving radiotherapy (OR 0.36 95% CI: 0.16-0.92). Also patients who perceived that they were not offered a choice had 0.23 the odds of receiving radiotherapy compared to patients who were active in the decision (95% CI: 0.12-0.43). Patients who identified as being passive in the decision had 2.21 the odds of receiving the treatment compared to those who were active (95% CI: 0.92-5.34). Additionally, patients treated with wide local excision had over 38 times the odds of having radiotherapy compared to patients having mastectomy (OR 38.03 95% CI: 20.92-69.13).

The model was robust; all variance inflation factors were under 10, in the goodness of fit χ^2 showed no significant difference between observed and expected values (Hosmer-Lemeshow = 4.18 d.f. = 8 P=0.840) and the area under the receiver operator characteristics curve was 0.907 showing excellent discrimination (Hosmer-Lemeshow, 2000).

A sub group analysis was conducted on patients treated with wide local excision, as breast cancer guidelines strongly recommend radiotherapy after wide local excision whereas it is only advisable after mastectomy if the patient is a high risk of recurrence (table 4). However, the number of patients not receiving radiotherapy following breast conserving surgery was low at 25 of 378 patients (6.61%). This meant that the number of variables the model would support was reduced. Functional status was retained in the model as the most complete measure of health, which predicted receipt of radiotherapy in the univariate analyses. As passitivity was not significant in the univariable analysis, choice was reduced to whether the patient identified that they took a role in the treatment decision compared to if they perceived that a choice was not offered to them. In the final model older age did not predict having radiotherapy after wide local excision. However those with a dependent functional status had

just a third of the odds of radiotherapy (OR 0.3 95% CI: 0.09-0.98) and patients perceiving that the option of radiotherapy was not discussed with them had around a quarter of the chance of receiving this adjuvant treatment (OR 0.26 95% CI: 0.09-0.70).

The model was robust; all variance inflation factors were under 10, in the goodness of fit χ^2 showed no significant difference between observed and expected values (Hosmer-Lemeshow = 1.33 d.f. = 5 P=0.931) and the area under the receiver operator characteristics curve was 0.737 showing satisfactory discrimination (Hosmer-Lemeshow, 2000).

Survival analyses included all of the 910 women in the study (mean age 77.01 95% CI: 76.55 – 77.46),of whom 178 died before the end point of the study (5/2/16): 71 of breast cancer and 107 of other causes. The mean follow up time was 3.76 years (95% CI: 3.69-3.83). Baseline characteristics of the sample are detailed in Table 1. The number of observed breast cancer deaths significantly exceeded those expected for participants whom did not have primary surgery, were aged ≥85 years, were steroid receptor negative and had a higher grade or stage tumour (Table 1). The same variables predicted increased hazard of breast cancer death in univariate Cox's regression analyses (Table 2).

Adjusting for tumour stage, comorbidity and functional status, women undergoing primary surgery had a third the hazard of dying of breast cancer (Table 2). Those who were steroid receptor test negative (vs. positive) had over twice the hazard of breast cancer death (Table 2).

Discussion

These results are in broad agreement with previous studies both in the UK and elsewhere. Surgery has become such a mainstay of treatment for early stage breast cancer that trials testing its efficacy for older patients are scarce and subject to poor recruitment[13;14]. Morgan *et al*'s (2014) Cochrane review of primary surgery vs. medical treatment with endocrine therapy for breast cancer patients aged ≥70 years included two trials (based in UK and Italy) which had breast cancer specific survival as an outcome. Combined analyses indicate reduced hazard of breast cancer death for patients undergoing primary surgery (HR 0.70 95% CI: 0.51 – 0.95)[15]. Amongst observational studies, Bourchardy *et al* (2007) found that both mastectomy and breast conserving surgery followed by adjuvant treatment significantly reduced the hazard of dying of breast cancer (HR 0.2 (95% CI: 0.1-0.7) & HR 0.1 (95% CI: 0.03-0.4) respectively) amongst 407 patients aged ≥80 years in the United States[16]. More recently Cortadellas *et al* (2013) also found that surgery increased breast cancer survival in a prospective cohort study of 259 Spanish breast cancer patients aged ≥80 years[17]. The

finding that surgery increases survival are by no means universal: Traa *et al* (2011) for example found that surgery did not significantly reduce the hazard of dying of breast cancer amongst a cohort of 346 breast cancer patients aged ≥75 years in the Netherlands (HR 0.78 95% CI: 0.44-1.39)[18]. However, Traa *et al* did not adjust for co-morbidities which they comment is a limitation of their results.

Previous cohort studies have adjusted for a range of explanatory variables that may ameliorate the effects of surgery on survival for older breast cancer patients. Adjustment for tumour characteristics was based on improved prognosis for receptor positive and earlier stage breast cancer. However, although we have found and effect of steroid receptor status we did not find an effect of stage; probably due to the inclusion of only early stage breast cancer patients. Older age was not found to predict breast cancer specific survival once tumour characteristics and surgical treatment were adjusted for. This finding supports breast cancer guidelines which state that age should not be the sole determinant in deciding treatment for patients[19]. However, it should be noted that the hazard of death for the oldest age group, women aged ≥85 years, was of borderline significance even adjusting for co-morbidities and functional status. Hence this result should be treated with caution.

This was a subsidiary study and as such was limited to the sample size, geographical area and health measures used in the main study. The number of events (71) per degree of freedom (14) from explanatory variables exceeded five in the final model and the sample size was therefore justifiable to support the analysis[20]. This subsidiary study could only assess survival outcomes at an average 3.8 years post diagnosis and longer term follow up is needed to explore these short term results further. Cancer specific survival may exhibit potential bias due to misclassification. However, this bias has been shown to have little impact on estimates for cancers with good survival rates (i.e. >80% at 5 years)[21]. Further limitations of the main study are discussed elsewhere[1]. Regarding the analysis reported here the slight under-representation of women aged ≥85 years is of the most relevance as this limits the generalizability of these findings to the oldest age group. However, as this study required patient consent, under-representation of the oldest patients is likely as capacity for informed consent decreases with older age[1].

In this large UK based cohort of patients aged ≥65 years diagnosed with early stage breast cancer, primary surgery reduced the hazard of dying of breast cancer by a third, independent of age, health and tumour characteristics.

Acknowledgements

This paper presented independent research funded by the Breast Cancer Campaign (2008NOVPR35), a National Institute for Health Research (NIHR) Programme Grant for Applied Research (RP-PG-0608-10168) and research arising from a Post-Doctoral Fellowship supported by the NIHR (PDF/01/2008/027). The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health. Ethical approval was granted by the National Research Ethics Service (10/H1014/32 & 33). We would like to thank the patients and NHS Trusts who took part in the study.

References

(1) Lavelle K, Sowerbutts A, Bundred N, Pilling M, Degner L, Stockton C *et al*. Is lack of surgery for older breast cancer patients in the UK explained by patient choice or poor health? A prospective cohort study. *British Journal of Cancer* 2014; **110**:573-583.

(2) Lavelle K, Moran A, Howell A, Bundred N, Campbell M, Todd C. Older women with operable breast cancer are less likely to have surgery. *British Journal of Surgery* 2007; **94**(10):1209-1215.

(3) Lavelle K, Downing A, Thomas JD, Lawrence G, Forman D, Oliver SE. Are lower rates of surgery amongst older women with breast cancer in the UK explained by co-morbidity? *British Journal of Cancer* 2012; **107**:1175-1180.

(4) Lawrence G, Kearins O, Lagord C, Cheung S, Sidhu J, Sagar C. The Second All Breast Cancer Report. 2011. National Cancer Intelligence Network.

(5) Foot C, Harrison T. How to improve cancer survival: Explaining England's relatively poor rates. 2011. The King's Fund.

(6) Moller H, Sandin F, Bray F, Klint A, Linklater KM, Purushotham A *et al*. Breast cancer survival in England, Norway and Sweden: a population-based comparison. *International Journal of Cancer* 2010; **127**(11):2630-2638.

(7) Cancer Research UK. Breast cancer mortality statistics. Available from: URL:http://www.cancerresearchuk.org/cancer-info/cancerstats/types/breast/mortality/uk-breast-cancer-mortality-statistics#age (accessed 20/07/15)

(8) Office of National Statistics. The National Statistics Socio-Economic Classification (NS-SEC rebased on the SOC2010). Available from: URL:http://www.ons.gov.uk/ons/guide-method/classifications/current-standard-classifications/soc2010/soc2010-volume-3-ns-sec--rebased-on-soc2010--user-manual/index.html (accessed 20/07/15)

(9) Charlson M, Pompei P, Ales K, MacKenzie C. A new method of classifying prognostic co-morbidity in longitudinal studies: development and validation. *Journal of Chronic Disease* 1987; **40**(5):373-383.

(10) Sharples LD, Todd CJ, Caine N, Tait S. Measurement properties of the Nottingham Health Profile and Short Form 36 health status measures in a population sample of elderly people living at home: results from ELPHS. *British Journal of Health Psychology* 2000; **5**:217-233.

(11) UICC. TNM Classification of Malignant Tumours, 7th Edition. Oxford: Wiley-Blackwell; 2009.

(12) StataCorp. Stata Statistical Software: Release 12. College Station, TX : StataCorp LP .; 2011.

(13) Reed MW, Wyld L, Ellis P, Bliss J, Leonard R, ACTION and ESTEeM Trial Management Groups. Breast cancer in older women: trials and tribulations. *Clinical Oncology (Royal College of Radiologists)* 2009; **21**(2):99-102.

(14) Ring A, Reed M, Leonard R, Kunkler I, Muss H, Wildiers H *et al*. The treatment of early breast cancer in women over the age of 70. *British Journal of Cancer* 2011; **105**(2):189-193.

(15) Morgan J, Wyld L, Collins KA, Reed M. Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus). *Cochrane Database of Systematic Reviews* 2014;(Issue 5. Art. No.: CD004272.).

(16) Bouchardy C, Rapiti E, Blagojevic S, Vlastos AT, Vlastos G. Older female cancer patients: importance, causes, and consequences of undertreatment. *Journal of Clinical Oncology* 2007; **25**(14):1858-1869.

(17) Cortadellas T, Gascon A, Cordoba O, Rabasa J, Rodriguez R, Espinosa-Bravo M *et al*. Surgery improves breast cancer-specific survival in octogenarians with early-stage breast cancer. *International Journal Of Surgery* 2013; **11**(7):554-557.

(18) Traa MJ, Meijs CM, de Jongh MA, van der Borst EC, Roukema JA. Elderly women with breast cancer often die due to other causes regardless of primary endocrine therapy or primary surgical therapy. *Breast* 2011; **20**(4):365-369.

(19) Senkus E, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rutgers E, Zackrisson S, Cardoso F. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2015 Sep 1;26(suppl 5):v8-30.

(20) Vittinghoff E, McCulloch C. Relaxing the rule of ten events per variable in logistic and Cox regression. *Am J Epidemiol* 2007; **165**:710-718.

(21) Sarfati D, Blakely T, Pearce N. Measuring cancer survival in populations: relative survival vs cancer-specific survival. *International Journal of Epidemiology* 2010; **39**(2):598-610.

TABLE 61: Baseline characteristics by observed and expected breast cancer-specific deaths (n = 910)

Variable	Category	n	Percent	No. Deaths Observed	No. Deaths Expected	Log ranks test# P*
Primary surgery	Yes	772	84.8	49	61.99	
	No	138	15.2	22	9.01	**<0.001**
Age group (years)	65-69	136	15.0	6	11.14	
	70-74	265	29.1	18	21.78	
	75-79	225	24.7	13	17.94	
	80-84	148	16.3	14	10.89	
	85+	136	15.0	20	9.26	**0.001**
Grade	1	168	18.5	7	13.28	
	2	489	53.7	28	38.70	
	3	183	20.1	32	13.36	**<0.001**
	Missing	70	7.7	4	5.67	**<0.001**
ER or PR positive	Yes	774	85.1	50	60.77	
	No	81	8.9	17	5.90	**<0.001**
	Missing	55	6.0	4	4.33	**<0.001**
Tumour Stage	I	403	44.3	19	32.06	
	II and IIIa	507	55.7	52	38.94	**0.002**
Co-morbidity (Charlson)	0	473	52.0	38	37.98	
	1	268	29.5	21	20.53	
	2+	169	18.6	12	12.49	0.985
Functional status	Independent (1-2)	758	83.3	55	60.38	
	Dependent (3-4)	148	16.3	16	10.38	0.061
	Missing	4	0.4	0	0.24	0.153
Total		**910**	**100%**	**71**	**71**	

* P values for each variable for complete data reported first followed by data including missings if relevant.
# The Log Rank test tests the equality of survivor function across groups

TABLE 62: Cox's proportional hazards regression of breast cancer-specific survival (unadjusted n=910, adjusted n=906)

Variable	Category	Unadjusted HR	Univariable 95% CI	P Value	Adjusted HR#	Multivariable 95% CI	P Value
Primary surgery	No	(ref)			(ref)		
	Yes	0.32	0.19-0.53	**<0.001**	0.36	0.20-0.66	**0.001**
Age group (years)	65-69	(ref)			(ref)		
	70-74	1.53	0.61-3.86	0.364	1.31	0.52-3.34	0.565
	75-79	1.35	0.51-3.54	0.548	1.04	0.39-2.77	0.933
	80-84	2.39	0.92-6.22	0.074	1.72	0.65-4.56	0.272
	85+	4.02	1.61-10.01	**0.003**	2.61	0.99-6.91	**0.053**
Grade	1	(ref)			(ref)		
	2	1.37	0.60-3.14	0.453	1.18	0.51-2.71	0.704
	3	4.55	2.01-10.31	**<0.001**	3.23	1.36-7.65	**0.008**
	Missing	1.34	0.39-4.57	0.642	1.10	0.30-4.00	0.890
ER or PR positive	Yes	(ref)			(ref)		
	No	3.50	2.02-6.08	**<0.001**	2.75	1.49-5.09	**0.001**
	Missing	1.12	0.41-3.11	0.825	1.60	0.54-4.79	0.396
Tumour Stage	I	(ref)			(ref)		
	II and IIIa	2.25	1.33-3.81	**0.002**	1.48	0.85-2.57	0.164
Co-morbidity (Charlson)	0	(ref)			(ref)		
	1	1.02	0.60-1.74	0.935	0.97	0.56-1.67	0.917
	2+	0.96	0.50-1.84	0.902	0.80	0.41-1.57	0.518
Functional status*	Independent (1-2)	(ref)			(ref)		
	Dependent (3-4)	1.69	0.97-2.95	0.064	1.00	0.53-1.88	0.995

Adjusted for all other variables in table
* Missing data omitted as only 4 cases. See Table 1

Appendix 4 Impact of primary surgery on short-term survival of older breast cancer patients in the UK: a prospective cohort study

Abstract

Introduction: Lack of surgery for older breast cancer patients may reduce breast cancer survival. Few previous studies adjust for comorbidity and tumour characteristics which also effect survival.

Methods: As part of a wider programme investigating older breast cancer patients' treatment, analyses of short-term survival (mean 3.8 years) was undertaken for 910 breast cancer patients aged ≥65 years diagnosed at 22 English hospitals from 1/7/10-31/12/12. Primary outcome is breast cancer specific survival (at 5/2/16). Independent variables include surgery, comorbidity, functional status and tumour characteristics recorded from patient interview (at diagnosis) and case note review (90 days post-diagnosis). Data analyses included Cox's multiple regression.

Results: Patients who had primary surgery (vs. those who did not) had 0.36 times the hazard of dying of breast cancer (95% CI: 0.20-0.66, p=0.001) adjusting for other factors. In univariate analysis women aged ≥85 years had an increased hazard of breast cancer death compared to 65-69 year olds (HR 4.02, 95% CI: 1.61-10.01, p=0.003). However when adjusted for surgery, tumour characteristics and general health this was only borderline significant at 5% level (p=0.053).

Conclusions: Surgery for older breast cancer patients reduces the hazard of breast cancer death by a third, independent of age, comorbidity and tumour characteristics.

Introduction

Women 65 years and older in the UK are less likely to have primary surgery for early operable breast cancer compared to younger postmenopausal women[1;2]. Previous studies demonstrate reduced odds of surgery from the age of 70 years and older[3;4]. The King's Fund reports that improved management of older cancer patients could reduce overall cancer mortality in England[5]. The impact of lack of surgery on older patients' survival needs to be investigated. There is good evidence that poor survival is a particular problem for older breast cancer patients in the UK. Moller *et al* (2010) found that the 5 year relative survival for women aged ≥80 years is 61% in UK compared to 74% in Norway & Sweden. Moreover the excess death rate for British breast cancer patients increases dramatically with age group compared to those in Norway and Sweden, particularly in the first year after diagnosis,[6] which 'leads to important questions about the adequacy of care provided for the oldest patients.' However, Moller *et al* did not investigate the effect of access to treatment on survival. Moreover, the proportion of patients with co-morbidities or frailty, and later stage breast cancer increase with age and both of these factors may also effect survival.

This study aims to investigate the impact of primary surgery, or lack thereof, on survival of women aged ≥65 years diagnosed with breast cancer in the UK, adjusting for pre-treatment measures of health and tumour characteristics.

Method

This paper analyses of short term (3.8 years) breast cancer specific survival, undertaken as a subsidiary study of a wider research programme involving a cohort of 944 women aged ≥65 years diagnosed with early stage (1-3a) breast cancer (from 01/07/10- 31/03/13) at 22 UK breast units. The main study, investigating the impact of health and choice on older patients' access to surgical treatments, is reported elsewhere[1]. This paper focuses on 910 members of the cohort with a diagnosis date up to 31/12/12 in order that all participants had > 3 years survival at the time of analysis. As breast cancer mortality in the UK rises sharply from the age of 70 years, 65-69 year olds are included here as a reference group[4;7]. Data on surgical treatment, pre-operative health measures and tumour characteristics were collected by patient interview (at diagnosis/ before surgery if undertaken) and/or case note review (at 3 months post diagnosis)[1]. Surgery rates did not differ significantly between breast units[1]. The core variables used in this survival analysis were collected for the entire sample, including 136 eligible participants aged 65-69 years. All participants were followed up to a census date of 5/2/16 i.e. 37 months from the last participant entering the study. The primary end point is breast cancer

specific mortality, which was defined as time from diagnosis to death due to breast cancer. Cause of death was based on underlying cause of death provided by the Health and Social Care Information Centre. Participants dying from other causes were censored at their date of death.

Independent variables include undergoing primary surgery (mastectomy or wide local excision) within 90 days of diagnosis, age group, socio-economic status[8], co-morbidity (Charlson Index 0, 1, 2+)[9] and functional status group (ELPHS ADL 1-2 vs. 3-4)[10]. Pre-treatment assessment of steroid receptor status, grade and tumour stage (1 vs. 2-3a) based on clinical, imaging and fine needle/core biopsy assessments were recorded[11]. Expected and observed deaths were compared using the log rank test (α <0.05). A disease free survival curve comparing patients who received vs those who did not receive surgery was plotted using the Kaplan–Meier method and compared by means of the log rank test. Cox's proportional hazards regression was used to examine the effect of surgery on survival adjusting for age, tumour stage, grade, steroid receptor status, co-morbidity and functional status. Data were analysed using Stata version 12.1[12]. Ethical approval was granted by the UK NHS National Research Ethics Service (10/H1014/32 & 33).

Results

Of the 910 women in the study (mean age 77.01 95% CI: 76.55 – 77.46), 178 died before the end point of the study (5/2/16): 71 of breast cancer and 107 of other causes. The mean follow up time was 3.76 years (95% CI: 3.69-3.83). Baseline characteristics of the sample are detailed in Table 1. The number of observed breast cancer deaths significantly exceeded those expected, for participants whom did not have primary surgery, were aged ≥85 years, were steroid receptor negative and had a higher grade or stage tumour (Table 1); the difference in death rate between patients who received primary surgery vs those who did not is illustrated in the Kaplan Meier plot (figure 1) (P <0.001). The same variables predicted increased hazard of breast cancer death in univariate Cox's regression analyses (Table 2).

Adjusting for tumour stage, comorbidity and functional status, women undergoing primary surgery had a third the hazard of dying of breast cancer compared to those not undergoing surgery (Table 2). Those who were steroid receptor test negative (vs. positive) had over twice the hazard of breast cancer death (Table 2).

Discussion

These results are in broad agreement with previous studies both in the UK and elsewhere. Surgery has become such a mainstay of treatment for early stage breast cancer that trials testing its efficacy for older patients are scarce and subject to poor recruitment[13;14]. Morgan *et al*'s (2014) Cochrane review of primary surgery vs. medical treatment with endocrine therapy for breast cancer patients aged ≥70 years included two trials (based in UK and Italy) which had breast cancer specific survival as an outcome. Combined analyses indicate reduced hazard of breast cancer death for patients undergoing primary surgery (HR 0.70 95% CI: 0.51 – 0.95)[15]. Amongst observational studies, Bourchardy *et al* (2007) found that both mastectomy and breast conserving surgery followed by adjuvant treatment significantly reduced the hazard of dying of breast cancer (HR 0.2 (95% CI: 0.1-0.7) & HR 0.1 (95% CI: 0.03-0.4) respectively) amongst 407 patients aged ≥80 years in the United States[16]. More recently Cortadellas *et al* (2013) also found that surgery increased breast cancer survival in a prospective cohort study of 259 Spanish breast cancer patients aged ≥80 years[17]. The finding that surgery increases survival are by no means universal: Traa *et al* (2011) for example found that surgery did not significantly reduce the hazard of dying of breast cancer amongst a cohort of 346 breast cancer patients aged ≥75 years in the Netherlands (HR 0.78 95% CI: 0.44-1.39)[18]. However, Traa *et al* did not adjust for co-morbidities, which they comment is a limitation of their results.

Previous cohort studies have adjusted for a range of explanatory variables that may ameliorate the effects of surgery on survival for older breast cancer patients. Adjustment for tumour characteristics was based on improved prognosis for receptor positive and earlier stage breast cancer. However, although we have found and effect of steroid receptor status we did not find an effect of stage; probably due to the inclusion of only early stage breast cancer patients. Being aged 65 years or older was not found to predict breast cancer specific survival once tumour characteristics and surgical treatment were adjusted for. This finding supports breast cancer guidelines which state that age should not be the sole determinant in deciding treatment for patients[19]. However, it should be noted that the hazard of death for the oldest age group, women aged ≥85 years, was of borderline significance even adjusting for co-morbidities and functional status. Hence this result should be treated with caution.

This was a subsidiary study and as such was limited to the sample size, geographical area and health measures used in the main study. The number of events (71) per degree of freedom (14) from explanatory variables exceeded five in the final model and the sample size was therefore justifiable to support the analysis[20]. This subsidiary study could only assess survival outcomes at an average 3.8 years post diagnosis and longer term follow up is needed to explore these short term results further. Cancer

specific survival may exhibit potential bias due to misclassification. However, this bias has been shown to have little impact on estimates for cancers with good survival rates (i.e. >80% at 5 years)[21]. Further limitations of the main study are discussed elsewhere[1]. Regarding the analysis reported here the slight under-representation of women aged ≥85 years is of the most relevance as this limits the generalizability of these findings in the oldest age group. However, as this study required patient consent, under-representation of the oldest patients is likely as capacity for informed consent decreases with older age[1].

In overview, in this large UK based cohort of patients aged ≥65 years diagnosed with early stage breast cancer, primary surgery reduced the hazard of dying of breast cancer by a third, independent of age, health and tumour characteristics.

Acknowledgements

This paper presented independent research funded by the Breast Cancer Campaign (2008NOVPR35), a National Institute for Health Research (NIHR) Programme Grant for Applied Research (RP-PG-0608-10168) and research arising from a Post-Doctoral Fellowship supported by the NIHR (PDF/01/2008/027). The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health. Ethical approval was granted by the National Research Ethics Service (10/H1014/32 & 33). We thank the patients and NHS Trusts who took part in the study.

References

(1) Lavelle K, Sowerbutts A, Bundred N, Pilling M, Degner L, Stockton C *et al*. Is lack of surgery for older breast cancer patients in the UK explained by patient choice or poor health? A prospective cohort study. *British Journal of Cancer* 2014; **110**:573-583.

(2) Lavelle K, Moran A, Howell A, Bundred N, Campbell M, Todd C. Older women with operable breast cancer are less likely to have surgery. *British Journal of Surgery* 2007; **94**(10):1209-1215.

(3) Lavelle K, Downing A, Thomas JD, Lawrence G, Forman D, Oliver SE. Are lower rates of surgery amongst older women with breast cancer in the UK explained by co-morbidity? *British Journal of Cancer* 2012; **107**:1175-1180.

(4) Lawrence G, Kearins O, Lagord C, Cheung S, Sidhu J, Sagar C. The Second All Breast Cancer Report. 2011. London: National Cancer Intelligence Network.

(5) Foot C, Harrison T. How to improve cancer survival: Explaining England's relatively poor rates. 2011. London: The King's Fund.

(6) Moller H, Sandin F, Bray F, Klint A, Linklater KM, Purushotham A *et al*. Breast cancer survival in England, Norway and Sweden: a population-based comparison. *International Journal of Cancer* 2010; **127**(11):2630-2638.

(7) Cancer Research UK. Breast cancer mortality statistics. Available from: URL:http://www.cancerresearchuk.org/cancer-info/cancerstats/types/breast/mortality/uk-breast-cancer-mortality-statistics#age (accessed 20/07/15)

(8) Office of National Statistics. The National Statistics Socio-Economic Classification (NS-SEC rebased on the SOC2010). Available from: URL:http://www.ons.gov.uk/ons/guide-method/classifications/current-standard-classifications/soc2010/soc2010-volume-3-ns-sec--rebased-on-soc2010--user-manual/index.html (accessed 20/07/15)

(9) Charlson M, Pompei P, Ales K, MacKenzie C. A new method of classifying prognostic co-morbidity in longitudinal studies: development and validation. *Journal of Chronic Disease* 1987; **40**(5):373-383.

(10) Sharples LD, Todd CJ, Caine N, Tait S. Measurement properties of the Nottingham Health Profile and Short Form 36 health status measures in a population sample of elderly people living at home: results from ELPHS. *British Journal of Health Psychology* 2000; **5**:217-233.

(11) UICC. TNM Classification of Malignant Tumours, 7th Edition. Oxford: Wiley-Blackwell; 2009.

(12) StataCorp. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP.; 2011.

(13) Reed MW, Wyld L, Ellis P, Bliss J, Leonard R, ACTION and ESTEeM Trial Management Groups. Breast cancer in older women: trials and tribulations. *Clinical Oncology (Royal College of Radiologists)* 2009; **21**(2):99-102.

(14) Ring A, Reed M, Leonard R, Kunkler I, Muss H, Wildiers H *et al*. The treatment of early breast cancer in women over the age of 70. *British Journal of Cancer* 2011; **105**(2):189-193.

(15) Morgan J, Wyld L, Collins KA, Reed M. Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus). *Cochrane Database of Systematic Reviews* 2014;(Issue 5. Art. No.: CD004272.).

(16) Bouchardy C, Rapiti E, Blagojevic S, Vlastos AT, Vlastos G. Older female cancer patients: importance, causes, and consequences of undertreatment. *Journal of Clinical Oncology* 2007; **25**(14):1858-1869.

(17) Cortadellas T, Gascon A, Cordoba O, Rabasa J, Rodriguez R, Espinosa-Bravo M *et al*. Surgery improves breast cancer-specific survival in octogenarians with early-stage breast cancer. *International Journal Of Surgery* 2013; **11**(7):554-557.

(18) Traa MJ, Meijs CM, de Jongh MA, van der Borst EC, Roukema JA. Elderly women with breast cancer often die due to other causes regardless of primary endocrine therapy or primary surgical therapy. *Breast* 2011; **20**(4):365-369.

(19) Senkus E, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rutgers E, Zackrisson S, Cardoso F. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2015 Sep 1;26(suppl 5):v8-30.

(20) Vittinghoff E, McCulloch C. Relaxing the rule of ten events per variable in logistic and Cox regression. *Am J Epidemiol* 2007; **165**:710-718.

(21) Sarfati D, Blakely T, Pearce N. Measuring cancer survival in populations: relative survival vs cancer-specific survival. *International Journal of Epidemiology* 2010; **39**(2):598-610.

TABLE 63: Baseline characteristics by observed and expected breast cancer-specific deaths (n = 910)

Variable	Category	n	Percent	No. Deaths Observed	No. Deaths Expected	Log ranks test# P*
Primary surgery	Yes	772	84.8	49	61.99	
	No	138	15.2	22	9.01	**<0.001**
Age group (years)	65-69	136	15.0	6	11.14	
	70-74	265	29.1	18	21.78	
	75-79	225	24.7	13	17.94	
	80-84	148	16.3	14	10.89	
	85+	136	15.0	20	9.26	**0.001**
Grade	1	168	18.5	7	13.28	
	2	489	53.7	28	38.70	
	3	183	20.1	32	13.36	**<0.001**
	Missing	70	7.7	4	5.67	**<0.001**
ER or PR positive	Yes	774	85.1	50	60.77	
	No	81	8.9	17	5.90	**<0.001**
	Missing	55	6.0	4	4.33	**<0.001**
Tumour Stage	I	403	44.3	19	32.06	
	II and IIIa	507	55.7	52	38.94	**0.002**
Co-morbidity (Charlson)	0	473	52.0	38	37.98	
	1	268	29.5	21	20.53	
	2+	169	18.6	12	12.49	0.985
Functional status	Independent (1-2)	758	83.3	55	60.38	
	Dependent (3-4)	148	16.3	16	10.38	0.061
	Missing	4	0.4	0	0.24	0.153
Total		**910**	**100%**	**71**	**71**	

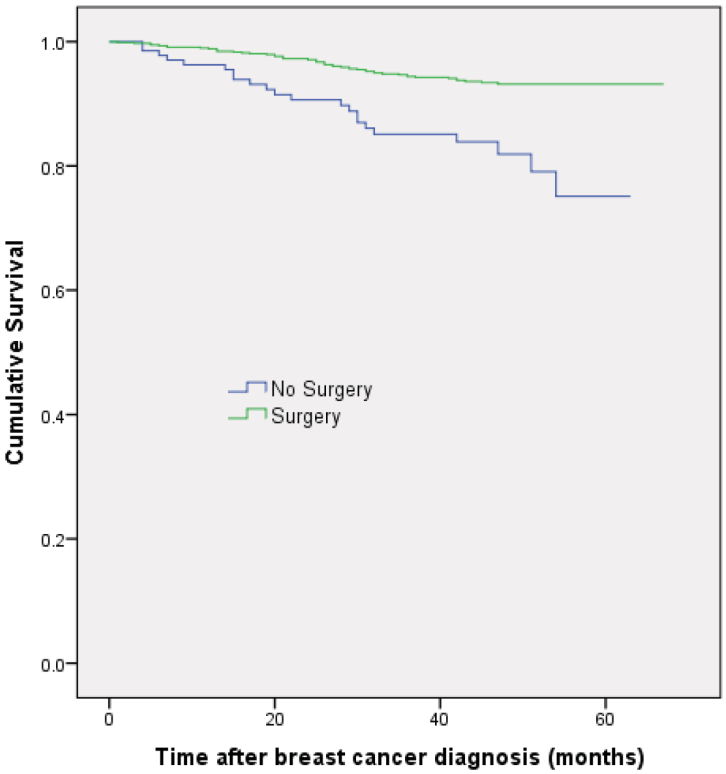
* P values for each variable for complete data reported first followed by data including missings if relevant.

The Log Rank test tests the equality of survivor function across groups

TABLE 64: Cox's proportional hazards regression of breast cancer-specific survival (unadjusted n = 910, adjusted n = 906)

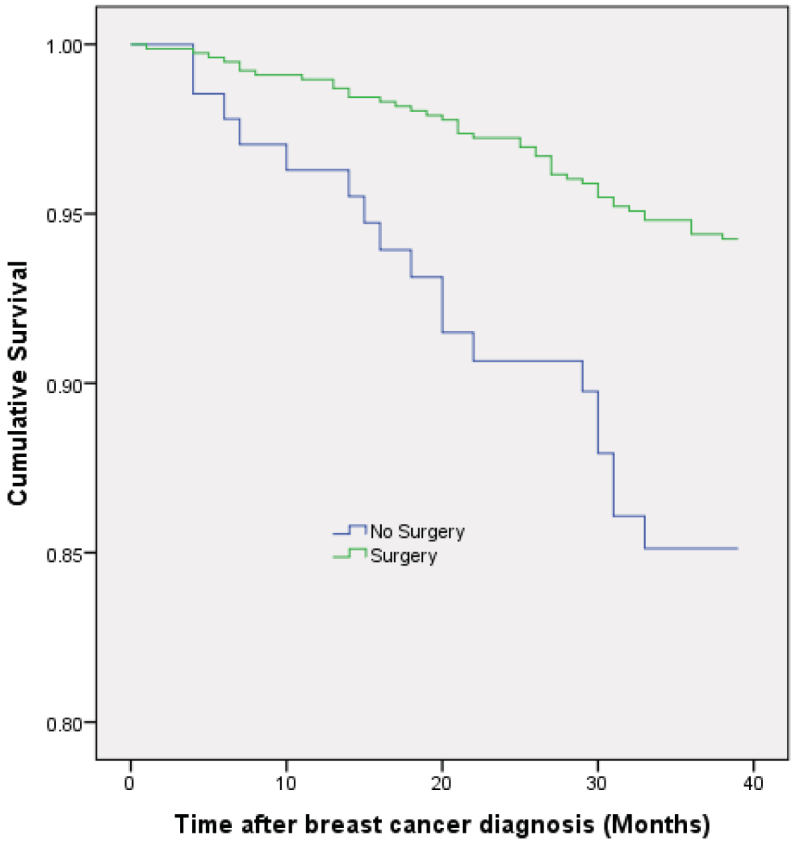
Variable	Category	Unadjusted HR	Univariable 95% CI	P Value	Adjusted HR#	Multivariable 95% CI	P Value
Primary surgery	No	(ref)			(ref)		
	Yes	0.32	0.19-0.53	**<0.001**	0.36	0.20-0.66	**0.001**
Age group (years)	65-69	(ref)			(ref)		
	70-74	1.53	0.61-3.86	0.364	1.31	0.52-3.34	0.565
	75-79	1.35	0.51-3.54	0.548	1.04	0.39-2.77	0.933
	80-84	2.39	0.92-6.22	0.074	1.72	0.65-4.56	0.272
	85+	4.02	1.61-10.01	**0.003**	2.61	0.99-6.91	**0.053**
Grade	1	(ref)			(ref)		
	2	1.37	0.60-3.14	0.453	1.18	0.51-2.71	0.704
	3	4.55	2.01-10.31	**<0.001**	3.23	1.36-7.65	**0.008**
	Missing	1.34	0.39-4.57	0.642	1.10	0.30-4.00	0.890
ER or PR positive	Yes	(ref)			(ref)		
	No	3.50	2.02-6.08	**<0.001**	2.75	1.49-5.09	**0.001**
	Missing	1.12	0.41-3.11	0.825	1.60	0.54-4.79	0.396
Tumour Stage	I	(ref)			(ref)		
	II and IIIa	2.25	1.33-3.81	**0.002**	1.48	0.85-2.57	0.164
Co-morbidity (Charlson)	0	(ref)			(ref)		
	1	1.02	0.60-1.74	0.935	0.97	0.56-1.67	0.917
	2+	0.96	0.50-1.84	0.902	0.80	0.41-1.57	0.518
Functional status*	Independent (1-2)	(ref)			(ref)		
	Dependent (3-4)	1.69	0.97-2.95	0.064	1.00	0.53-1.88	0.995

Adjusted for all other variables in table
* Missing data omitted as only 4 cases. See Table 1



No. at risk			
No Surgery	138	114	80
Surgery	772	734	654

FIGURE 22. Kaplan Meier breast cancer-specific survival curve for patients not treated with surgery vs. treated with surgery for breast cancer



No. at risk					
No Surgery	138	129	114	98	84
Surgery	772	761	734	710	689

FIGURE 23. Kaplan Meier breast cancer-specific survival curve for patients not treated with surgery vs. treated with surgery for breast cancer (patients censored at 37 months).

Appendix 5 Congruence between patients' preferred and actual role in the surgical treatment decision: impact on post-surgical health-related quality of life

Background

In addition to survival, quality of life is an important treatment outcome for older cancer patients.[1] There is evidence that active involvement in treatment decisions increases patient satisfaction and post treatment Health Related Quality of Life (HRQoL). [2] Along with ethical, legal and social issues in health care, this has led to patients being encouraged to be more active in making treatment decisions.[3] However, reviews of the literature indicate that older patients may prefer to be passive in treatment decisions.[4] In our nested qualitative study some patients expressed distress at being required to be more active in the treatment decision than they preferred. The benefits of active involvement may be limited if the patient prefers not to be involved. If so soliciting, then meeting, patients' preferred decision making style should be recommended rather than encouraging active involvement indiscriminately. Studies investigating the impact of congruence, (i.e. getting the treatment decision making style you prefer) on HRQoL, are limited. Hack et al found no association amongst 205 Canadian breast cancer patients.[1] However both HRQoL and decisional preferences were measured at 3 years post surgery when the impact of both surgery/decisional role would be considerably diluted. Moreover no baseline data on pre- surgical HRQoL were available. Thus it is still an open issue as to whether there is a relationship between congruence and HRQoL when these are more proximally measured around the time of surgery. The aims of this study were thus:

1. To investigate the impact of older patients getting or not getting the treatment decision making style they prefer on post-surgical HRQoL.

2. To investigate the impact of surgery on HRQoL for older patients.

Methods

The Control Preference Scale (CPS) is a widely used and validated scale measuring the degree to which patients **prefer** to be and perceive they **actually are** involved in specific treatment decisions.[5] Patients are asked to choose between five options from 'I prefer to make the final decision about which treatment I will receive' to 'I prefer to leave all decisions regarding my treatment to my doctor' and then identify the role they actually played in the treatment decision (Table 1).

We have recruited a cohort of women aged ≥65 years diagnosed with early stage invasive breast cancer. [6] In our current dataset of 943 women aged ≥65 years diagnosed in Northwest England (01/07/2010 to 31/03/2013) with early stage invasive breast cancer CPS scales were completed on both preferred and actual role for 673 of the 801 patients who had surgery. This measure was taken at a face to face interview within 30 days of diagnosis and before surgery. We also took a self reported measure of HRQoL (EORTC- C30)[7] at this interview and repeated the measure in a postal survey sent 30 days after surgery. EORTC-C30 is scored on a 1-100 scale, in which a higher score indicates a better quality of life. EORTC-C30 was returned by 625 of the 801 surgical patients (78%). 546 of whom had also completed CPSs. EORTC-C30 completed within 2 weeks (and before the commencement of follow up adjuvant treatment - radiotherapy and/or chemotherapy) by 434 participants (380 of whom also had completed CPSs).

The above data collection only included surgical patients. This was extended by including non-surgical patients to investigate the impact of surgery on HRQoL for older patients. A time frame to be equivalent to 30 days post-surgery for non-surgical patients was set at 60 days post diagnosis and the survey sent out at 54 days to allow for postage/ participant delay. However the follow up HRQoL survey was only sent out to non-surgical patients in a subsample of sites which recruited women aged ≥70 years only (n = 462). The follow up HRQoL survey was returned by 338 (73%) (309 of whom also had completed CPSs) and completed within 2 weeks by 246 participants (225 of whom also had completed CPSs).

Analyses

Univariable analysis investigated the association between achieving the congruence (i.e. the patient actually playing the decisional role they prefer) and difference in quality of life pre vs. post-surgery (paired t-tests).

Multiple linear regression investigated the effect of role congruence (i.e. achieved vs. not achieved) on the outcome of difference in HRQoL pre vs. post surgery. Patient age, social class and pre- treatment measures of health are also adjusted for. According to Tabachnick & Fidell's guidelines, the sample size for multiple linear regression should be at least ≥ 50 + 8p and ≥ 104 + p (where p = number of distinct variables). [8] The sample should therefore support the inclusion of up to 48 explanatory variables.

This analysis was extended by including non-surgical patients and thereby investigating the impact of surgery on HRQoL for older patients (paired t test) and adjusting for role in treatment decision making (in terms of the extent to which they achieved congruence) in multiple linear regression analyses.

Results

Patients preferred and actual role in the surgical decision are detailed in Table 2. As can be seen there is little congruence between patients' preferred and actual roles in the treatment decision making, as revealed by their CPS scores. Only 163 of 673 patients actually received their preferred role in the decision, and the vast majority (125) of these were when they both wanted the decision to be made by the doctor and indicated this to be the case in actuality. According to Landis and Koch this represents a 'slight' level of agreement (kappa 0.039).[9] The largest source of disagreement was amongst patients who indicated that their actual role was more passive than they would have preferred (442 patients); only 68 patients indicated their actual role to have been more involved than they would have preferred. The difference in HRQoL pre and post-surgery was not associated with congruence either in the univariate (P = 0.830, two sample t test) or multivariate analyses (P = 0.940) adjusting for age, tumour stage, socio-economic status, co-morbidity and functional health status (Table 3).

Of the 225 patients in the sub-sample investigating the effect of surgery on HRQoL in the extended analyses, 59 (26%) achieved congruence i.e. got the treatment making decision style they preferred. Change in HRQoL was not associated with congruence (P = 0.133) nor with receipt of primary surgery (P = 0.841) either in the univariate analyses (t tests) or in multiple linear regression analysis adjusting for the effects of each other: P = 0.135 and P = 0.729 respectively.

Conclusion

Achieving the preferred level of involvement in the surgical treatment decision, and undergoing the surgery itself, had no impact on post-surgical HRQoL, in this sample of older breast cancer patients.

TABLE 65: Control Preferences Scale (CPS)[6]

Option	Control Preference Scale[6]
A	I prefer to make the decision about which treatment I will receive.
B	I prefer to make the final decision about my treatment after seriously considering my doctor's opinion.
C	I prefer that my doctor and I share responsibility for deciding which treatment is best for me.
D	I prefer that my doctor make the final decision about which treatment will be used but seriously considers my opinion.
E	I prefer to leave all decisions regarding treatment to my doctor.

TABLE 66: Preferred vs. actual role in treatment decision

		Actual role					
		A	**B**	**C**	**D**	**E**	**Total**
Preferred role	**A**	**5**	5	3	1	32	**46**
	B	3	**12**	2	1	51	**69**
	C	11	19	**15**	5	230	**280**
	D	4	6	1	**6**	112	**129**
	E	10	6	3	5	**125**	**149**
	Total	**33**	**48**	**24**	**18**	**550**	**673**

Agreement = 24.2%, Kappa = 0.039, P=0001

TABLE 67: Multiple regression of difference in HRQoL post vs. pre surgery (n = 379)

Variable		P Value	Coefficient†	95% CI	
				Lower	Upper
CPS Congruent	Yes: Got decision making style preferred	(ref)			
	No: Did not get decision making style preferred	0.945	0.15	-4.03	4.33
Age	Years	0.396	0.13	-0.17	0.44
Socio-economic status*	Professional/ managerial	(ref)			
	Intermediate	0.444	1.73	-2.72	6.18
	Manual	0.210	3.16	-1.79	8.10
Tumour stage	Stage 1	(ref)			
	Stage 2 &3a	0.595	-0.98	-4.61	2.64
Co-morbidity (Charlson)	0	(ref)			
	1+	0.904	-0.23	-4.01	3.54
Functional status ELPHS ADL	Scale 1-4 (increase = worse)	0.727	0.63	-2.93	4.20

†Adjusted for all other variables in the table
* 1 missing value not included

References

1. Wedding U, Pientka L, Höffken K. Quality-of-life in elderly patients with cancer: A short review. European Journal of Cancer, 2007; 43(15):2203 - 2210 doi:10.1016/j.ejca.2007.06.001 https://www.sciencedirect.com/science/article/pii/S0959804907004650?via%3Dihub

2. Hack TF, Degner LF, Watson P, Sinha L. Do patients benefit from participating in medical decision making? Longitudinal follow-up of women with breast cancer. Psycho-oncology, 2006; 15(1):9-19. doi:10.1002/pon.907

3. Tariman JD, Berry DL, Cochrane B, Doorenbos A, Schepp K. Preferred and actual participation roles during health care decision making in persons with cancer: a systematic review. *Ann Oncol* 2010; 21 (6): 1145-1151. doi: 10.1093/annonc/mdp534 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4200024/

4. Pinquart M, Duberstein PR. Information needs and decision-making processes in older cancer patients. Critical reviews in Oncology/Haematology 2004; 51: 69-80 doi: http://dx.doi.org/10.1016/j.critrevonc.2004.04.002

5. Degner LF, Kristjanson LJ, Bowman D, Sloan JA, Carriere KC, O'Neil J *et al*. Information needs and decisional preferences in women with breast cancer. JAMA 1997; 277(18):1485-1492. https://onlinelibrary.wiley.com/doi/abs/10.1046/j.1365-2648.1995.22010134.x

6. Lavelle K, Sowerbutts A, Bundred N, Pilling M, Degner L, Stockton C et al. Is lack of surgery for older breast cancer patients in the UK explained by patient choice or poor health? A prospective cohort study. British Journal of Cancer 2014; **110**:573-583. https://www.ncbi.nlm.nih.gov/pubmed/20162669

7. http://groups.eortc.be/qol/eortc-qlq-c30 (accessed 20 Feb 2017)

8. Tabachnick B, Fidell L. Using Multivariate Statistics (Fourth Edition). 2001. Allyn & Bacon: Boston 2001. p 117

9. Landis JR, Koch GG The measurement of observer agreement for categorical data. Biometrics 1977:33(1):159-174 https://www.jstor.org/stable/pdf/2529310.pdf?refreqid=excelsior%3A8ea484dcd72882787f2eccec2ed2cf53

Appendix 6 Relationship between change in perometer/bioimpedance spectroscopy from 6 to 24 months and the lymphoedema checklist questions

There were greater increases (from 6 to 24 months) in exact perometer values in those women with swelling at 24 months ($p < 0.001$) and in those with heaviness at 24 months ($p = 0.001$).

There were greater increases (from 6 to 24 months) in exact perometer values in those women with swelling between 6 and 24 months ($p = 0.003$) and in those with heaviness between 6 and 24 months ($p = 0.005$).

TABLE 68 Considering lymphoedema checklist responses at 24 months

Change from 6 to 24 months	No swelling at 24 months	Swelling at 24 months	*p*-value
Perometer	*n* = 323; –0.4 (4.7)	*n* = 222 2.0 (8.0)	< 0.001
BIS	*n* = 310; –0.3 (8.0)	*n* = 206; –1.0 (12.7)	0.48
	No numbness at 24 months	Numbness at 24 months	
Perometer	*n* = 145; 0.1 (5.7)	*n* = 408; 0.8 (6.6)	0.28
BIS	*n* = 139; –1.8 (9.4)	*n* = 385; –0.2 (10.2)	0.12
	No heaviness at 24 months	Heaviness at 24 months	
Perometer	*n* = 303; –0.2 (5.3)	*n* = 231; 1.7 (7.5)	0.001
BIS	*n* = 290; –0.8 (8.4)	*n* = 216; –0.4 (11.9)	0.69

TABLE 69 Considering lymphoedema checklist responses between 6 and 24 months

Change from 6 month to 24 months	No swelling between 6 and 24 months	Swelling between 6 and 24 months	*p*-value
Perometer	*n* = 261; –0.3 (4.5)	*n* = 372; 1.1 (7.3)	0.003
BIS	*n* = 255; 0.4 (8.3)	*n* = 338; –1.1 (11.6)	0.076
	No numbness between 6 and 24 months	Numbness between 6 and 24 months	
Perometer	*n* = 64; 0.4 (6.0)	*n* = 569; 0.5 (6.4)	0.91
BIS	*n* = 62; 0.2 (11.9)	*n* = 531; –0.5 (10.1)	0.63
	No heaviness between 6 and 24 months	Heaviness between 6 and 24 months	
Perometer	*n* = 245; –0.4 (5.3)	*n* = 387; 1.0 (6.9)	0.005
BIS	*n* = 237; –0.7 (9.5)	*n* = 356; –0.3 (10.8)	0.62

Appendix 7 L-Dex multifrequency bioimpedance lymphoedema

The 85 patients with lymphoedema are made up of 39 with both perometer and BIS ≥ 10, 30 with only BIS ≥ 10 and 16 with only perometer ≥ 10.

Bioimpedance spectroscopy value by 6 months against lymphoedema by 18 or 24 months.

Lymphoedema defined by perometer > 10% and clinical lymphoedema or appropriately applied sleeve.

In all the analyses that follow, any patients diagnosed with a perometer value > 10% by 6 months were excluded from the analysis ($n = 87$) and any patients with a clinical lymphoedema or sleeve applied before 6 months were excluded from the analysis.

There is a significant relationship between both BIS category by 6 months and lymphoedema defined by perometer of > 10% by 18 months ($p < 0.001$) and clinical lymphoedema or appropriately applied sleeve by 18 months ($p < 0.001$).

For lymphoedema defined by perometer of > 10%, the significant relationship appears to be as a result of the higher rate of lymphoedema, 24%, in those with > 10.

For clinical lymphoedema or applied sleeve, there appears to be a small increase in lymphoedema rate across the < 3, > 3 to < 5, and > 5 to < 10 categories; the rate increased from 7% and 16% across the three categories. The significant relationship appears mainly to be as a result of the higher rate of lymphoedema, 36%, in those with BIS of > 10.

TABLE 70 Bioimpedance spectroscopy value by 6 months against lymphoedema by 18 months

	Lymphoedema defined by perometer of > 10%		Clinical lymphoedema or appropriately applied sleeve	
BIS value by 6 months	No lymphoedema by 18 months ($n = 662$)	Lymphoedema by 18 months ($n = 77$)	No lymphoedema by 18 months ($n = 643$)	Lymphoedema by 18 months ($n = 114$)
< 3	327 (93%)	23 (7%)	324 (93%)	25 (7%)
> 3 to < 5	80 (91%)	8 (9%)	78 (90%)	9 (10%)
> 5 to < 10	156 (92%)	14 (8%)	145 (84%)	27 (16%)
> 10	99 (76%)	32 (24%)	96 (64%)	53 (36%)

24 months

TABLE 71 Bioimpedance spectroscopy value by 6 months against lymphoedema by 24 months

	Lymphoedema defined by perometer of > 10%		Clinical lymphoedema or appropriately applied sleeve	
BIS value by 6 months	No lymphoedema by 24 months ($n = 596$)	Lymphoedema by 24 months ($n = 101$)	No lymphoedema by 24 months ($n = 577$)	Lymphoedema by 24 months ($n = 137$)
< 3	298 (91%)	30 (9%)	297 (91%)	31 (9%)
> 3 to < 5	68 (85%)	12 (15%)	66 (85%)	12 (15%)
> 5 to < 10	142 (87%)	21 (13%)	128 (78%)	36 (22%)
> 10	88 (70%)	38 (30%)	86 (60%)	58 (40%)

Appendix 8 Lymphoedema scoring models

Lymphoedema scoring model for 10% perometer volume increase definition

Of the 1097 patients in the data set, 326 were classified as having either an appropriately applied sleeve or clinical lymphoedema.

There were 51 patients who were identified as being given their sleeve as part of the PLACE trial; these patients were excluded from consideration in the following analysis.

A further nine patients were excluded because of issues with the sleeve application. These issues included having a sleeve applied to the contralateral arm, having a sleeve when entering the study, and having hand swelling only.

There were 266 patients with an appropriately applied sleeve or clinical lymphoedema in the reduced 1037 patient data set. There were 25 patients with sleeves applied who were deemed not to have clinical lymphoedema due to insufficient evidence in the notes; there were 29 patients who did not have a sleeve applied but were deemed to have clinical lymphoedema.

Model at 6 months

The variables considered for the scoring model were: perometer at 6 months (categorical), BIS at 6 months (categorical), TOI at 6 months, FACT-B total at 6 months, ARM subscale at 6 months, lymphoedema checklist questions at 6 months (swelling, numbness, heaviness), B3 at 6 months (categorical: 0–2, considerable swelling vs. 3–4, little to no swelling), age, BMI at 6 months, ER status, number of positive nodes, adjuvant chemotherapy and adjuvant radiotherapy.

Prediction scoring model 1

A total of 711 patients were included in this analysis.

Variable at 6 months	OR (95% CI)	*p*-value
Perometer		
≥ 3% to < 5% increase vs. < 3% increase	1.92 (0.96 to 3.86)	< 0.001
≥ 5% to < 10% increase vs. < 3% increase	7.36 (4.10 to 13.24)	
BIS		
≥ 3 to < 5 increase vs. < 3 increase	1.39 (0.57 to 3.38)	0.030
≥ 5 to < 10 increase vs. < 3 increase	1.87 (0.96 to 3.64)	
≥ 10 increase vs. < 3 increase		
BMI (kg/m^2)		
> 25 to ≤ 30 vs. ≤ 25	1.53 (0.80 to 2.91)	0.015
> 30 vs. ≤ 25	2.53 (1.34 to 4.77)	
Number of positive nodes (per-node increase)	1.08 (1.04 to 1.12)	< 0.001

A scoring model was produced based on the regression coefficients from the final model. The individual scores are the regression coefficients for binary or categorical variables rounded to the nearest 0.5 and the regression coefficients for continuous variables to 2 decimal places due to their per-unit increase interpretation. The total 'diagnostic' score is given by summing the individual scores. A patient with a higher total score is more likely to have a 10% perometer volume increase.

Variable at 6 months	Score
Perometer	
< 3% increase	0
≥ 3% to < 5% increase	0.5
≥ 5% to < 10% increase	2
BIS	
< 3 increase	0
≥ 3 to < 5 increase	0.5
≥ 5 to < 10 increase	0.5
≥ 10 increase	1
BMI (kg/m^2)	
≤ 25	0
> 25 to ≤ 30	0.5
> 30	1
Number of positive nodes	0.08 × number of positive nodes

This scoring model gives an AUROC of 0.80 (95% CI 0.74–0.85) (*Figure 24*).

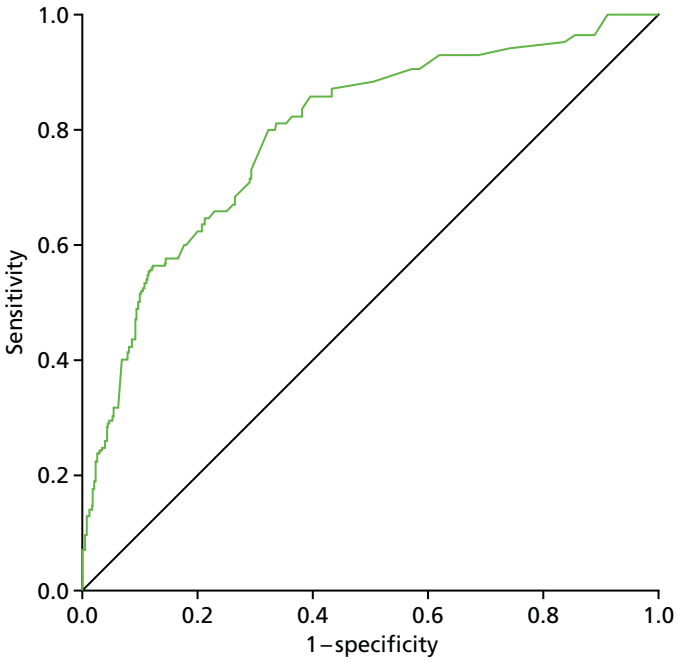


FIGURE 24 Prediction scoring model 1: AUROC curve. Diagonal segments are produced by ties.

For a cut-off score of 1.58, where a patient with a score of ≥ 1.58 would be predicted to have a 10% perometer volume increase, the scoring model would give a sensitivity of 80.0% (68/85), specificity of 67.7% (424/626), PPV of 25.2% (68/270) and NPV of 96.1% (424/441). The cut-off score was chosen to maximise the sum of the sensitivity and specificity, giving equal weight to sensitivity and specificity.

Prediction scoring model 2: excluding bioimpedance spectroscopy at 6 months

A total of 740 patients were included in this analysis.

Variable at 6 months	OR (95% CI)	*p*-value
Perometer		
≥ 3% to < 5% increase vs. < 3% increase	2.47 (1.27 to 4.79)	< 0.001
≥ 5% to < 10% increase vs. < 3% increase	9.10 (5.24 to 15.79)	
BMI (kg/m^2)		
> 25 to ≤ 30 vs. ≤ 25	1.53 (0.82 to 2.86)	0.025
> 30 vs. ≤ 25	2.34 (1.26 to 4.35)	
Number of positive nodes (per-node increase)	1.08 (1.04 to 1.11)	< 0.001

A scoring model was produced based on the regression coefficients from the final model as described previously. The total 'diagnostic' score is given by summing the individual scores. A patient with a higher total score is more likely to have a 10% perometer volume increase.

Variable at 6 months	Score
Perometer	
< 3% increase	0
≥ 3% to < 5% increase	1
≥ 5% to < 10% increase	2
BMI (kg/m^2)	
≤ 25	0
> 25 to ≤ 30	0.5
> 30	1
Number of positive nodes	0.07 × number of positive nodes

This scoring model gives an AUROC of 0.77 (95% CI 0.71 to 0.82) (*Figure 25*).

For a cut-off score of 1.41, where a patient with a score of 1.41 or above would be predicted to have a 10% perometer volume increase, the scoring model would give a sensitivity of 72.1% (62/86), a specificity of 72.2% (472/654), a PPV of 25.4% (62/244) and a NPV of 95.2% (472/496). The cut-off score was chosen to maximise the sum of the sensitivity and specificity, giving equal weight to sensitivity and specificity.

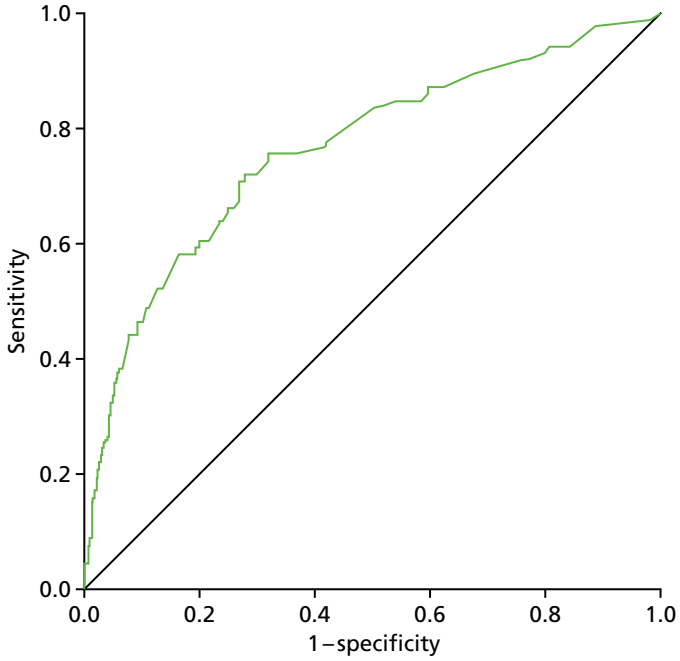


FIGURE 25 Prediction scoring model 2: AUROC curve. Diagonal segments are produced by ties.

Prediction scoring model at 1 month

The variables considered for the scoring model were perometer at 1 month (categorical), BIS at 1 month (categorical), TOI at pre-surgery, FACT-B total at pre-surgery, ARM subscale at pre-surgery, lymphoedema checklist questions at pre-surgery (swelling, numbness, heaviness), age, BMI at pre-surgery, ER status, number of positive nodes, adjuvant chemotherapy and adjuvant radiotherapy.

Prediction scoring model 3

A total of 506 patients were included in this analysis.

Variable	OR (95% CI)	*p*-value
Perometer at 1 month		
≥ 3% to < 5% increase vs. < 3% increase	2.21 (1.09 to 4.48)	< 0.001
≥ 5% to < 10% increase vs. < 3% increase	3.68 (1.92 to 7.03)	
≥ 10% increase vs. < 3% increase	7.42 (2.21 to 24.93)	
BIS at 1 month		
≥ 3 to < 5 increase vs. < 3 increase	2.11 (1.00 to 4.46)	0.013
≥ 5 to < 10 increase vs. < 3 increase	1.00 (0.49 to 2.04)	
≥ 10 increase vs. < 3 increase	2.54 (1.33 to 4.85)	
Lymphoedema checklist swelling at pre surgery (yes vs. no)	1.89 (1.00 to 3.59)	0.051
Number of positive nodes (per-node increase)	1.08 (1.03 to 1.12)	< 0.001

A scoring model was produced based on the regression coefficients from the final model as described previously. The total 'diagnostic' score is given by summing the individual scores. A patient with a higher total score is more likely to have a 10% perometer volume increase.

Variable	Score
Perometer at 1 month	
< 3% increase	0
≥ 3% to < 5% increase	1
≥ 5% to < 10% increase	1.5
≥ 10% increase	2
BIS at 1 month	
< 3 increase	0
≥ 3 to < 5 increase	0.5
≥ 5 to < 10 increase	0.5
≥ 10 increase	1
Lymphoedema checklist swelling at pre surgery	
No	0
Yes	0.5
Number of positive nodes	0.07 × number of positive nodes

This scoring model gives an AUROC of 0.71 (95% CI 0.65 to 0.77) (*Figure 26*).

For a cut-off score of 1.25, where a patient with a score of ≥ 1.25 would be predicted to have a 10% perometer volume increase, the scoring model would give a sensitivity of 65.5% (55/84), specificity of 69.9% (295/422), PPV of 30.2% (55/182), and NPV of 91.0% (295/324). The cut-off score was chosen to maximise the sum of the sensitivity and specificity, giving equal weight to sensitivity and specificity.

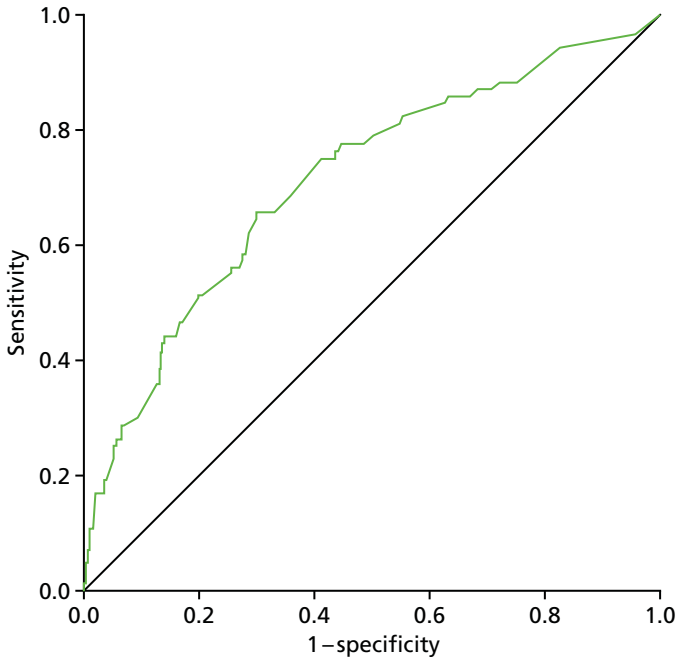


FIGURE 26 Prediction scoring model 3: AUROC curve. Diagonal segments are produced by ties.

Prediction scoring model 4: excluding bioimpedance spectroscopy at 1 month

A total of 522 patients were included in this analysis.

Variable	OR (95% CI)	*p*-value
Perometer at 1 month		
≥ 3 to < 5% increase vs. < 3% increase	2.11 (1.06 to 4.19)	< 0.001
≥ 5 to < 10% increase vs. < 3% increase	4.02 (2.18 to 7.39)	
≥ 10% increase vs. < 3% increase	8.89 (2.86 to 27.64)	
Lymphoedema checklist swelling at pre surgery (yes vs. no)	2.22 (1.21 to 4.09)	0.010
Number of positive nodes (per-node increase)	1.08 (1.04 to 1.12)	< 0.001

A scoring model was produced based on the regression coefficients from the final model as described previously. The total 'diagnostic' score is given by summing the individual scores. A patient with a higher total score is more likely to have a 10% perometer volume increase.

Variable	Score
Perometer at 1 month	
< 3% increase	0
≥ 3% to < 5% increase	0.5
≥ 5% to < 10% increase	1.5
≥ 10% increase	2
Lymphoedema checklist swelling at pre surgery	
No	0
Yes	1
Number of positive nodes	0.07 × number of positive nodes

This scoring model gives an AUROC of 0.71 (95% CI 0.64 to 0.77) (*Figure 27*).

For a cut-off score of 0.82, where a patient with a score of ≥ 0.82 would be predicted to have a 10% perometer volume increase, the scoring model would give a sensitivity of 62.9% (56/89), specificity of 70.7% (306/433), PPV of 30.6% (56/183), and NPV of 90.3% (306/339). The cut-off score was chosen to maximise the sum of the sensitivity and specificity, giving equal weight to sensitivity and specificity.

Scoring model with clinical lymphoedema or appropriately applied sleeve

Prediction scoring model at 6 months

The variables considered for the scoring model were perometer at 6 months (categorical), BIS at 6 months (categorical), TOI at 6 months, FACT-B total at 6 months, ARM subscale at 6 months, lymphoedema checklist questions at 6 months (swelling, numbness, heaviness), B3 at 6 months (categorical: 0–2, considerable swelling vs. 3–4, little to no swelling), age, BMI at 6 months, ER status, number of positive nodes, adjuvant chemotherapy and adjuvant radiotherapy.

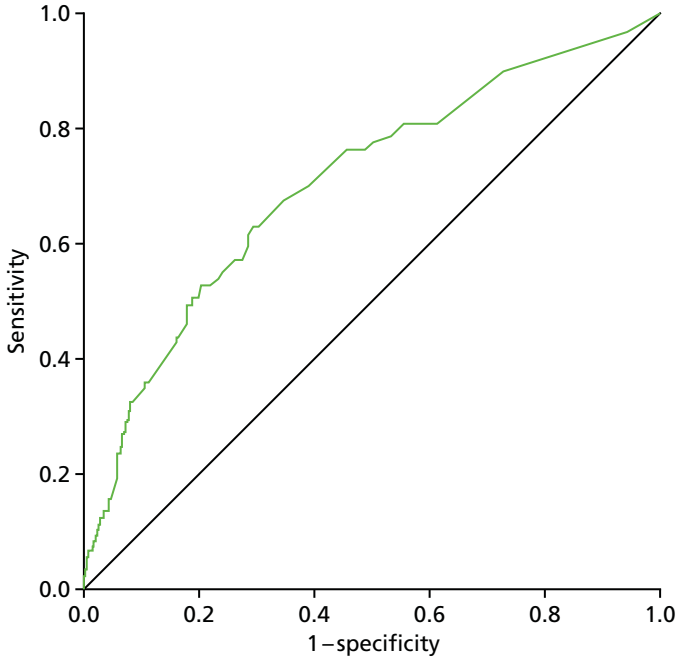


FIGURE 27 Clinical lymphoedema prediction scoring model at 6 months. Diagonal segments are produced by ties.

Patients who had a perometer value ≥ 10 before or at 6 months were excluded from the analysis.

A total of 528 patients were included in this analysis.

Prediction model at 6 months

Variable at 6 months	OR (95% CI)	*p*-value
Perometer		
≥ 3% to < 5% increase vs. < 3% increase	1.99 (0.97 to 4.09)	< 0.001
≥ 5% to < 10% increase vs. < 3% increase	4.47 (2.25 to 8.85)	
BIS		
≥ 3 to < 5 increase vs. < 3 increase	1.80 (0.69 to 4.67)	0.002
≥ 5 to < 10 increase vs. < 3 increase	2.85 (1.38 to 5.89)	
≥ 10 increase vs. < 3 increase	3.68 (1.80 to 7.55)	
Lymphoedema checklist swelling (yes vs. no)	2.15 (1.21 to 3.82)	0.009
ER status (negative vs. positive)	0.38 (0.15 to 0.97)	0.042
Adjuvant radiotherapy (yes vs. no)	4.52 (1.51 to 13.56)	0.007

A scoring model was produced based on the regression coefficients from the final model as described previously. The total 'diagnostic' score is given by summing the individual scores. A patient with a higher total score is more likely to have a clinical lymphoedema or require a sleeve.

Prediction scoring model at 6 months

Variable at 6 months	Score
Perometer	
< 3% increase	0
≥ 3% to < 5% increase	0.5
≥ 5% to < 10% increase	1.5
BIS	
< 3 increase	0
≥ 3 to < 5 increase	0.5
≥ 5 to < 10 increase	1
≥ 10 increase	1.5
Lymphoedema checklist swelling	
No	0
Yes	1
ER status	
Negative	0
Positive	1
Adjuvant radiotherapy	
No	0
Yes	1.5

This scoring model gives an AUROC of 0.78 (95% CI 0.72 to 0.84) (*Figure 28*).

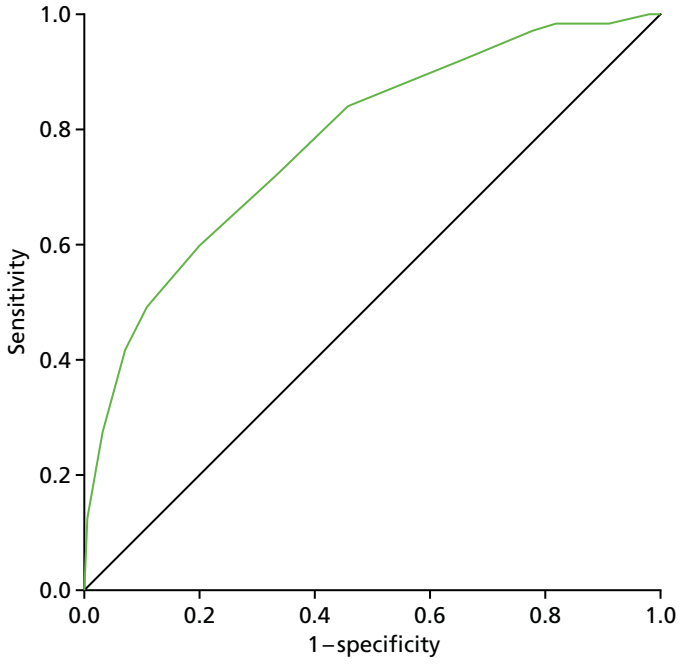


FIGURE 28 Prediction scoring model 2: AUROC curve. Diagonal segments are produced by ties.

For a cut-off score of 4, where a patient with a score of 4 or above would be predicted to have clinical lymphoedema or a sleeve applied, the scoring model would give a sensitivity of 59.4% (41/69), specificity of 80.4% (369/459), PPV of 31.3% (41/131) and NPV of 92.9% (369/397). The cut-off score was chosen to maximise the sum of the sensitivity and specificity, giving equal weight to sensitivity and specificity.

Prediction scoring model: excluding bioimpedance spectroscopy at 6 months

A total of 548 patients were included in this analysis.

Prediction Model –excluding BIS at 6 months.

Variable at 6 months	OR (95% CI)	*p*-value
Perometer		
≥ 3% to < 5% increase vs. < 3% increase	2.69 (1.36 to 5.31)	< 0.001
≥ 5% to < 10% increase vs. < 3% increase	5.89 (3.07 to 11.30)	
Lymphoedema checklist swelling (yes vs. no)	2.31 (1.33 to 4.02)	0.003
ER status (negative vs. positive)	0.40 (0.16 to 0.98)	0.045
Adjuvant radiotherapy (yes vs. no)	4.74 (1.61 to 13.92)	0.005

A scoring model was produced based on the regression coefficients from the final model as described previously. The total 'diagnostic' score is given by summing the individual scores. A patient with a higher total score is more likely to have a clinical lymphoedema or require a sleeve.

Prediction scoring model: excluding bioimpedance spectroscopy at 6 months

Variable at 6 months	Score
Perometer	
< 3% increase	0
≥ 3% to < 5% increase	1
≥ 5% to < 10% increase	2
Lymphoedema checklist swelling	
No	0
Yes	1
ER status	
Negative	0
Positive	1
Adjuvant radiotherapy	
No	0
Yes	1.5

This scoring model gives an AUROC of 0.76 (95% CI 0.70 to 0.82) (*Figure 29*).

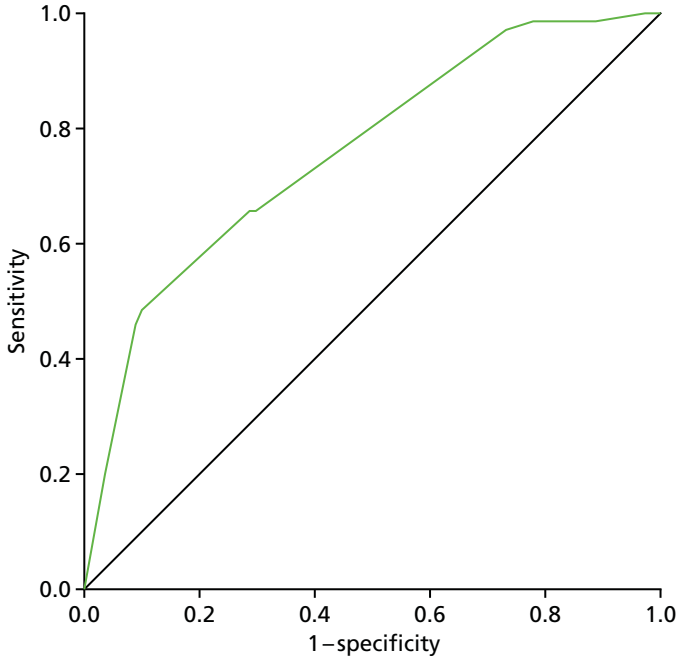


FIGURE 29 Prediction of clinical lymphoedema excluding BIS at 6 months. Diagonal segments are produced by ties.

For a cut-off score of 4, where a patient with a score of ≥ 4 would be predicted to have clinical lymphoedema or a sleeve applied, the scoring model would give a sensitivity of 48.6% (34/70), specificity of 90.0% (430/478), PPV of 41.5% (34/82) and NPV of 92.3% (430/466). The cut-off score was chosen to maximise the sum of the sensitivity and specificity, giving equal weight to sensitivity and specificity.

Prediction scoring model at 1 month

The variables considered for the scoring model were: perometer at 1 month (categorical), BIS at 1 month (categorical), TOI at pre-surgery, FACT-B total at pre-surgery, ARM subscale at pre-surgery, lymphoedema checklist questions at pre-surgery (swelling, numbness, heaviness), B3 at pre-surgery (categorical: 0–2, considerable swelling vs. 3–4, little to no swelling), age, BMI at pre-surgery, ER status, number of positive nodes, adjuvant chemotherapy and adjuvant radiotherapy.

A total of 794 patients were included in this analysis.

Prediction model at 1 month

Variable at 1 month	OR (95% CI)	*p*-value
Perometer		
≥ 3% to < 5% increase vs. < 3% increase	1.39 (0.82 to 2.36)	< 0.001
≥ 5% to < 10% increase vs. < 3% increase	3.40 (2.14 to 5.40)	
≥ 10% increase vs. < 3% increase	4.07 (1.56 to 10.62)	
BIS		
≥ 3 to < 5 increase vs. < 3 increase	2.06 (1.19 to 3.58)	0.005
≥ 5 to < 10 increase vs. < 3 increase	1.01 (0.62 to 1.64)	
≥ 10 increase vs. < 3 increase	1.96 (1.21 to 3.15)	
Adjuvant radiotherapy (yes vs. no)	1.91 (1.09 to 3.34)	0.023
Number of positive nodes (per-node increase)	1.05 (1.02 to 1.08)	< 0.001

A scoring model was produced based on the regression coefficients from the final model. The individual scores are the regression coefficients for binary or categorical variables rounded to the nearest 0.5 and the regression coefficients for continuous variables to 2 decimal places due to their per-unit increase interpretation. The total 'diagnostic' score is given by summing the individual scores. A patient with a higher total score is more likely to have a clinical lymphoedema or require a sleeve.

Prediction scoring model at 1 month

Variable at 1 month	Score
Perometer	
< 3% increase	0
≥ 3% to < 5% increase	0.5
≥ 5% to < 10% increase	1
≥ 10% increase	1.5
BIS	
< 3 increase	0
≥ 3 to < 5 increase	0.5
≥ 5 to < 10 increase	0.5
≥ 10 increase	0.5
Adjuvant radiotherapy	
No	0
Yes	0.5
Number of positive nodes	0.05 × number of positive nodes

This scoring model gives an AUROC of 0.67 (95% CI 0.63 to 0.72) (*Figure 30*).

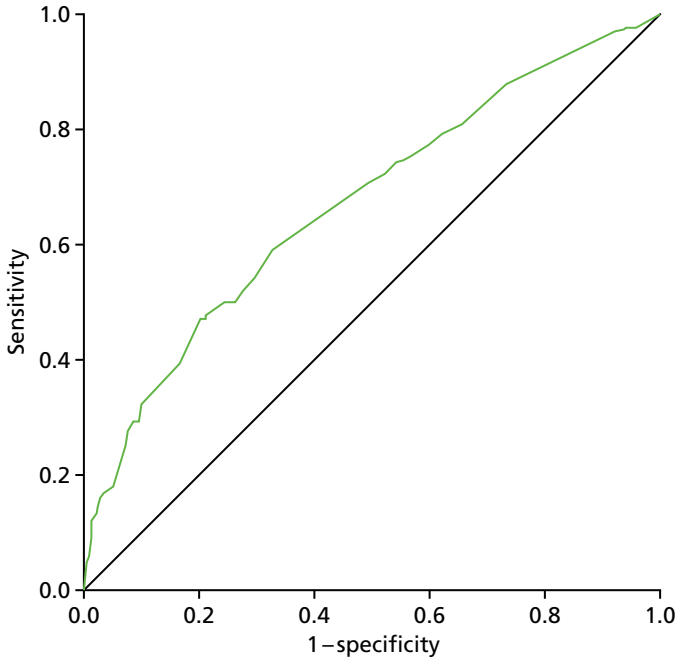


FIGURE 30 Prediction scoring model of clinical lymphoedema at 1 month. Diagonal segments are produced by ties.

For a cut-off score of 1.55, where a patient with a score of ≥ 1.55 would be predicted to have clinical lymphoedema or a sleeve applied, the scoring model would give a sensitivity of 47.1% (82/174), specificity of 79.8% (495/620), PPV of 39.6% (82/207), and NPV of 84.3% (495/587). The cut-off score was chosen to maximise the sum of the sensitivity and specificity, giving equal weight to sensitivity and specificity.

Prediction scoring model: excluding bioimpedance spectroscopy at 1 month

A total of 837 patients were included in this analysis.

Variable at 1 month	OR (95% CI)	*p*-value
Perometer		
≥ 3% to < 5% increase vs. < 3% increase	1.45 (0.88 to 2.41)	< 0.001
≥ 5% to < 10% increase vs. < 3% increase	3.61 (2.33 to 5.59)	
≥ 10% increase vs. < 3% increase	5.70 (2.32 to 14.02)	
Adjuvant radiotherapy (yes vs. no)	1.93 (1.12 to 3.31)	0.018
Number of positive nodes (per-node increase)	1.05 (1.02 to 1.08)	0.001

A scoring model was produced based on the regression coefficients from the final model. The individual scores are the regression coefficients for binary or categorical variables rounded to the nearest 0.5 and the regression coefficients for continuous variables to 2 decimal places due to their per unit increase interpretation. The total 'diagnostic' score is given by summing the individual scores. A patient with a higher total score is more likely to have a clinical lymphoedema or require a sleeve.

Variable at 1 month	Score
Perometer	
< 3% increase	0
≥ 3% to < 5% increase	0.5
≥ 5% to < 10% increase	1
≥ 10% increase	1.5
Adjuvant radiotherapy	
No	0
Yes	0.5
Number of positive nodes	0.05 × number of positive nodes

Note: the ARM subscale is statistically significant if included in the above model. However, only 558 patients would be included in the model and the AUC is not improved by a large amount by its inclusion (AUC 0.67, 95% CI 0.62 to 0.73).

This scoring model gives an AUROC of 0.67 (95% CI 0.62 to 0.71) (*Figure 31*).

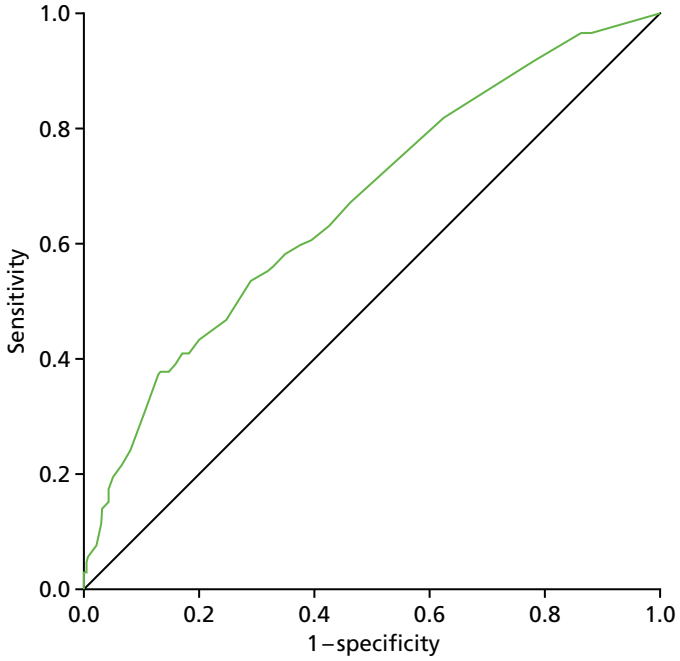


FIGURE 31 Prediction scoring model of clinical lymphoedema at 1 month excluding BIS. Diagonal segments are produced by ties.

For a cut-off score of 1.55, where a patient with a score of ≥ 1.55 would be predicted to have a clinically identified lymphoedema or sleeve applied, the scoring model would give a sensitivity of 53.6% (98/183), specificity of 70.9% (464/654), PPV of 34.0% (98/288), and NPV of 84.5% (464/549). The cut-off score was chosen to maximise the sum of the sensitivity and specificity, giving equal weight to sensitivity and specificity.

Appendix 9 Composite end-points analysis

TABLE 72 Clinical lymphoedema/appropriately applied sleeve

	Time point					
	At 3 months	At 6 months	At 9 months	At 12 months	At 18 months	At 24 months
Measure	29	48	46	43	31	24
Perometer ≥ 10%	11/27 (41%)	17 (35%)	19 (41%)	14/41 (34%)	12/30 (40%)	10 (42%)
Perometer ≥ 9%	11/27 (41%)	22 (46%)	24 (52%)	15/41 (37%)	12/30 (40%)	12 (50%)
Perometer ≥ 8%	14/27 (52%)	23 (48%)	27 (59%)	18/41 (44%)	13/30 (43%)	13 (54%)
Perometer ≥ 5%	16/27 (59%)	31 (65%)	39 (85%)	28/41 (68%)	21/30 (70%)	17 (71%)
BIS of ≥ 10	10/27 (37%)	27/47 (57%)	28/43 (65%)	17/39 (44%)	14/29 (48%)	10/23 (43%)
B3 of ≤ 2	14/23 (61%)	28/39 (72%)	21/42 (50%)	19/35 (54%)	13/24 (54%)	8/21 (38%)
Perometer ≥ 10% or B3 of ≤ 2	22/26 (85%)	32/41 (78%)	28/44 (64%)	26/38 (68%)	17/27 (63%)	15 (63%)
Perometer ≥ 9% or B3 of ≤ 2	22/26 (85%)	34/42 (81%)	31/44 (70%)	26/38 (68%)	17/27 (63%)	16 (67%)
Perometer ≥ 8% or B3 of ≤ 2	23/26 (88%)	35/42 (83%)	33/44 (75%)	27/38 (71%)	17/27 (63%)	17 (71%)
Perometer ≥ 5% and B3 of ≤ 2	6/23 (26%)	20/44 (45%)	19/42 (45%)	15/37 (41%)	12/26 (46%)	5/21 (24%)
Perometer ≥ 8% and B3 of ≤ 2	5/24 (21%)	16/45 (36%)	15/44 (34%)	10/38 (26%)	9/27 (33%)	4/21 (19%)

In all of the following tables, the best NPV rates with lymphoedema (at that time point) and the best PPV rates [i.e. the best at finding patients with lymphoedema (at that time point)] are shown.

TABLE 73 At 3 months

Measure	Sensitivity	Specificity	PPV	NPV
Perometer ≥ 10%	11/27 (41%)	828/850 (97%)	11/33 (33%)	828/844 (98%)
Perometer ≥ 9%	11/27 (41%)	818/850 (96%)	11/43 (26%)	818/834 (98%)
Perometer ≥ 8%	14/27 (52%)	801/850 (94%)	14/63 (22%)	801/814 (98%)
Perometer ≥ 5%	16/27 (59%)	728/850 (86%)	16/138 (12%)	728/739 (99%)
BIS ≥ 10	10/27 (37%)	753/836 (90%)	10/93 (11%)	753/770 (98%)
B3 of ≤ 2	14/23 (61%)	593/750 (79%)	14/171 (8%)	593/602 (99%)
Volume ≥ 200 ml	16/27 (59%)	640/849 (75%)	16/225 (7%)	640/651 (98%)
Volume ≥ 250 ml	10/27 (37%)	698/849 (82%)	10/161 (6%)	698/715 (98%)
Volume ≥ 300 ml	8/27 (30%)	748/849 (88%)	8/109 (7%)	748/767 (98%)
Perometer ≥ 10% or B3 of ≤ 2	22/26 (85%)	564/735 (77%)	22/193 (11%)	564/568 (99%)
Perometer ≥ 9% or B3 of ≤ 2	22/26 (85%)	561/736 (76%)	22/197 (11%)	561/565 (99%)
Perometer ≥ 8% or B3 of ≤ 2	23/26 (88%)	553/740 (75%)	23/210 (11%)	553/556 (99%)
Perometer ≥ 5% or B3 of ≤ 2	24/27 (89%)	510/755 (68%)	24/269 (9%)	510/513 (99%)
BIS ≥ 10 or B3 of ≤ 2	19/25 (76%)	515/735 (70%)	19/239 (8%)	515/521 (99%)
Perometer ≥ 10% or BIS of ≥ 10	13/26 (50%)	720/817 (88%)	13/110 (12%)	720/733 (98%)
Perometer ≥ 5% and B3 of ≤ 2	6/23 (26%)	811/845 (96%)	6/40 (15%)	811/828 (98%)
Perometer ≥ 8% and B3 of ≤ 2	5/24 (21%)	841/860 (98%)	5/24 (21%)	841/860 (98%)
Perometer ≥ 9% and B3 of ≤ 2	3/24 (13%)	850/864 (98%)	3/17 (18%)	850/871 (98%)
Perometer ≥ 10% and B3 of ≤ 2	3/24 (13%)	857/865 (99%)	3/11 (27%)	857/878 (98%)
Volume ≥ 200 ml and B3 of ≤ 2	7/23 (30%)	786/828 (95%)	7/49 (14%)	786/802 (98%)
Volume ≥ 250 ml and B3 of ≤ 2	5/25 (20%)	808/845 (96%)	5/42 (12%)	808/828 (98%)
Perometer ≥ 10% and BIS ≥ 10	8/28 (29%)	861/869 (99%)	8/16 (50%)	861/881 (98%)
Perometer ≥ 9% and BIS ≥ 10	8/28 (29%)	858/869 (99%)	8/19 (42%)	858/878 (98%)
Perometer ≥ 10% and BIS ≥ 10 and B3 of ≤ 2	3/26 (12%)	871/876 (99%)	3/8 (38%)	871/894 (97%)
Perometer ≥ 9% and BIS ≥ 10 and B3 of ≤ 2	3/26 (12%)	868/875 (99%)	3/10 (30%)	868/891 (97%)

Those patients with lymphoedema at 3 months are not included in the numbers in *Table 74*.

TABLE 74 At 6 months

Measure	Sensitivity	Specificity	PPV	NPV
Perometer ≥ 10%	17/48 (35%)	732/776 (94%)	17/61 (28%)	732/763 (96%)
Perometer ≥ 9%	22/48 (46%)	723/776 (93%)	22/75 (29%)	723/749 (97%)
Perometer ≥ 8%	23/48 (48%)	715/776 (92%)	23/84 (27%)	715/740 (97%)
Perometer ≥ 5%	31/48 (65%)	631/776 (81%)	31/176 (18%)	631/648 (97%)
BIS ≥ 10	24/47 (57%)	630/759 (83%)	27/156 (17%)	630/650 (97%)
B3 ≤ 2	28/39 (72%)	556/703 (79%)	28/175 (16%)	556/567 (98%)
Perometer ≥ 10% or B3 ≤ 2	32/41 (78%)	521/689 (76%)	32/200 (16%)	521/530 (98%)
Perometer ≥ 9% or B3 ≤ 2	34/42 (81%)	514/690 (74%)	34/210 (16%)	514/522 (98%)
Perometer ≥ 8% or B3 ≤ 2	35/42 (83%)	508/692 (73%)	35/219 (16%)	508/515 (99%)
Perometer ≥ 5% or B3 ≤ 2	39/43 (91%)	454/704 (64%)	39/289 (13%)	454/458 (99%)
BIS ≥ 10 or B3 ≤ 2	37/43 (86%)	455/692 (66%)	37/274 (14%)	455/461 (99%)
Perometer ≥ 5% and B3 ≤ 2	20/44 (45%)	733/775 (95%)	20/62 (32%)	733/757 (97%)
Perometer ≥ 8% and B3 ≤ 2	16/45 (36%)	763/787 (97%)	16/40 (40%)	763/792 (96%)
Perometer ≥ 9% and B3 ≤ 2	16/45 (36%)	765/789 (97%)	16/40 (40%)	765/794 (96%)
Perometer ≥ 10% and B3 ≤ 2	13/46 (28%)	767/790 (97%)	13/36 (36%)	767/800 (96%)
Perometer ≥ 10% and BIS ≥ 10	15/48 (31%)	758/789 (96%)	15/46 (33%)	758/791 (96%)
Perometer ≥ 9% and BIS ≥ 10	20/48 (42%)	753/789 (95%)	20/56 (36%)	753/781 (96%)
Perometer ≥ 10% and BIS ≥ 10 and B3 ≤ 2	13/47 (28%)	776/792 (98%)	13/29 (45%)	776/810 (96%)
Perometer ≥ 9% and BIS ≥ 10 and B3 ≤ 2	16/46 (35%)	775/792 (98%)	16/33 (48%)	775/805 (96%)

Those patients with lymphoedema up to 6 months are not included in the numbers in *Table 75*.

TABLE 75 At 9 months

Measure	Sensitivity	Specificity	PPV	NPV
Perometer ≥ 10%	19/46 (41%)	580/594 (98%)	19/33 (58%)	580/607 (96%)
Perometer ≥ 9%	24/46 (52%)	577/594 (97%)	24/41 (59%)	577/599 (96%)
Perometer ≥ 8%	27/46 (59%)	568/594 (96%)	27/53 (51%)	568/587 (97%)
Perometer ≥ 5%	39/46 (85%)	522/594 (88%)	39/111 (35%)	522/529 (99%)
BIS ≥ 10	28/43 (65%)	511/577 (89%)	28/94 (30%)	511/526 (97%)
B3 ≤ 2	21/42 (50%)	445/526 (85%)	21/102 (21%)	445/466 (95%)
Perometer ≥ 10% or B3 ≤ 2	28/44 (64%)	428/518 (83%)	28/118 (24%)	428/444 (96%)
Perometer ≥ 9% or B3 ≤ 2	31/44 (70%)	425/518 (82%)	31/124 (25%)	425/438 (97%)
Perometer ≥ 8% or B3 ≤ 2	33/44 (75%)	418/519 (81%)	33/134 (25%)	418/429 (97%)
Perometer ≥ 5% or B3 ≤ 2	41/46 (89%)	385/525 (73%)	41/181 (23%)	385/390 (99%)
BIS ≥ 10 or B3 ≤ 2	35/44 (80%)	377/513 (73%)	35/171 (20%)	377/386 (98%)
Perometer ≥ 5% and B3 ≤ 2	19/42 (45%)	582/595 (98%)	19/32 (59%)	582/605 (96%)
Perometer ≥ 8% and B3 ≤ 2	15/44 (34%)	595/601 (99%)	15/21 (71%)	595/624 (95%)
Perometer ≥ 9% and B3 ≤ 2	14/44 (32%)	597/602 (99%)	14/19 (74%)	597/627 (95%)
Perometer ≥ 10% and B3 ≤ 2	12/44 (27%)	597/602 (99%)	12/17 (71%)	597/629 (95%)
Perometer ≥ 10% and BIS ≥ 10	15/46 (33%)	587/598 (98%)	15/26 (58%)	587/618 (95%)
Perometer ≥ 9% and BIS ≥ 10	18/46 (39%)	585/598 (98%)	18/31 (58%)	585/613 (95%)
Perometer ≥ 10% and BIS ≥ 10 and B3 ≤ 2	10/44 (23%)	600/604 (99%)	10/14 (71%)	600/634 (95%)
Perometer ≥ 9% and BIS ≥ 10 and B3 ≤ 2	11/44 (25%)	600/604 (99%)	11/15 (73%)	600/633 (95%)

Those patients with lymphoedema up to 9 months are not included in the numbers in *Table 76*.

TABLE 76 At 12 months

Measure	Sensitivity	Specificity	PPV	NPV
Perometer ≥ 10%	14/41 (34%)	649/666 (97%)	14/31 (45%)	649/676 (96%)
Perometer ≥ 9%	15/41 (37%)	639/666 (96%)	15/42 (36%)	639/665 (96%)
Perometer ≥ 8%	18/41 (44%)	631/666 (95%)	18/53 (34%)	631/654 (96%)
Perometer ≥ 5%	28/41 (68%)	588/666 (88%)	28/106 (26%)	588/601 (98%)
BIS ≥ 10	17/39 (44%)	573/641 (89%)	17/85 (20%)	573/595 (96%)
B3 ≤ 2	19/35 (54%)	484/585 (83%)	19/120 (16%)	484/500 (97%)
Perometer ≥ 10% or B3 ≤ 2	26/38 (68%)	469/580 (81%)	26/137 (19%)	469/481 (98%)
Perometer ≥ 9% or B3 ≤ 2	26/38 (68%)	463/580 (80%)	26/143 (18%)	463/475 (97%)
Perometer ≥ 8% or B3 ≤ 2	27/38 (71%)	458/582 (79%)	27/151 (18%)	458/469 (98%)
Perometer ≥ 5% or B3 ≤ 2	32/39 (82%)	431/588 (73%)	32/189 (17%)	431/438 (98%)
BIS ≥ 10 or B3 ≤ 2	26/37 (70%)	423/576 (73%)	26/179 (15%)	423/434 (97%)
Perometer ≥ 5% and B3 ≤ 2	15/37 (41%)	641/663 (97%)	15/37 (41%)	641/663 (97%)
Perometer ≥ 8% and B3 ≤ 2	10/38 (26%)	657/669 (98%)	10/22 (45%)	657/685 (96%)
Perometer ≥ 9% and B3 ≤ 2	8/38 (21%)	660/671 (98%)	8/19 (42%)	660/690 (96%)
Perometer ≥ 10% and B3 ≤ 2	7/38 (18%)	664/671 (99%)	7/14 (50%)	664/695 (96%)
Perometer ≥ 10% and BIS ≥ 10	9/40 (23%)	658/669 (98%)	9/20 (45%)	658/689 (96%)
Perometer ≥ 9% and BIS ≥ 10	9/40 (23%)	653/669 (98%)	9/25 (36%)	653/684 (95%)
Perometer ≥ 10% and BIS ≥ 10 and B3 ≤ 2	5/38 (13%)	668/674 (99%)	5/11 (45%)	668/701 (95%)
Perometer ≥ 9% and BIS ≥ 10 and B3 ≤ 2	5/38 (13%)	667/674 (99%)	5/12 (42%)	667/700 (95%)

Those patients with lymphoedema up to 12 months are not included in the numbers in *Table 77*.

TABLE 77 At 18 months

Measure	Sensitivity	Specificity	PPV	NPV
Perometer ≥ 10%	12/30 (40%)	551/568 (97%)	12/29 (41%)	551/569 (97%)
Perometer ≥ 9%	12/30 (40%)	547/568 (96%)	12/33 (36%)	547/565 (97%)
Perometer ≥ 8%	13/30 (43%)	535/568 (94%)	13/46 (28%)	535/552 (97%)
Perometer ≥ 5%	21/30 (70%)	491/568 (86%)	21/98 (21%)	491/500 (98%)
BIS ≥ 10	14/29 (48%)	491/542 (91%)	14/65 (22%)	491/506 (97%)
B3 ≤ 2	13/24 (54%)	434/513 (85%)	13/92 (14%)	434/445 (98%)
Perometer ≥ 10% or B3 ≤ 2	17/27 (63%)	415/503 (83%)	17/105 (16%)	415/425 (98%)
Perometer ≥ 9% or B3 ≤ 2	17/27 (63%)	414/504 (82%)	17/107 (16%)	414/424 (98%)
Perometer ≥ 8% or B3 ≤ 2	17/27 (63%)	404/504 (80%)	17/117 (15%)	404/414 (98%)
Perometer ≥ 5% or B3 ≤ 2	22/28 (79%)	377/508 (74%)	22/153 (14%)	377/383 (98%)
BIS ≥ 10 or B3 ≤ 2	18/25 (75%)	370/486 (76%)	18/134 (13%)	370/377 (98%)
Perometer ≥ 5% and B3 ≤ 2	12/26 (46%)	548/573 (96%)	12/37 (32%)	548/562 (98%)
Perometer ≥ 8% and B3 ≤ 2	9/27 (33%)	565/577 (98%)	9/21 (43%)	565/583 (97%)
Perometer ≥ 9% and B3 ≤ 2	8/27 (30%)	567/577 (98%)	8/18 (44%)	567/586 (97%)
Perometer ≥ 10% and B3 ≤ 2	8/27 (30%)	570/578 (99%)	8/16 (50%)	570/589 (97%)
Perometer ≥ 10% and BIS ≥ 10	9/29 (31%)	560/569 (98%)	9/18 (50%)	560/580 (97%)
Perometer ≥ 9% and BIS ≥ 10	9/29 (31%)	560/569 (98%)	9/18 (50%)	560/580 (97%)
Perometer ≥ 10% and BIS ≥ 10 and B3 ≤ 2	6/27 (22%)	574/580 (99%)	6/12 (50%)	574/595 (96%)
Perometer ≥ 9% and BIS ≥ 10 and B3 ≤ 2	6/27 (22%)	574/580 (99%)	6/12 (50%)	574/595 (96%)

Those patients with lymphoedema up to 18 months are not included in the numbers in *Table 78*.

TABLE 78 At 24 months

Measure	Sensitivity	Specificity	PPV	NPV
Perometer ≥ 10%	10/24 (42%)	511/530 (96%)	10/29 (34%)	511/525 (97%)
Perometer ≥ 9%	12/24 (50%)	507/530 (96%)	12/35 (34%)	507/519 (98%)
Perometer ≥ 8%	13/24 (54%)	503/530 (95%)	13/40 (33%)	503/514 (98%)
Perometer ≥ 5%	17/24 (71%)	454/530 (86%)	17/93 (18%)	454/461 (98%)
BIS ≥ 10	10/23 (43%)	447/491 (91%)	10/54 (19%)	447/460 (97%)
B3 ≤ 2	8/21 (38%)	404/467 (87%)	8/71 (11%)	404/417 (97%)
Perometer ≥ 10% or B3 ≤ 2	15/24 (63%)	391/465 (84%)	15/89 (17%)	391/400 (98%)
Perometer ≥ 9% or B3 ≤ 2	16/24 (67%)	389/466 (83%)	16/93 (17%)	389/397 (98%)
Perometer ≥ 8% or B3 ≤ 2	17/24 (71%)	388/467 (83%)	17/96 (18%)	388/395 (98%)
Perometer ≥ 5% or B3 ≤ 2	20/24 (83%)	343/470 (73%)	20/147 (14%)	343/347 (99%)
BIS ≥ 10 or B3 ≤ 2	13/23 (57%)	349/444 (79%)	13/108 (12%)	349/359 (97%)
Perometer ≥ 5% and B3 ≤ 2	5/21 (24%)	515/527 (98%)	5/17 (29%)	515/531 (97%)
Perometer ≥ 8% and B3 ≤ 2	4/21 (19%)	519/530 (98%)	4/15 (27%)	519/536 (97%)
Perometer ≥ 9% and B3 ≤ 2	4/21 (19%)	522/531 (98%)	4/13 (31%)	522/539 (97%)
Perometer ≥ 10% and B3 ≤ 2	3/21 (14%)	524/532 (98%)	3/11 (27%)	524/542 (97%)
Perometer ≥ 10% and BIS ≥ 10	6/23 (26%)	520/529 (98%)	6/15 (40%)	520/537 (97%)
Perometer ≥ 9% and BIS ≥ 10	7/23 (30%)	518/528 (98%)	7/17 (41%)	518/534 (97%)
Perometer ≥ 10% and BIS ≥ 10 and B3 ≤ 2	2/21 (10%)	526/532 (99%)	2/8 (25%)	526/545 (97%)
Perometer ≥ 9% and BIS ≥ 10 and B3 ≤ 2	3/21 (14%)	525/531 (99%)	3/9 (33%)	525/543 (97%)

Appendix 10 National Institute for Health and Care Excellence medical technology assessment

NICE Medical Tech Assessment

WS2 BEA study to determine the optimal method of detection and threshold for lymphoedema intervention: A multi-center prospective study

Background

- A complication of axillary node clearance (ANC) for breast cancer is that patients have an increased risk of developing arm lymphoedema.
- Early detection of arm swelling is recommended by comparing pre-surgical arm measurements with repeated measurements after surgery.
- Early detection may enable early intervention which may prevent the development of lymphoedema
- This prospective multi-centre study evaluated arm volume measurements in lymphoedema in 1100 women to define an optimal threshold for intervention to prevent lymphoedema.

Methods

- Out of the 1100 women recruited to the trial, 629 women undergoing axillary node clearance (ANC) surgery for breast cancer from 9 centres in England, median age is 55 years (range 22-90 years), have undergone pre-operative and subsequent regular measurements post-surgery (1, 3, 6, 9, 12 months, then 6 monthly), of arm volume by perometry (Perometer 350 NT; www.pero-system.de) and multi-frequency bioimpedance spectroscopy (BIS) (L-Dex® U400; www.impedimed.com) measurements and currently have minimum 24 months follow-up surveillance,.
- Change in arm volume was calculated using relative arm volume change (RAVC).
- The primary endpoint of lymphoedema was defined as ≥10% limb volume change compared to the contralateral arm by perometry [1].
- BIS L-Dex change of 10 was considered diagnostic of lymphoedema.

The optimal threshold for intervention in lymphoedema and predictive risk factors for the development of lymphoedema were assessed using Cox regression, log -rank and Kaplan-Meier analyses.

Methods

There is considerable variation in the definitions of lymphoedema and methods of measurement, ranging from the more conservative ≥10% limb volume change (LVC) by perometry, through changes of 200 mls by perometry, to the more liberal increase of 2cm in circumference [2]. For the purposes of this study, we used a greater than 10% arm volume increase (AVI) since baseline (compared to the contralateral arm) as measured by perometer on at least two occasions to identify women with lymphoedema secondary to axillary node clearance [3]. Lymphoedema determined by BIS is a difference of ≥10 units from baseline.

Arms were measured using a 350S perometer with standard perometer software supplied by Pero System, Germany. The average of 2 perometer measurements was used at each visit to exclude intra-observer variability.

Intracellular fluid was measured using the L-DEX®U400 bioimpedance spectroscopy device on loan from ImpediMed Ltd., Australia.

At least 50% of breast cancer patients gain weight in the first year after diagnosis, and this is often associated with increased risk of lymphoedema. Nonetheless, if careful contralateral arm measurements are not performed, weight gain, rather than true lymphoedema, can lead to inappropriate fitting of compression sleeves. BIS results are unaltered by weight gain and we tested whether the BIS results were similar to, more sensitive and/or more specific than, perometer measurements in detecting early arm swelling.

Self-reported symptoms

Patients were asked to complete a lymphoedema questionnaire which used 3 items from the Lymphedema and Breast Cancer Questionnaire (LBCQ) about heaviness, numbness and swelling, as well as FACT-B+4 Health Survey Questionnaire and the EQ-5D in order to assess self-reported upper limb symptoms, physical functioning and quality of life respectively. All questionnaires were completed pre-operatively and then again at 3 and 6 months post-surgery, with the exception of the EQ-5D which was not completed at 3 months post-surgery.

Statistical analysis

Statistical analysis included sensitivity and specificity analysis of the BIS L-Dex score against the 'gold standard' perometer assessment at 6 and 18 months using statistical techniques recommended by Bland and Altman [4, 5]. The BIS value cut off level was checked using ROC analysis and confirmed using later results. Assessment of the relationship between the two methods of measurement up to 2 years in predicting lymphoedema was performed.

The analysis for the current report involved comparison of the baseline and 6 and 18 month post-surgery measurements using paired t-tests and data were described using means and ranges, sensitivity and specificity, univariate and multivariate analyses. ROC analysis and Cox regression and Log-Rank testing was performed for univariate and multivariate analyses. Descriptive methods were used for all other data presented.

Results

Out of the 1100 patients entered into the study, we report data from the first 629 (all with a minimum 24 month follow-up), their median age is 56 years ranging from 22 to 90, 42% had a mastectomy and ANC, 89% were node positive., 66% had a histology of infiltrating ductal carcinoma and the majority (82%) were ER positive(table). Seventy-eight percent received post-operative radiotherapy, 65% received chemotherapy and 81% were given endocrine treatment.

Forty-one patients (7%) had no post 1 month perometer measurements. A further 117 (19%) were lost to follow-up by 24 months. Median time to developing lymphoedema was 12.0 months (range: 2.5-60.8).

Lymphoedema incidence (RAVC of $\geq$10%) is shown below (*Table 79*). The cut-off of 10% showed the strongest relationship with quality of life measures at 18 and 24 months compared to other cut-off values.

Using time to diagnosis of lymphoedema and Kaplan-Meier estimates of those developing lymphoedema by each time point, 15.6% were diagnosed by 12 months and 24% of women by perometry and in 45% of women by BIS by 24 months.

References

1. 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 > or =65 years. British Journal of Cancer. 2007 96(8):1197-203

2. Mansel RE, Fallowfield L, Kissin M, Goyal A, Newcombe RG, Dixon JM, Yiangou C, Horgan K, Bundred N, Monypenny I, England D, Sibbering M, Abdullah TI, Barr L, Chetty U, Sinnett DH, Fleissig A, Clarke D, Ell PJ. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial.J Natl Cancer Inst. 2006 May 3; 98(9):599-609.

3. Brennan MJ. J Pain Symptom Manage. Lymphedema following the surgical treatment of breast cancer: a review of pathophysiology and treatment. 1992; 7(2):110-6.

4. DiSipio T, Rye Newman B, and Hayes Incidence of unilateral arm lymphedema after breast cancer: a systematic review and met analysis, Lancet Oncology 2013:14:500- 515

5. Shaitelman SF, Cromwell KD, Rasmussen JC, Stout N, Armer J, Lasinski B, Cormier JN. Recent Progress in the treatment and prevention of Cancer–Related lymphoedema.CA Cancer Clin2015:65:55-81.

Appendix 11 Lymphoedema rates

Lymphoedema rates using perometer RAVI of ≥ 10% (primary end point)

Lymphoedema by 24 months was detected in 24% of women by perometry and in 45% of women by BIS. There was a moderate correlation between perometer and BIS at 6 months (r = 0.61), with a sensitivity of 75% (95% CI 64% to 84%), specificity of 85% (95% CI 83% to 88%) and PPV of BIS of 31% (95% CI 25% to 39%) (see *Table 2*). Sensitivity remained similar at 24 months (75%, 95% CI 64% to 83%), although specificity was higher (91%, 95% CI 89% to 93%), as was PPV of BIS (54%, 95% CI 44% to 63%).

The sensitivity and specificity values for BIS fall below the percentage of 95% required according to the study protocol.

TABLE 79 Lymphoedema rates during 24 months' follow-up

	Follow-up date					
	≤ 3 months	> 3 to ≤ 6 months	> 6 to ≤ 9 months	> 9 to ≤ 12 months	> 12 to ≤ 18 months	> 18 to ≤ 24 months
n at risk	1001	925	848	798	722	647
Lymphoedema						
During interval	33	54	27	24	31	25
Total number	33	57	114	138	169	194
KM[a] probability of event	3.4%	9.0%	11.9%	14.6%	18.2%	21.4%

a 1 – Kaplan–Meier estimates.

TABLE 80 Lymphoedema rates defined by clinical lymphoedema/applied sleeve

	Follow-up date					
	≤ 3 months	> 3 to ≤ 6 months	> 6 to ≤ 9 months	> 9 to ≤ 12 months	> 12 to ≤ 18 months	> 18 to ≤ 24 months
n at risk	999	928	856	789	697	622
Lymphoedema						
During interval	29	48	46	43	31	24
Total number	29	77	123	166	197	221

Appendix 12 Sensitivity and specificity of perometer and bioimpedance spectroscopy

Women who developed a relative arm-volume increase of > 5% to < 10% after 6 months required lymphoedema treatment in 44% by 24 months, whereas an arm-volume increase of < 3% was associated with a 9% lymphoedema rate at 24 months ($p < 0.0001$).

TABLE 81 Sensitivity and specificity of perometer and BIS at 6 and 24 months

	Perometer		
Time point	≥ 10%	< 10%	Total
6 months			
BIS (≥ 10)	29	68	97
BIS (< 10)	12	382	394
Total	41	450	491
24 months			
BIS (≥ 10)	38	29	67
BIS (< 10)	14	321	335
Total	52	350	402

Appendix 13 Comparison of perometer and bioimpedance spectroscopy

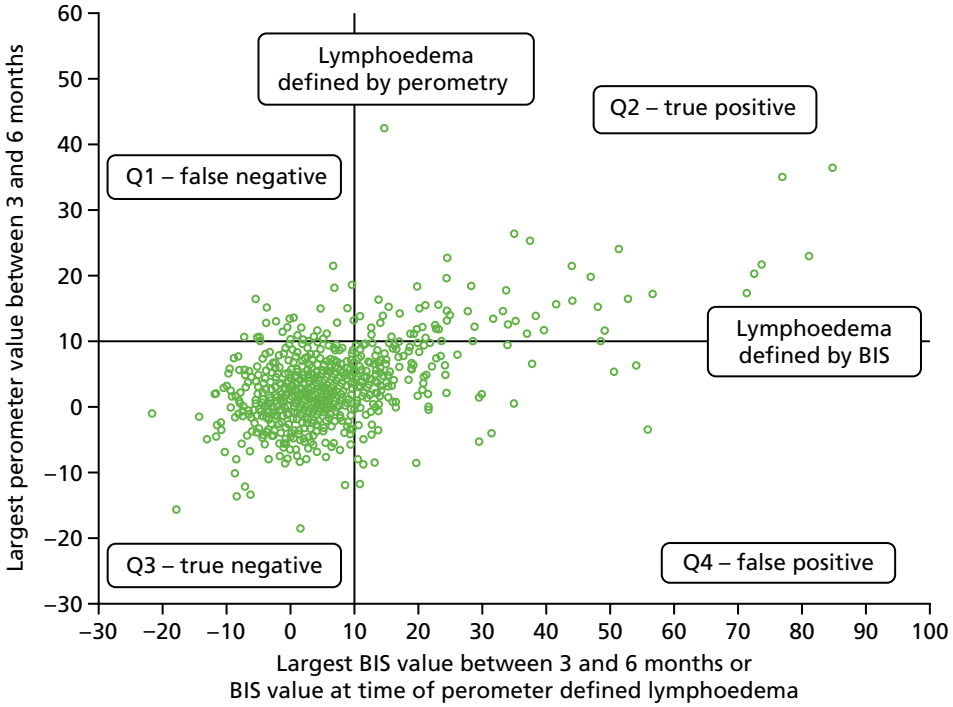


FIGURE 32 Comparison of perometer and BIS at 6 months. Q1, perometer only ≥ 10; Q2, both ≥ 10; Q3, neither ≥ 10; Q4, BIS only ≥ 10. Sensitivity, 69% (59/86; 95% CI 58% to 77%); specificity, 82% (698/851; 95% CI 79% to 84%); PPV, 28% (59/212; 95% CI 22% to 34%); NPV, 96% (698/725; 95% CI 95% to 97%).

Perometer after 6 months up to 18 months

The perometer after 6 months up to 18 months variable excludes those patients with lymphoedema up to and including 6 months.

For those patients with lymphoedema according to the perometer ≥ 10% definition, the BIS value used is the one at the time of the indicated lymphoedema. For those patients without lymphoedema according to the perometer ≥ 10% definition, the BIS value is the largest value between 9 and 18 months.

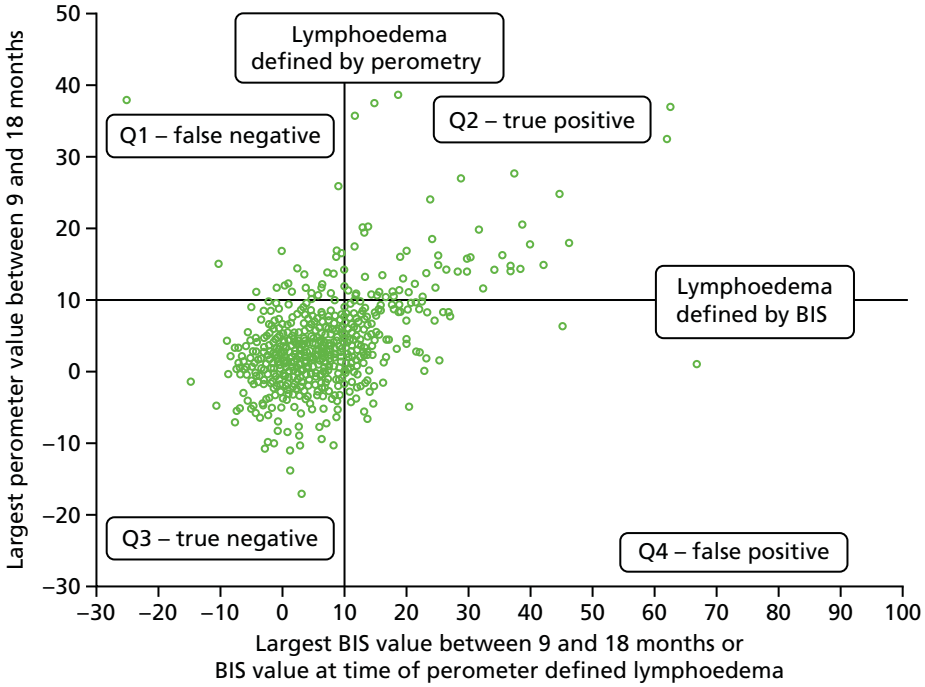


FIGURE 33 Comparison of perometer and BIS at 18 months. Q1, perometer only ≥ 10; Q2, both ≥ 10; Q3, neither ≥ 10; Q4, BIS only ≥ 10. Sensitivity, 68% (53/78; 95% CI 57% to 77%); specificity, 81% (600/738; 95% CI 78% to 84%); PPV, 28% (53/191; 95% CI 22% to 34%); NPV, 96% (600/625; 95% CI 94% to 97%).

Perometer after 6 months up to 24 months (excludes those patients with lymphoedema up to and including 6 months)

For those patients with lymphoedema according to the perometer ≥ 10% definition, the BIS value used is the one at the time of the indicated lymphoedema. For those patients without lymphoedema, the BIS value used is the largest value between 9 and 24 months.

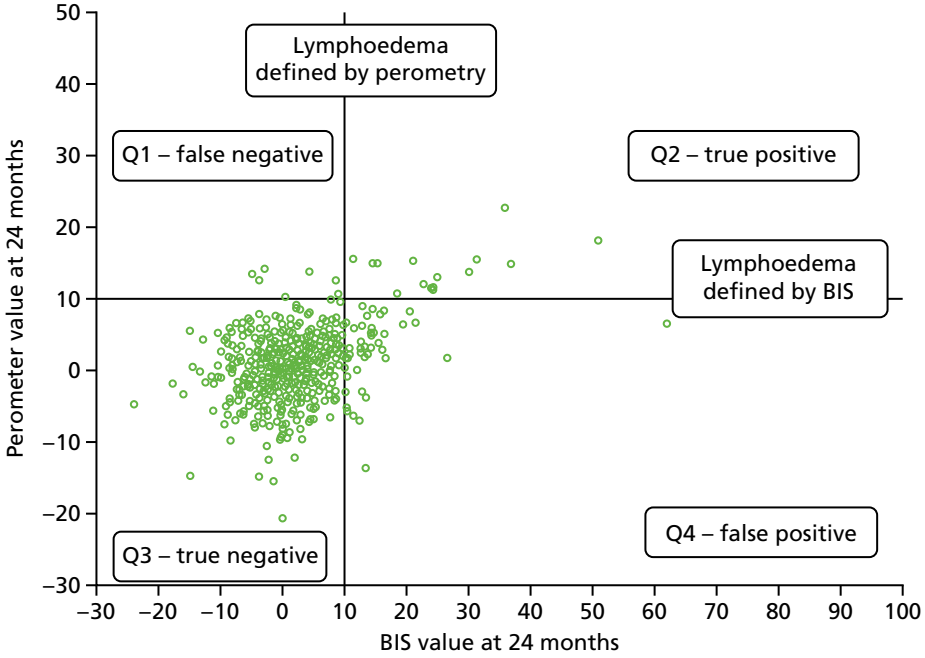


FIGURE 34 Comparison of perometer and BIS after 6 months up to 24 months. Q1, perometer only ≥ 10; Q2, both ≥ 10; Q3, neither ≥ 10; Q4, BIS only ≥ 10. Sensitivity, 68% (15/22; 95% CI 58% to 76%); specificity, 79% (572/722; 95% CI 76% to 82%); PPV, 31% (68/218; 95% CI 25% to 38%); NPV, 95% (572/604; 95% CI 93% to 96%).

Clinical lymphoedema/appropriately applied sleeve by 6 months

TABLE 82 Perometer and sleeve/clinical lymphoedema

By 6 months	No sleeve or clinical lymphoedema	Sleeve or clinical lymphoedema	Total
Perometer (< 10%)	820 (94%)	45 (60%)	865
Perometer (≥ 10%)	55 (6%)	30 (40%)	85
Total	875	75	950
Sensitivity, 40% (30/75; 95% CI 30% to 51%); specificity, 94% (820/875; 95% CI 92% to 95%); PPV, 35% (30/85; 95% CI 26% to 46%); NPV, 95% (820/865; 95% CI 93% to 96%).			

TABLE 83 Bioimpedance spectroscopy and sleeve/clinical lymphoedema

By 6 months	No sleeve or clinical lymphoedema	Sleeve or clinical lymphoedema	Total
BIS (< 10)	690 (80%) true negative	34 (46%) false negative	724
BIS (≥ 10)	170 (20%) false positive	40 (54%) true positive	210
Total	860	74	934
Sensitivity, 54% (40/74; 95% CI 43% to 65%); specificity, 80% (690/860; 95% CI 77% to 83%); PPV, 19% (40/210; 95% CI 25% to 39%); NPV, 95% (690/724; 95% CI 94% to 97%).			

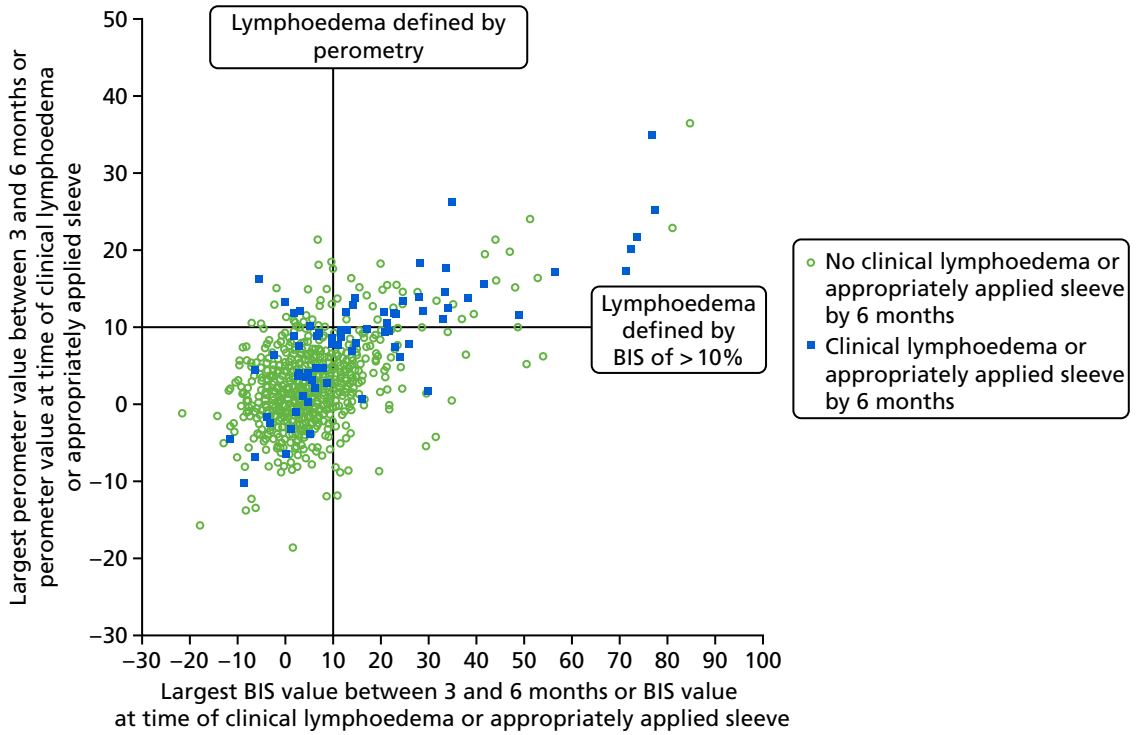


FIGURE 35 Comparison of RAVI > 10% and BIS > 10% with sleeve application. Note that those patients with no clinical lymphoedema or appropriately applied sleeve by 6 months may have had an appropriately applied sleeve at a later time point.

Clinical lymphoedema/appropriately applied sleeve from 6 months up to 18 months

The clinical lymphoedema/appropriately applied sleeve between 6 and 18 months variable excludes those patients with lymphoedema up to and including 6 months.

For those patients with lymphoedema, the BIS and perometer values used are those at the time of the indicated lymphoedema. For those without lymphoedema, the BIS and perometer values used are the largest value between 9 and 18 months.

TABLE 84 Perometer and sleeve/clinical lymphoedema

After 6 months up to 18 months	No sleeve or clinical lymphoedema	Sleeve or clinical lymphoedema	Total
Perometer (< 10%)	693 (95%)	72 (62%)	765
Perometer (≥ 10%)	33 (5%)	45 (38%)	78
Total	726	117	843
Sensitivity, 38% (45/117; 95% CI 30% to 48%); specificity, 95% (693/726; 95% CI 94% to 97%); PPV, 58% (45/78; 95% CI 47% to 68%); NPV, 91% (693/765; 95% CI 88% to 92%).			

TABLE 85 BIS and sleeve/clinical lymphoedema

After 6 months up to 18 months	No sleeve or clinical lymphoedema	Sleeve or clinical lymphoedema	Total
BIS (< 10)	581 (82%) true negative	52 (47%) false negative	633
BIS (≥ 10)	126 (18%) false positive	59 (53%) true positive	185
Total	707	111	818
Sensitivity, 53% (59/111; 95% CI 44% to 62%); specificity, 82% (581/707; 95% CI 79% to 85%); PPV, 32% (59/185; 95% CI 26% to 39%); NPV, 92% (581/633; 95% CI 89% to 94%).			

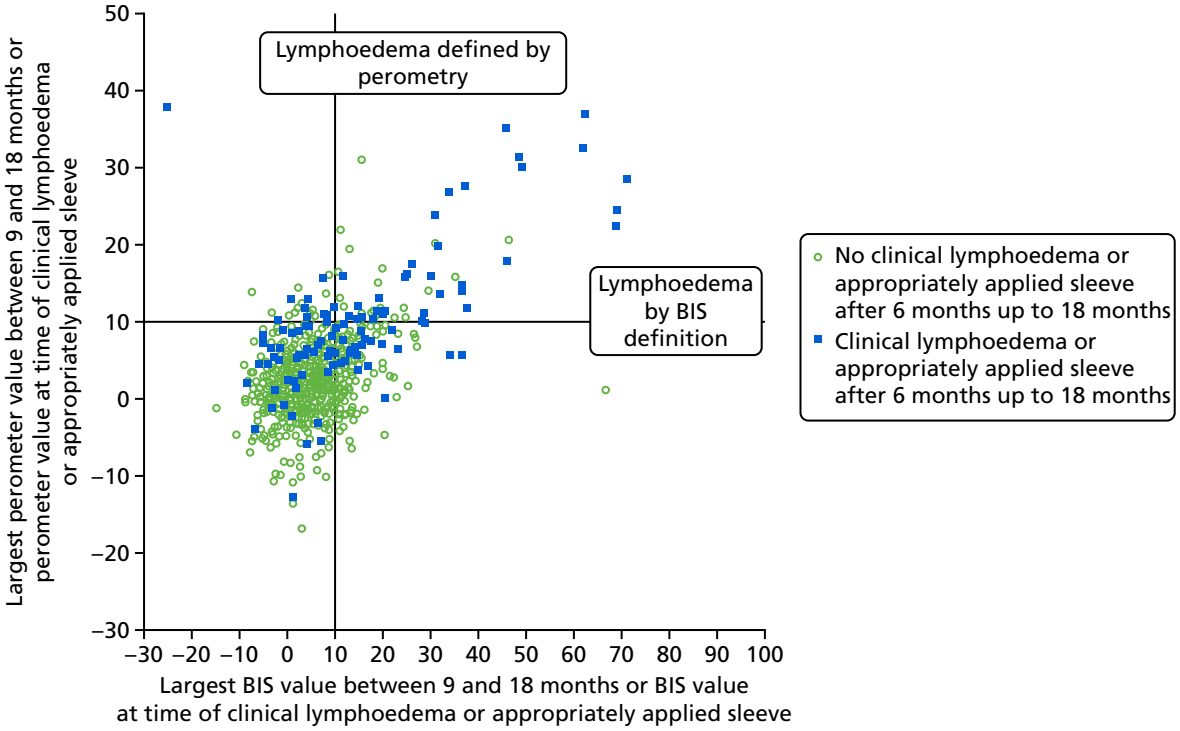


FIGURE 36 Comparison of RAVI > 10% and BIS with sleeve application (6–18 months). Note that those patients with no clinical lymphoedema or appropriately applied sleeve by 6 months may have had clinical lymphoedema or an appropriately applied sleeve at a later time point.

Clinical lymphoedema/appropriately applied sleeve after 6 months up to 24 months

The clinical lymphoedema/appropriately applied sleeve after 6 months up to 24 months variable excludes those patients with lymphoedema up to and including 6 months.

For those patients with lymphoedema, the BIS and perometer values used are those at the time of lymphoedema diagnosis. For those patients without lymphoedema, the BIS and perometer values used are the largest value between 9 and 24 months.

TABLE 86 Perometer and sleeve/clinical lymphoedema

After 6 months up to 24 months	No sleeve or clinical lymphoedema	Sleeve or clinical lymphoedema	Total
Perometer (< 10%)	667 (94%)	86 (61%)	753
Perometer (≥ 10%)	39 (6%)	55 (39%)	94
Total	706	141	847

Sensitivity, 39% (55/141; 95% CI 31% to 47%); specificity, 94% (667/706; 95% CI 93% to 96%); PPV, 59% (55/94; 95% CI 48% to 68%); NPV, 89% (667/753; 95% CI 86% to 91%).

TABLE 87 Bioimpedance spectroscopy and sleeve/clinical lymphoedema

After 6 months up to 24 months	No sleeve or clinical lymphoedema	Sleeve or clinical lymphoedema	Total
BIS (< 10)	556 (80%)	65 (49%)	621
BIS (≥ 10)	136 (20%)	69 (51%)	205
Total	692	134	826

Sensitivity, 51% (69/134; 95% CI 43% to 60%); specificity, 80% (556/692; 95% CI 77% to 83%); PPV, 34% (69/205; 95% CI 28% to 40%); NPV, 90% (556/621; 95% CI 87% to 92%).

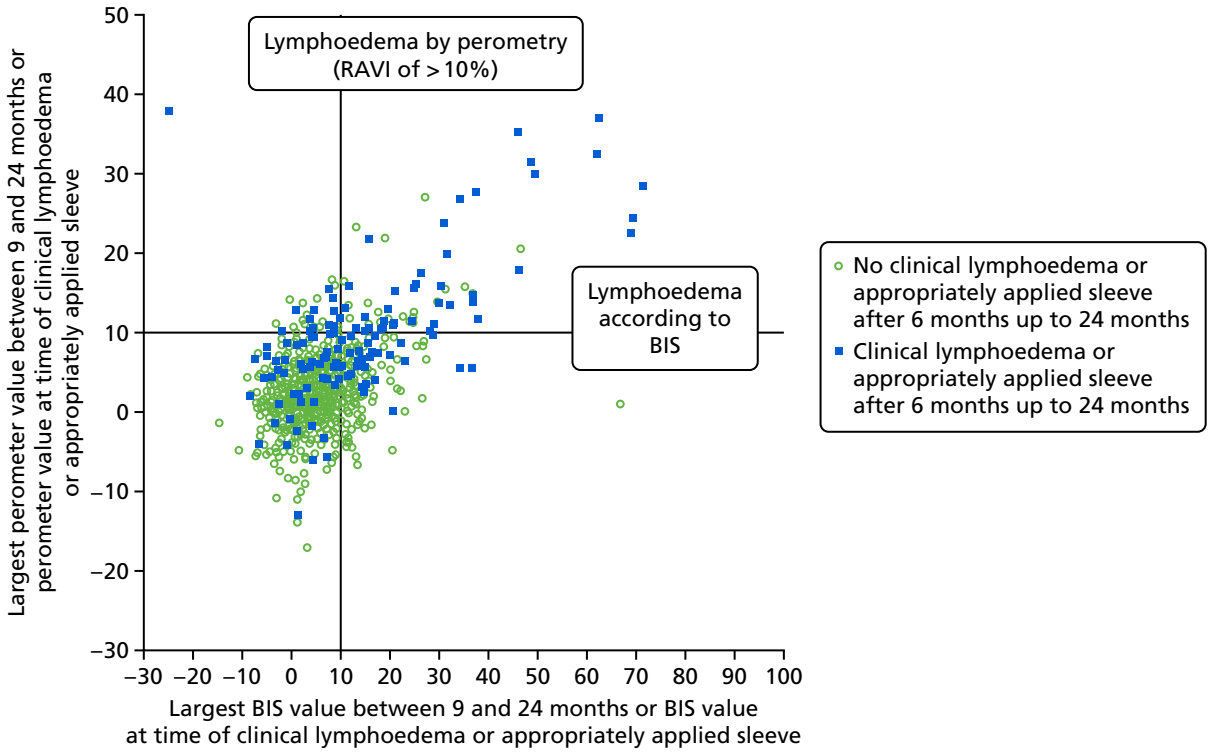


FIGURE 37 Comparison of RAVI of > 10% and BIS with sleeve application (6–24 months). Note that those patients with no clinical lymphoedema or appropriately applied sleeve after 6 months up to 24 months may have had clinical lymphoedema or sleeve applied at a later time point.

Clinical lymphoedema/appropriately applied sleeve after 18 months up to 24 months

The clinical lymphoedema/appropriately applied sleeve after 18 months up to 24 months variable excludes those patients with lymphoedema up to and including 18 months.

For all patients, the BIS and perometer values used are those at 24 months.

TABLE 88 Perometer and sleeve/clinical lymphoedema

After 18 months up to 24 months	No sleeve or clinical lymphoedema	Sleeve or clinical lymphoedema	Total
Perometer (< 10%)	524 (96%)	14 (58%)	538
Perometer (≥ 10%)	21 (4%)	10 (42%)	31
Total	545	24	569

Sensitivity, 42% (10/24; 95% CI 24% to 61%); specificity, 96% (524/545; 95% CI 94% to 97%); PPV, 32% (10/31; 95% CI 19% to 50%); NPV, 97% (524/538; 95% CI 96% to 98%).

TABLE 89 Bioimpedance spectroscopy and sleeve/clinical lymphoedema

After 18 months up to 24 months	No sleeve or clinical lymphoedema	Sleeve or clinical lymphoedema	Total
BIS (< 10)	460 (91%) true negative	13 (57%) false negative	473
BIS (≥ 10)	45 (9%) false positive	10 (43%) true positive	55
Total	505	23	528

Sensitivity, 43% (10/23; 95% CI 26% to 63%); specificity, 91% (460/505; 95% CI 88% to 93%); PPV, 18% (10/55; 95% CI 10% to 30%); NPV, 97% (460/473; 95% CI 95% to 98%).

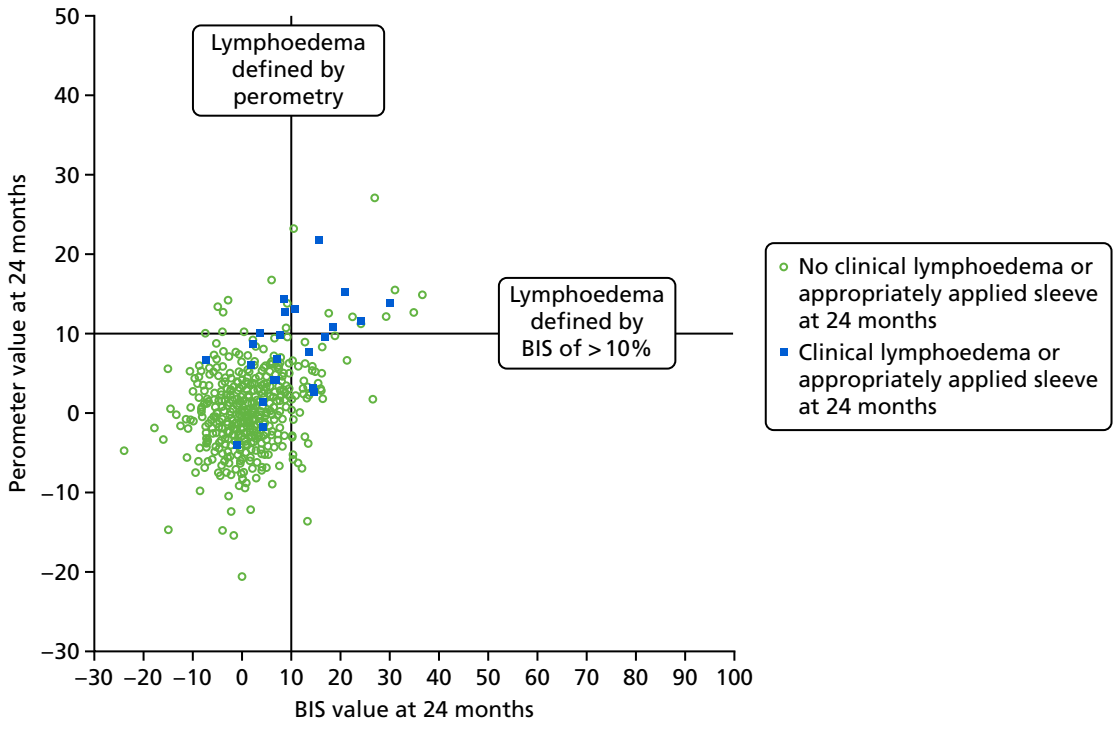


FIGURE 38 Comparison of BIS and perometer values at 24 months. Note that those with no lymphoedema or appropriately applied sleeve by 24 months may have had an appropriately applied sleeve at a later time point.

Appendix 14 Combined perometer or bioimpedance spectroscopy versus clinical lymphoedema/appropriately applied sleeve

Combined perometer or bioimpedance spectroscopy versus clinical lymphoedema/appropriately applied sleeve

TABLE 90 Combined perometer or BIS vs. sleeve/clinical lymphoedema

By 6 months	No sleeve or clinical lymphoedema	Sleeve or clinical lymphoedema	Total
Perometer and BIS < 10	663 (78%)	28 (38%)	691
Perometer or BIS ≥ 10	192 (22%)	45 (62%)	237
Total	855	73	928

Sensitivity, 62% (45/73; 95% CI 50% to 72%); specificity, 78% (663/855; 95% CI 75% to 80%); PPV, 19% (45/237; 95% CI 15% to 24%); NPV, 96% (663/691; 95% CI 94% to 97%).

Clinical lymphoedema/appropriately applied sleeve after 6 months up to 18 months

For those patients with lymphoedema, the BIS and perometer values used are those at the time of the indicated lymphoedema. For those patients without lymphoedema, the BIS and perometer values used are the largest value between 9 and 18 months.

The 71 patients with lymphoedema are made up of 33 with both perometer and BIS of ≥ 10, 26 with only BIS of ≥ 10 and 12 with only perometer ≥ 10.

Clinical lymphoedema/appropriately applied sleeve after 6 months up to 24 months (excludes those patients with lymphoedema up to and including 6 months).

Bioimpedance spectroscopy and perometer values used are those at the time of the indicated lymphoedema. For those patients without lymphoedema, the BIS and perometer values used are the largest value between 9 and 24 months.

TABLE 91 Combined perometer or BIS vs. sleeve/clinical lymphoedema

After 6 months up to 18 months	No sleeve or clinical lymphoedema	Sleeve or clinical lymphoedema	Total
Perometer and BIS < 10	566 (80%)	42 (37%)	608
Perometer or BIS ≥ 10	139 (20%)	71 (63%)	210
Total	705	113	818

Sensitivity, 63% (71/113; 95% CI 54% to 71%); specificity, 80% (566/705; 95% CI 77% to 83%); PPV, 34% (71/210; 95% CI 28% to 40%); NPV, 93% (566/608; 95% CI 91% to 95%).

Appendix 15 Factors predicting lymphoedema development after 1 month's and 6 months' analysis

Factors predicting lymphoedema development after 1 months' and 6 months' analysis

Two analyses were performed: one looked at the situation described above (lymphoedema after 6 months and up to 2 years), and the other looks at the time to first lymphoedema including all follow-up data (1 month visit was excluded as per the protocol [version 5.2] and the NIHR programme grant response letter). Both RAVI (>10%) and sleeve application were considered in these analyses.

Lymphoedema development after 6 months surveillance (i.e. 6 months up to 2 years and the time to first lymphoedema within that time period). Patients with lymphoedema at 3 or 6 months are excluded because the inclusion of the RAVI variable, which is determined at 6 months, means there would need to be a ≥10% category RAVI variable but this is also used as the outcome event. In addition, excluding these patients is part of the study protocol (version 5.2) and the NIHR programme grant response letter.

For RAVI >10 univariate analysis revealed BMI ($p<0.002$), number of nodes involved (Median 2(range 0-41 ($p<0.001$)), and largest RAVI change by six months ($p<0.001$: (HR = 5.58 for ≥5%-<10% vs <3%, 95% CI 3.61 – 8.62)) and BIS >10% ($p<0.001$) all predicted lymphoedema development from six months up to two years.

The multivariable analysis included RAVI change by six months ($p<0.001$: (HR = 5.22 for ≥5%-<10%, 95% CI 3.22-8.47)) along with number of nodes involved (HR 1.05, 95% CI 1.02 – 1.07), adjuvant chemotherapy HR = 1.61 (1.01-2.55), BMI >30 (HR 1.87, 95% CI 1.16 – 3.02) and BIS >10% ($p=0.069$) in the model for predicting lymphoedema development after six months up to two years

TABLE 92: Univariate and multivariable analyses of predictors of lymphoedema (defined by perometry) after 6 months

	Univariate		Multivariable	
Variable	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (per year increase)	1.01 (0.99-1.02)	0.31	-	-
BMI at baseline (ref ≤25) >25-≤30 >30	 0.81 (0.48-1.36) 1.78 (1.13-2.79)	0.002 0.42 0.013	 0.96 (0.56-1.67) 1.87 (1.16-3.02)	0.008 0.90 0.010
ER negative	1.27 (0.79-2.05)	0.33	-	-
Nodes positive (per node increase)	1.05 (1.03-1.08)	<0.001	1.05 (1.02-1.07)	<0.001
Adjuvant CT (yes)	1.24 (0.81-1.88)	0.32	1.61 (1.01-2.55)	0.044
Adjuvant RT (yes)	1.43 (0.80-2.55)	0.23	-	-
Previous SN biopsy	0.68 (0.44-1.03)	0.069	-	-
Arm measurements – 6 months (ref <3%inc) ≥3<5% inc ≥5<10% inc	 1.88 (1.06-3.33) 5.58 (3.61-8.62)	<0.001 0.030 <0.001	 1.87 (1.03-3.41) 5.22 (3.22-8.47)	<0.001 0.041 <0.001
– BIS at 6 months (ref <3% inc) ≥3<5% inc ≥5<10% inc ≥10% inc	 1.48 (0.74-2.95) 1.37 (0.79-2.39) 3.70 (2.30-5.95)	<0.001 0.26 0.26 <0.001	 1.54 (0.77-3.11) 1.25 (0.70-2.24) 1.98 (1.18-3.33)	0.069 0.22 0.44 0.010

Smoking, type of surgery, weight gain and histological tumour type were ns
[N=1100: those with lymphoedema ≤6 months have been excluded]

TABLE 93: Time to lymphoedema from after 6 months to 24 months (excluding lymphoedema to 6 months) - Clinical lymphoedema/appropriately applied sleeve

	Univariate		Multivariable	
Variable	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (per year increase)	1.00 (0.99-1.01)	>0.99	-	-
BMI at baseline (ref ≤25) >25-≤30 >30	 1.09 (0.72-1.65) 1.18 (0.77-1.80)	0.76 0.67 0.45	-	-
ER negative	0.63 (0.38-1.05)	0.076	0.51 (0.30-0.86)	0.012
Nodes positive (per node increase)	1.04 (1.02-1.06)	<0.001	-	-
Adjuvant CT (yes)	1.78 (1.19-2.66)	0.005	1.92 (1.24-2.96)	0.003
Adjuvant RT (yes)	2.23 (1.23-4.03)	0.008	2.03 (1.11-3.71)	0.021
Previous SN biopsy	0.93 (0.65-1.33)	0.68	-	-
Arm measurements – perometer at 6 months (ref <3% inc) ≥3-<5% inc ≥5-10% inc ≥10% inc	 1.94 (1.15-3.26) 3.84 (2.47-5.96) 12.56 (7.84-20.14)	<0.001 0.013 <0.001 <0.001	 1.57 (0.92-2.69) 3.13 (1.97-4.98) 7.90 (4.78-13.06)	<0.001 0.099 <0.001 <0.001
Arm measurements – BIS at 6 months (ref <3% inc) ≥3-<5% inc ≥5-10% inc ≥10% inc	 1.27 (0.60-2.67) 2.39 (1.47-3.89) 5.65 (3.63-8.79)	<0.001 0.53 <0.001 <0.001	 1.48 (0.69-3.14) 2.51 (1.50-4.20) 4.06 (2.51-6.58)	<0.001 0.31 <0.001 <0.001

TABLE 94: FACT-B at 6, 12, 18 and 24 months respectively

Perometer >10%			
Lymphoedema at...	Mean (SD)		
Time (n=no, n=yes)	Lymphoedema -No	Lymphoedema -Yes	
At 6 months (660:58)	107.4 (21.5)	101.0 (21.4)	P=0.030
At 12 months (628:55)	112.0 (21.1)	103.7 (22.8)	P=0.005
At 18 months (566:59)	113.6 (20.2)	106.2 (21.5)	P=0.008
At 24 months (541:68)	114.1 (20.1)	108.0 (25.3)	P=0.059
Sleeve application			
Lymphoedema at...	Mean (SD)		
Time (n=no, n=yes)	Lymphoedema -No	Lymphoedema -Yes	
By 6 months (683:60)	107.1 (21.5)	99.6 (23.5)	P=0.011
By 12 months (577:121)	112.9 (20.4)	104.6 (24.3)	P=0.001
By 18 months (518:124)	114.1 (19.9)	107.3 (21.6)	P=0.001
By 24 months (466:151)	114.8 (19.8)	108.5 (23.8)	P=0.003

TABLE 95: FACT-B TOI at 6, 12, 18 and 24 months respectively

Perometer >10%			
Lymphoedema at...	Mean (SD)		
Time (n=no, n=yes)	Lymphoedema -No	Lymphoedema -Yes	
At 6 months (690:63)	64.7 (15.5)	58.0 (16.1)	P=0.001
At 12 months (585:123)	70.0 (14.2)	63.6 (17.0)	P<0.001
At 18 months (523:128)	70.9 (14.0)	65.6 (14.6)	P<0.001
At 24 months (472:152)	71.5 (13.7)	67.0 (16.5)	P=0.003
Sleeve application			
Lymphoedema at...	Mean (SD)		
Time (n=no, n=yes)	Lymphoedema -No	Lymphoedema -Yes	
At 6 months (669:59)	65.0 (15.4)	58.1 (15.3)	P=0.001
At 12 months (637:56)	69.3 (14.6)	62.9 (16.2)	P=0.002
At 18 months (570:63)	70.4 (14.2)	64.6 (14.2)	P=0.002
At 24 months (546:70)	71.1 (13.9)	65.2 (17.8)	P=0.009

TABLE 96: Lymphoedema symptoms at 6, 12, 18 and 24 months respectively

Perometer 10%			
Lymphoedema at....	% (no.) with swelling		
Time (n=no, n=yes)	Lymphoedema -No	Lymphoedema -Yes	
At 6 months (601:55)	31% (186)	91% (50)	P<0.001
At 12 months (591:53)	37% (219)	91% (48)	P<0.001
At 18 months (524:61)	36% (187)	89% (54)	P<0.001
At 24 months (525:70)	35% (185)	87% (61)	P<0.001
Sleeve application			
Lymphoedema at....	% (no.) with swelling		
Time (n=no, n=yes)	Lymphoedema -No	Lymphoedema -Yes	
By 6 months (620:60)	30% (189)	90% (54)	P<0.001
By 12 months (540:119)	31% (167)	89% (106)	P<0.001
By 18 months (473:127)	28% (134)	88% (112)	P<0.001
By 24 months (449:153)	28% (126)	80% (123)	P<0.001

	Perometer 10%		
Lymphoedema at...	% (no.) with numbness		
Time (n=no, n=yes)	Lymphoedema -No	Lymphoedema -Yes	
At 6 months (643:56)	78% (500)	77% (43)	P=0.87
At 12 months (631:53)	77% (483)	75% (40)	P=0.86
At 18 months (557:60)	75% (419)	80% (48)	P=0.41
At 24 months (535:68)	74% (394)	78% (53)	P=0.45
Sleeve application			
Lymphoedema at....	% (no.) with numbness		
Time (n=no, n=yes)	Lymphoedema -No	Lymphoedema -Yes	
By 6 months (663:60)	78% (514)	77% (46)	P=0.88
By 12 months (581:119)	75% (435)	84% (100)	P=0.032
By 18 months (507:128)	74% (375)	83% (106)	P=0.037
By 24 months (465:146)	73% (338)	77% (113)	P=0.26

Perometer 10%			
Lymphoedema at....	% (no.) with heaviness		
Time (n=no, n=yes)	Lymphoedema -No	Lymphoedema -Yes	
At 6 months (620:57)	38% (233)	67% (38)	P<0.001
At 12 months (590:53)	40% (237)	66% (35)	P<0.001
At 18 months (523:59)	39% (202)	85% (50)	P<0.001
At 24 months (516:67)	40% (208)	73% (49)	P<0.001
Sleeve application			
Lymphoedema at....	% (no.) with heaviness		
Time (n=no, n=yes)	Lymphoedema -No	Lymphoedema -Yes	
By 6 months (640:60)	37% (239)	68% (41)	P<0.001
By 12 months (544:112)	37% (203)	67% (75)	P<0.001
By 18 months (477:121)	35% (169)	74% (90)	P<0.001
By 24 months (441:149)	37% (164)	64% (95)	P<0.001

Conclusions

- Post-operative monitoring will allow early intervention and treatment of arm swelling in patients with ≥3%-<10% RAVC.
- Perometer RAVC≥10% is the optimal diagnostic and monitoring test.
- Arm measurements from baseline after axillary surgery necessary and increases greater than 3% should lead to further surveillance to prevent lymphoedema development.
- Perometer RAVC≥10% is the optimal diagnostic and monitoring test.
- Arm measurements from baseline after axillary surgery necessary and increases greater than 3% should lead to further surveillance to prevent lymphoedema development.
- Perometer measurement is the optimal technique for measuring and predicting the development of lymphoedema.
- Baseline BMI, no. of involved nodes, and relative arm volume increase ≥3% are

Appendix 16 Quality-of-life variables

Change over time in quality-of-life variables analysis notes

Generalised estimating equations (GEEs) were used to assess how the TOI, FACT-B total score and the ARM subscale changed over time.

Trial Outcome Index

Owing to the negative skew of the TOI variable, a transformation [LN(120 – TOI)] was used for the analysis so that a linear GEE model could be used.

In a model only including the time variable, the EMM of TOI at each time point is presented in the table below. A total of 997 patients had some data in the model.

Time point	Estimated marginal mean of TOI (95% CI)
Pre surgery	68.0 (67.2 to 68.9)
3 months	63.5 (62.5 to 64.5)
6 months	65.4 (64.4 to 66.4)
12 months	70.2 (69.2 to 71.1)
18 months	70.6 (69.6 to 71.5)
24 months	71.0 (70.0 to 71.9)

Time–lymphoedema status interaction

A GEE analysis that included an interaction term between lymphoedema status by 6 months and time found that the interaction was statistically significant ($p = 0.003$), showing the pattern of change over time was different between the groups.

The main effect for the time variable was statistically significant ($p < 0.001$). The main effect for the lymphoedema status by 6 months variable was statistically significant ($p = 0.006$), showing that there was a difference between the lymphoedema status groups overall.

The EMMs from the interaction term in the GEE analysis are presented below.

	Estimated marginal mean of TOI (95% CI)		
Time point	Without lymphoedema by 6 months ($n = 883$)	With lymphoedema by 6 months ($n = 87$)	*p*-value
Pre surgery	68.3 (67.4 to 69.2)	67.0 (63.9 to 70.0)	0.42
3 months	63.8 (62.7 to 64.8)	61.4 (57.8 to 64.8)	0.19
6 months	66.0 (64.9 to 67.1)	60.1 (56.4 to 63.5)	0.001
12 months	70.7 (69.8 to 71.7)	65.3 (61.8 to 68.5)	0.001
18 months	71.1 (70.2 to 72.1)	65.4 (61.9 to 68.6)	0.001
24 months	71.4 (70.4 to 72.4)	67.6 (64.0 to 71.0)	0.033

The *p*-values in this table have not been adjusted for multiple testing.

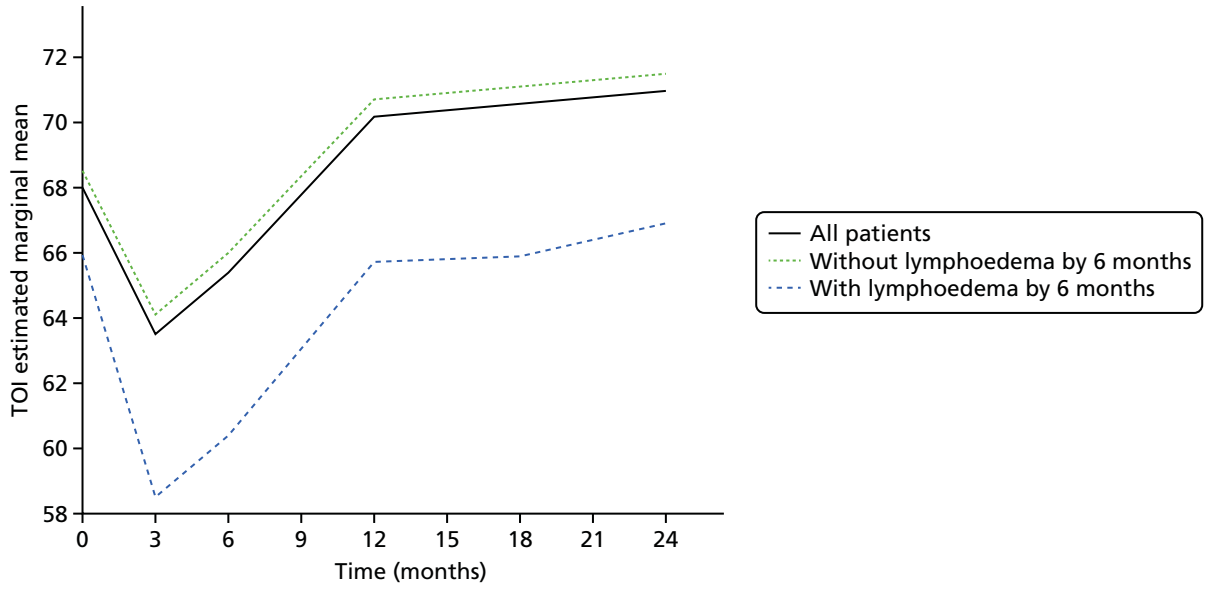


FIGURE 39 Graph of TOI EMMs.

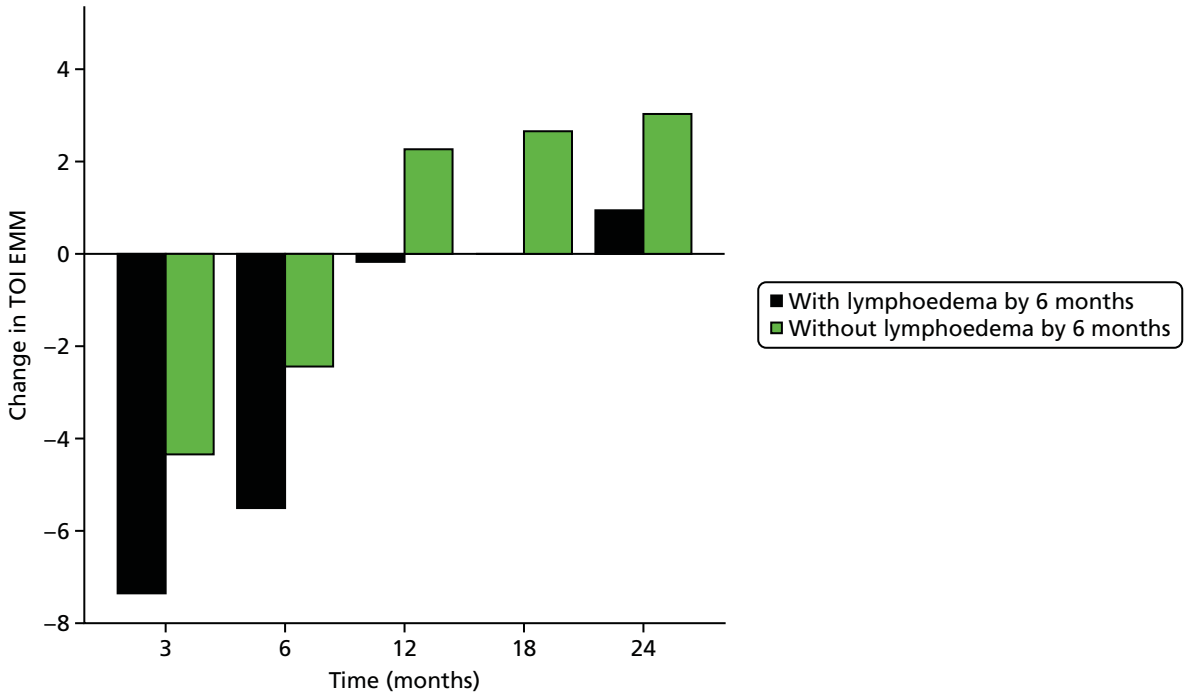


FIGURE 40 Graph of change in TOI EMMs.

FACT-B total score

Owing to the negative skew of the FACT-B total score variable, a transformation [LN(160 – FACT-B)] was used for the analysis so that a linear GEE model could be used.

In a model only including the time variable, the EMM of FACT-B at each time point is presented in the table below. A total of 996 patients had some data in the model.

Time point	Estimated marginal mean of FACT-B total score (95% CI)
Pre surgery	110.5 (109.3 to 111.7)
3 months	107.4 (106.0 to 108.7)
6 months	109.4 (108.0 to 110.8)
12 months	114.8 (113.5 to 116.1)
18 months	115.2 (113.9 to 116.5)
24 months	115.5 (114.2 to 116.9)

Time–lymphoedema status interaction

A GEE analysis that included an interaction term between lymphoedema status by 6 months and time found that the interaction was borderline statistically significant ($p = 0.055$), showing that there was some indication of pattern of change that was different between the groups.

The main effect for the time variable was statistically significant ($p < 0.001$). The main effect for the lymphoedema status by 6 months variable was statistically significant ($p = 0.032$), showing that there was a difference between the lymphoedema status groups overall.

The EMMs from the interaction term in the GEE analysis are presented below.

	Estimated marginal mean of FACT-B total score (95% CI)		
Time point	Without lymphoedema by 6 months ($n = 882$)	With lymphoedema by 6 months ($n = 87$)	*p*-value
Pre surgery	110.9 (109.7 to 112.2)	109.4 (105.0 to 113.4)	0.48
3 months	107.8 (106.3 to 109.2)	105.3 (100.3 to 109.9)	0.32
6 months	110.1 (108.6 to 111.5)	104.0 (98.7 to 108.8)	0.018
12 months	115.5 (114.1 to 116.8)	109.5 (104.5 to 114.0)	0.012
18 months	115.9 (114.5 to 117.2)	109.2 (104.2 to 113.7)	0.005
24 months	116.0 (114.6 to 117.4)	111.8 (106.5 to 116.7)	0.11

The *p*-values in this table have not been adjusted for multiple testing.

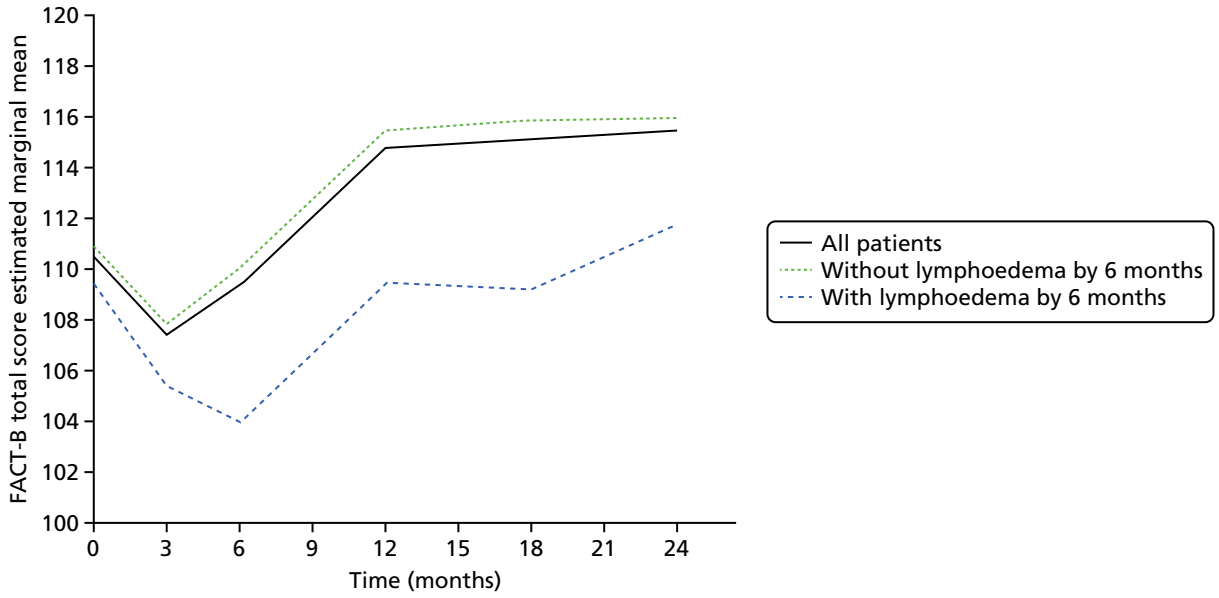


FIGURE 41 Graph of FACT-B total score EMMs.

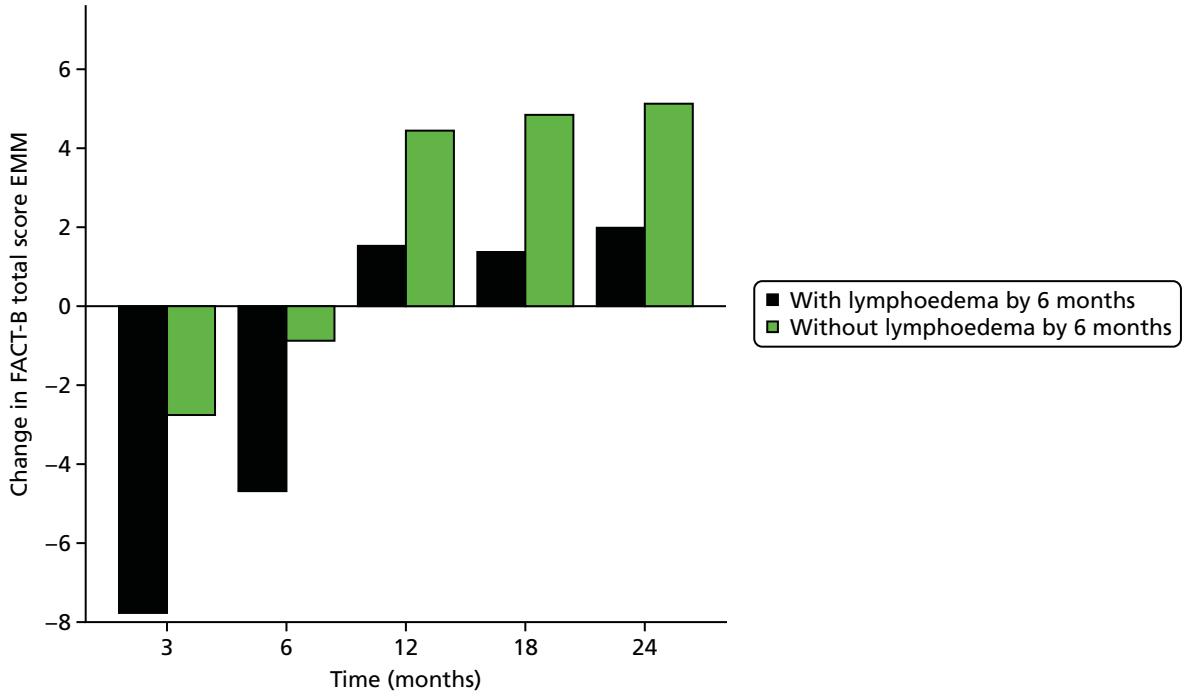


FIGURE 42 Graph of change in FACT-B total score EMMs.

ARM subscale

Owing to the negative skew of the ARM subscale variable, a transformation [LN(22 – ARM)] was used for the analysis so that a linear GEE model could be used.

In a model including only the time variable, the EMM of ARM at each time point is presented in the table below. A total of 995 patients had some data in the model.

Time point	Estimated marginal mean of ARM subscale (95% CI)
Pre surgery	18.7 (18.5 to 18.9)
3 months	16.1 (15.9 to 16.3)
6 months	15.9 (15.6 to 16.1)
12 months	16.0 (15.8 to 16.3)
18 months	16.1 (15.9 to 16.4)
24 months	16.4 (16.1 to 16.6)

Time–lymphoedema status interaction

A GEE analysis that included an interaction term between lymphoedema status by 6 months and time found that the interaction was not statistically significant ($p = 0.25$), showing the pattern of change over time was not significantly different between the groups.

The main effect for the time variable was statistically significant ($p < 0.001$). The main effect for the lymphoedema status by 6 months variable was statistically significant ($p < 0.001$), showing that there was a difference between the lymphoedema status groups overall.

The EMMs from the interaction term in the GEE analysis are presented below.

	Estimated marginal mean of ARM subscale (95% CI)		
Time point	Without lymphoedema by 6 months ($n = 882$)	With lymphoedema by 6 months ($n = 87$)	*p*-value
Pre surgery	18.7 (18.6 to 18.9)	18.6 (17.9 to 19.1)	0.62
3 months	16.2 (15.9 to 16.4)	15.7 (14.7 to 16.5)	0.29
6 months	16.2 (15.8 to 16.3)	14.0 (13.0 to 14.8)	< 0.001
12 months	16.2 (15.9 to 16.4)	14.4 (13.4 to 15.3)	< 0.001
18 months	16.3 (16.0 to 16.5)	14.7 (13.5 to 15.6)	0.001
24 months	16.5 (16.3 to 16.8)	15.2 (14.2 to 16.0)	0.003

The *p*-values in this table have not been adjusted for multiple testing.

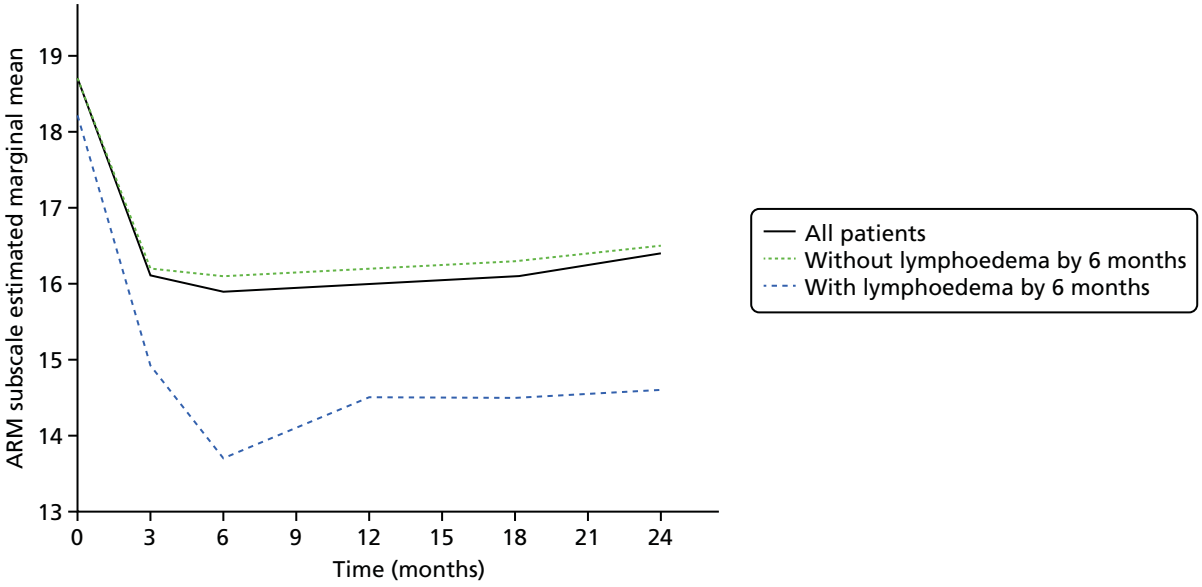


FIGURE 43 Graph of ARM subscale EMMs.

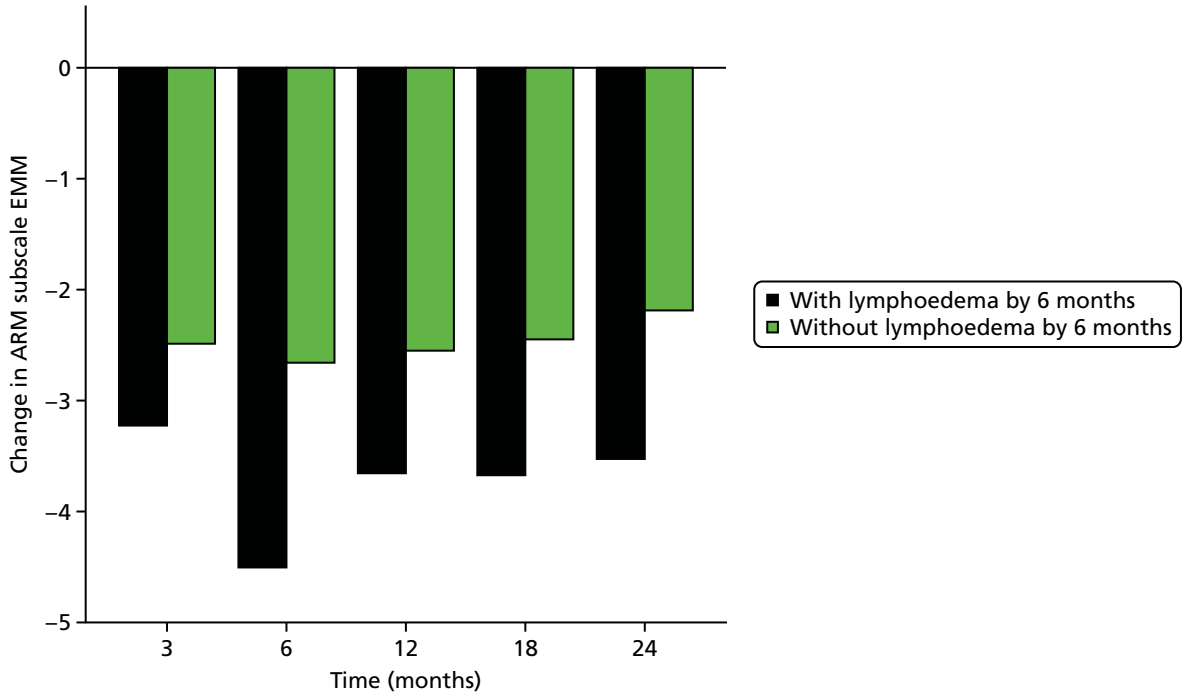


FIGURE 44 Graph of change in ARM subscale EMMs.

Clinical lymphoedema/appropriately applied sleeve

Trial Outcome Index

Owing to the negative skew of the TOI variable, a transformation [LN(120 – TOI)] was used for the analysis so that a linear GEE model could be used.

Time–lymphoedema status interaction

A GEE analysis that included an interaction term between lymphoedema status by 6 months and time found that the interaction was not statistically significant ($p = 0.58$), showing the pattern of change over time was not significantly different between the groups.

The main effect for the time variable was statistically significant ($p < 0.001$). The main effect for the lymphoedema status by 6 months variable was statistically significant ($p = 0.004$), showing that there was a difference between the lymphoedema status groups overall.

The EMMs from the interaction term in the GEE analysis are presented below.

Time point	Estimated marginal mean of TOI (95% CI)		*p*-value
	Without lymphoedema by 6 months ($n = 861$)	With lymphoedema by 6 months ($n = 77$)	
Pre surgery	68.5 (67.6 to 69.4)	65.9 (62.5 to 69.1)	0.14
3 months	64.1 (63.1 to 65.2)	58.5 (54.1 to 62.7)	0.009
6 months	66.0 (64.9 to 67.1)	60.4 (56.3 to 64.2)	0.005
12 months	70.7 (69.8 to 71.7)	65.7 (61.6 to 69.5)	0.012
18 months	71.1 (70.2 to 72.1)	65.9 (62.1 to 69.4)	0.005
24 months	71.5 (70.5 to 72.5)	66.9 (63.1 to 70.4)	0.013

The *p*-values in this table have not been adjusted for multiple testing.

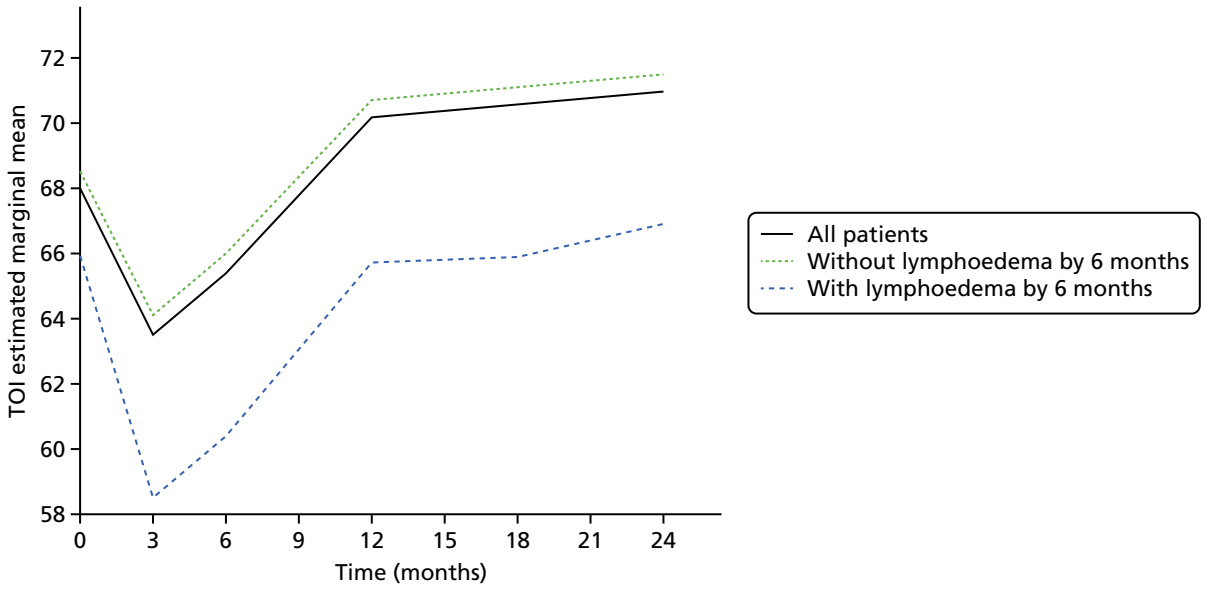


FIGURE 45 Graph of TOI EMMs.

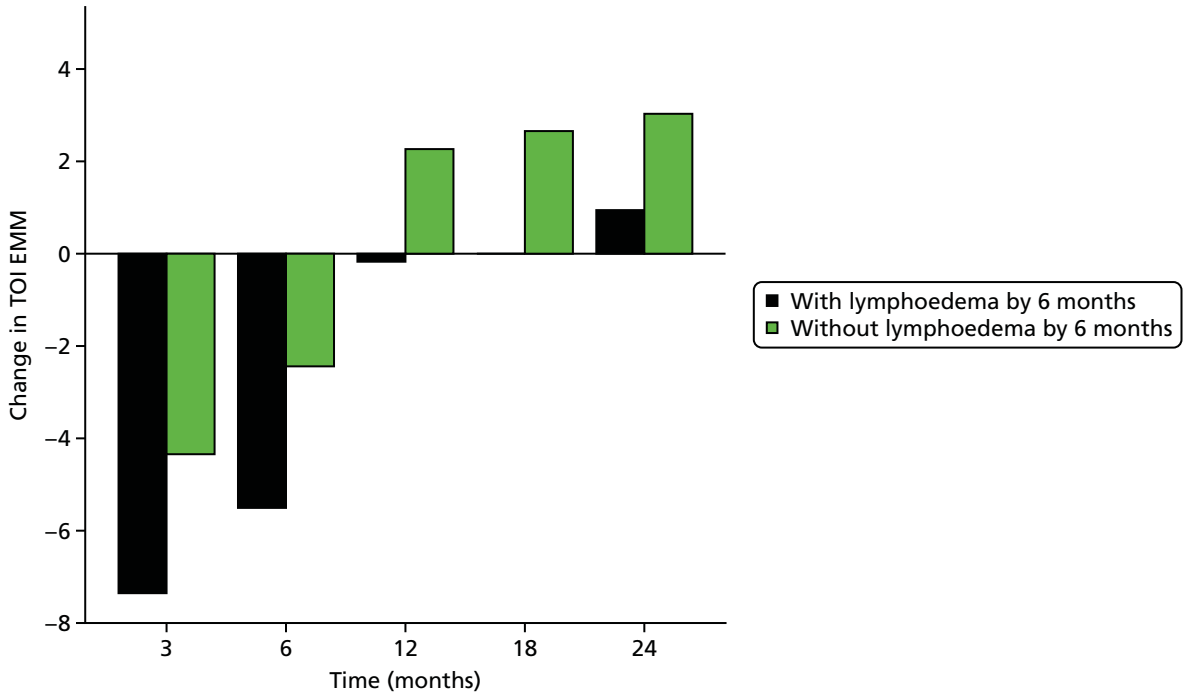


FIGURE 46 Graph of change in TOI EMMs.

FACT-B total score

Owing to the negative skew of the FACT-B total score variable, a transformation [LN(160 – FACT-B)] was used for the analysis so that a linear GEE model could be used.

Time–lymphoedema status interaction

A GEE analysis that included an interaction term between lymphoedema status by 6 months and time found that the interaction was not statistically significant ($p = 0.37$), showing the pattern of change over time was not significantly different between the groups.

The main effect for the time variable was statistically significant ($p < 0.001$). The main effect for the lymphoedema status by 6 months variable was statistically significant ($p = 0.011$), showing that there was a difference between the lymphoedema status groups overall.

The EMMs from the interaction term in the GEE analysis are presented below.

Time point	Estimated marginal mean of FACT-B total score (95% CI)		*p*-value
	Without lymphoedema by 6 months ($n = 860$)	With lymphoedema by 6 months ($n = 77$)	
Pre surgery	111.1 (109.8 to 112.3)	108.1 (103.1 to 112.7)	0.23
3 months	108.3 (106.9 to 109.7)	100.4 (94.2 to 106.0)	0.006
6 months	110.2 (108.7 to 111.6)	103.4 (97.3 to 109.0)	0.020
12 months	115.5 (114.2 to 116.8)	109.7 (103.5 to 115.2)	0.042
18 months	115.9 (114.6 to 117.2)	109.5 (104.1 to 114.4)	0.011
24 months	116.2 (114.8 to 117.6)	110.1 (104.6 to 115.1)	0.020

The *p*-values in this table have not been adjusted for multiple testing.

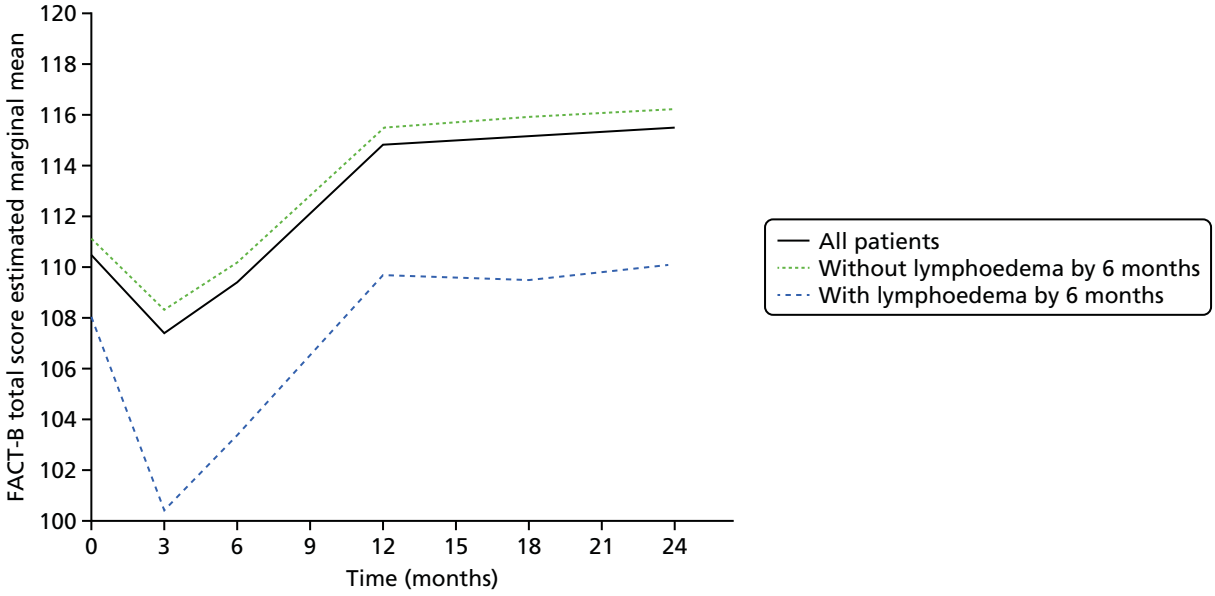


FIGURE 47 Graph of FACT-B total score EMMs.

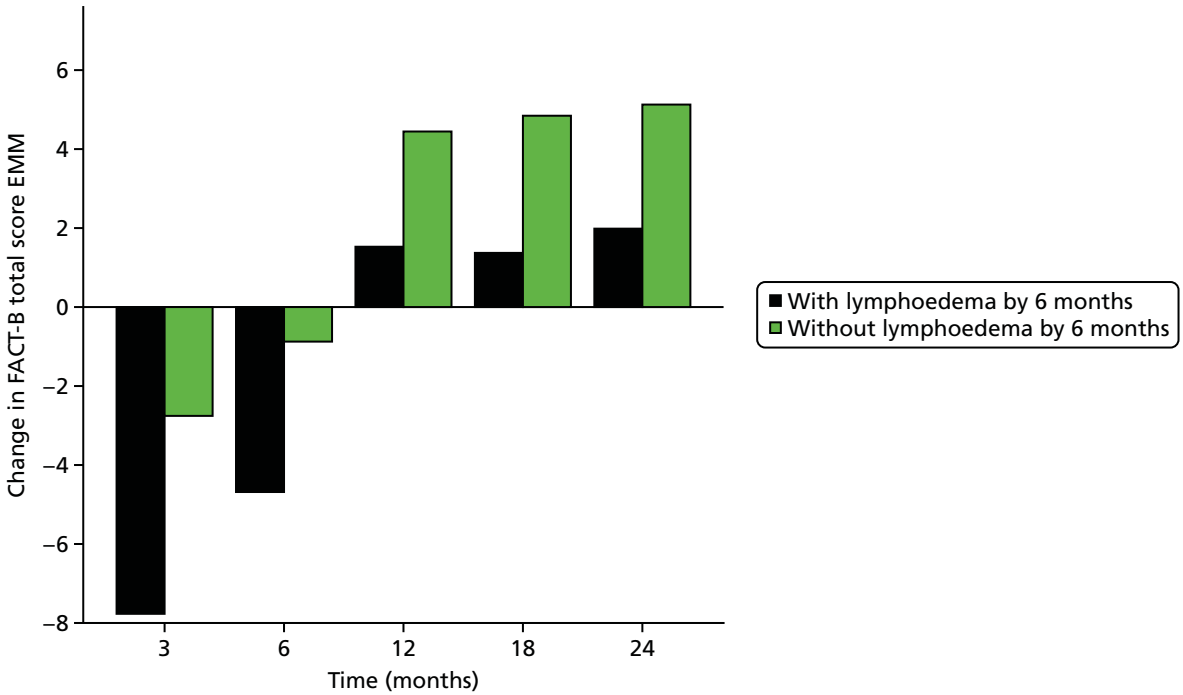


FIGURE 48 Graph of change in FACT-B total score EMMs.

ARM subscale

Owing to the negative skew of the ARM subscale variable, a transformation [LN(22 – ARM)] was used for the analysis so that a linear GEE model could be used.

Time–lymphoedema status interaction

A GEE analysis that included an interaction term between lymphoedema status by 6 months and time found that the interaction was not statistically significant ($p = 0.33$), showing the pattern of change over time was not significantly different between the groups.

The main effect for the time variable was statistically significant ($p < 0.001$). The main effect for the lymphoedema status by 6 months variable was statistically significant ($p < 0.001$), showing that there was a difference between the lymphoedema status groups overall.

The EMMs from the interaction term in the GEE analysis are presented below.

Time point	Estimated marginal mean of ARM subscale (95% CI)		*p*-value
	Without lymphoedema by 6 months ($n = 859$)	With lymphoedema by 6 months ($n = 77$)	
Pre surgery	18.7 (18.6 to 18.9)	18.2 (17.4 to 18.9)	0.12
3 months	16.2 (16.0 to 16.5)	14.9 (13.7 to 16.0)	0.014
6 months	16.1 (15.8 to 16.3)	13.7 (12.6 to 14.6)	< 0.001
12 months	16.2 (15.9 to 16.4)	14.5 (13.5 to 15.4)	< 0.001
18 months	16.3 (16.0 to 16.5)	14.5 (13.3 to 15.5)	0.001
24 months	16.5 (16.3 to 16.8)	14.6 (13.6 to 15.6)	< 0.001

The *p*-values in this table have not been adjusted for multiple testing.

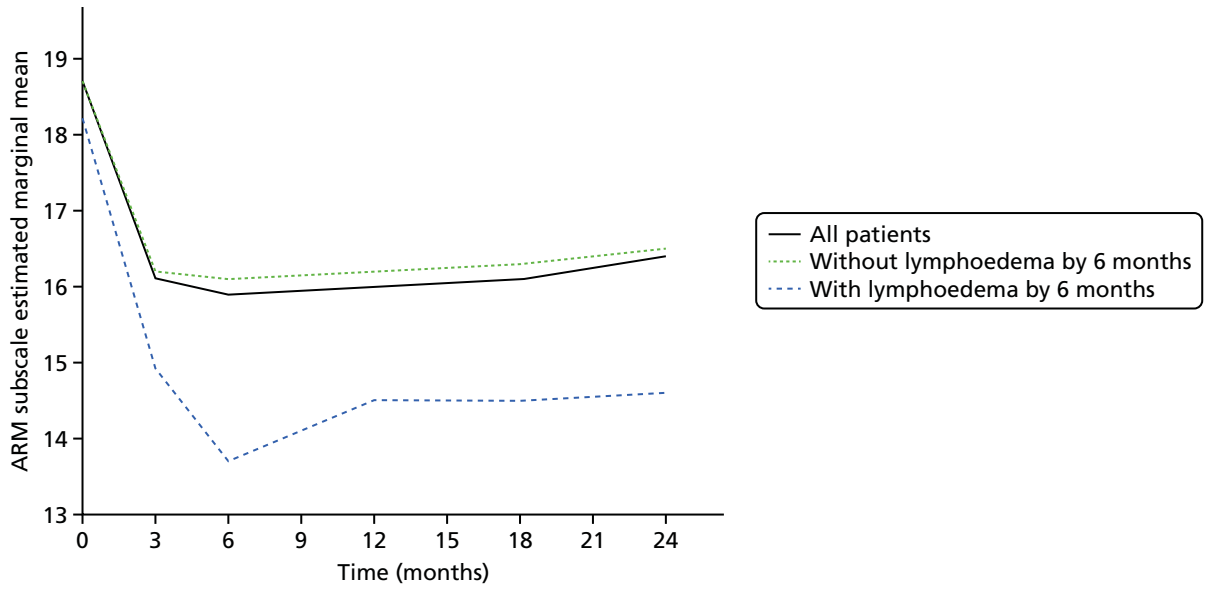


FIGURE 49 Graph of ARM subscale EMMs.

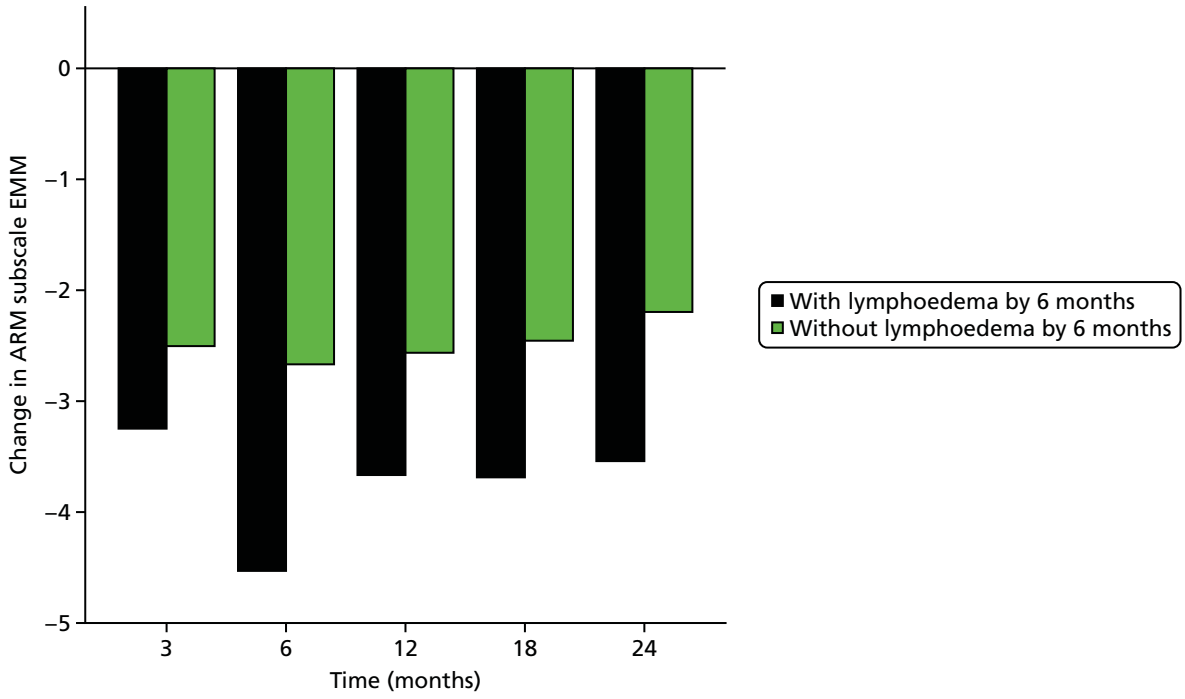


FIGURE 50 Graph of change in ARM subscale EMMs.

Associations between the 6-month lymphoedema checklist variables and changes in QoL from baseline and perometer/BIS from 1 month.

Appendix 17 Generalised estimating equations analysis

Analysis notes

Generalised estimating equations were used to assess the relationship between arm measurements (perometer and L-Dex) and TOI, the selected QoL measure.

Log-transformation

Owing to the negative skew of the TOI variable, a transformation [LN(120 – TOI)] was used throughout the analysis so that linear GEE models could be used.

Time variable

A time variable was included in each of the models and it was statistically significant in every analysis considered. It appears that, generally, there was an improvement in TOI over time from a minimum at the first time point considered, 3 months, to a maximum at the final time point considered, 24 months.

In a model only including the time variable, the estimated marginal means of TOI at each time point is presented in the table below.

Time point (months)	Estimated marginal mean of TOI (95% CI)
3	64.1 (62.8 to 65.4)
6	66.0 (64.7 to 67.3)
9	69.7 (68.4 to 70.9)
12	70.5 (69.4 to 71.7)
18	70.6 (69.4 to 71.8)
24	71.0 (69.8 to 72.2)

TABLE 97 Combined perometer or BIS vs. sleeve/clinical lymphoedema

After 6 months up to 24 months	No sleeve or clinical lymphoedema	Sleeve or clinical lymphoedema	Total
Perometer and BIS of < 10	537 (78%)	52 (38%)	589
Perometer or BIS of ≥ 10	154 (22%)	85 (62%)	239
Total	691	137	828

Sensitivity, 62% (85/137; 95% CI 54% to 70%); specificity, 78% (537/691; 95% CI 74% to 81%); PPV, 36% (85/239; 95% CI 30% to 42%); NPV, 91% (537/589; 95% CI 89% to 93%).

Diagnostic accuracy for composite end points

Those patients with lymphoedema at 3 months are not included in the numbers in *Table 98*.

TABLE 98 At 6 months

Measure	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
Perometer ≥ 10%	17/48 (35%)	732/776 (94%)	17/61 (28%)	732/763 (96%)	749/824 (91%)
Perometer ≥ 9%	22/48 (46%)	723/776 (93%)	22/75 (29%)	723/749 (97%)	745/824 (90%)
Perometer ≥ 5%	31/48 (65%)	631/776 (81%)	31/176 (18%)	631/648 (97%)	662/824 (80%)
BIS ≥ 10	24/47 (57%)	630/759 (83%)	27/156 (17%)	630/650 (97%)	657/806 (82%)
B3 ≤ 2	28/39 (72%)	556/703 (79%)	28/175 (16%)	556/567 (98%)	584/742 (79%)
Perometer ≥ 5% or B3 ≤ 2	39/43 (91%)	454/704 (64%)	39/289 (13%)	454/458 (99%)	493/747 (66%)
Perometer ≥ 9% and B3 ≤ 2	16/45 (36%)	765/789 (97%)	16/40 (40%)	765/794 (96%)	781/834 (94%)
Perometer ≥ 10% and B3 ≤ 2	13/46 (28%)	767/790 (97%)	13/36 (36%)	767/800 (96%)	780/836 (93%)

Those patients with lymphoedema up to 9 months are not included in the numbers in *Table 99*.

TABLE 99 At 12 months

Measure	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
Perometer ≥ 10%	14/41 (34%)	649/666 (97%)	14/31 (45%)	649/676 (96%)	663/707 (94%)
Perometer ≥ 9%	15/41 (37%)	639/666 (96%)	15/42 (36%)	639/665 (96%)	654/707 (93%)
Perometer ≥ 5%	28/41 (68%)	588/666 (88%)	28/106 (26%)	588/601 (98%)	616/707 (87%)
BIS ≥ 10	17/39 (44%)	573/641 (89%)	17/85 (20%)	573/595 (96%)	590/680 (87%)
B3 ≤ 2	19/35 (54%)	484/585 (83%)	19/120 (16%)	484/500 (97%)	503/620 (81%)
Perometer ≥ 5% or B3 ≤ 2	32/39 (82%)	431/588 (73%)	32/189 (17%)	431/438 (98%)	463/627 (74%)
Perometer ≥ 9% and B3 ≤ 2	8/38 (21%)	660/671 (98%)	8/19 (42%)	660/690 (96%)	668/709 (94%)
Perometer ≥ 10% and B3 ≤ 2	7/38 (18%)	664/671 (99%)	7/14 (50%)	664/695 (96%)	671/709 (95%)

Those patients with lymphoedema up to 18 months are not included in the numbers in *Table 100*.

TABLE 100 At 24 months

Measure	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
Perometer ≥ 10%	10/24 (42%)	511/530 (96%)	10/29 (34%)	511/525 (97%)	521/554 (94%)
Perometer ≥ 9%	12/24 (50%)	507/530 (96%)	12/35 (34%)	507/519 (98%)	519/554 (94%)
Perometer ≥ 5%	17/24 (71%)	454/530 (86%)	17/93 (18%)	454/461 (98%)	471/554 (85%)
BIS of ≥ 10	10/23 (43%)	447/491 (91%)	10/54 (19%)	447/460 (97%)	457/514 (89%)
B3 ≤ 2	8/21 (38%)	404/467 (87%)	8/71 (11%)	404/417 (97%)	412/488 (84%)
Perometer ≥ 5% or B3 ≤ 2	20/24 (83%)	343/470 (73%)	20/147 (14%)	343/347 (99%)	363/494 (73%)
Perometer ≥ 9% and B3 ≤ 2	4/21 (19%)	522/531 (98%)	4/13 (31%)	522/539 (97%)	526/552 (95%)
Perometer ≥ 10% and B3 ≤ 2	3/21 (14%)	524/532 (98%)	3/11 (27%)	524/542 (97%)	527/553 (95%)

Appendix 18 Workstream 3

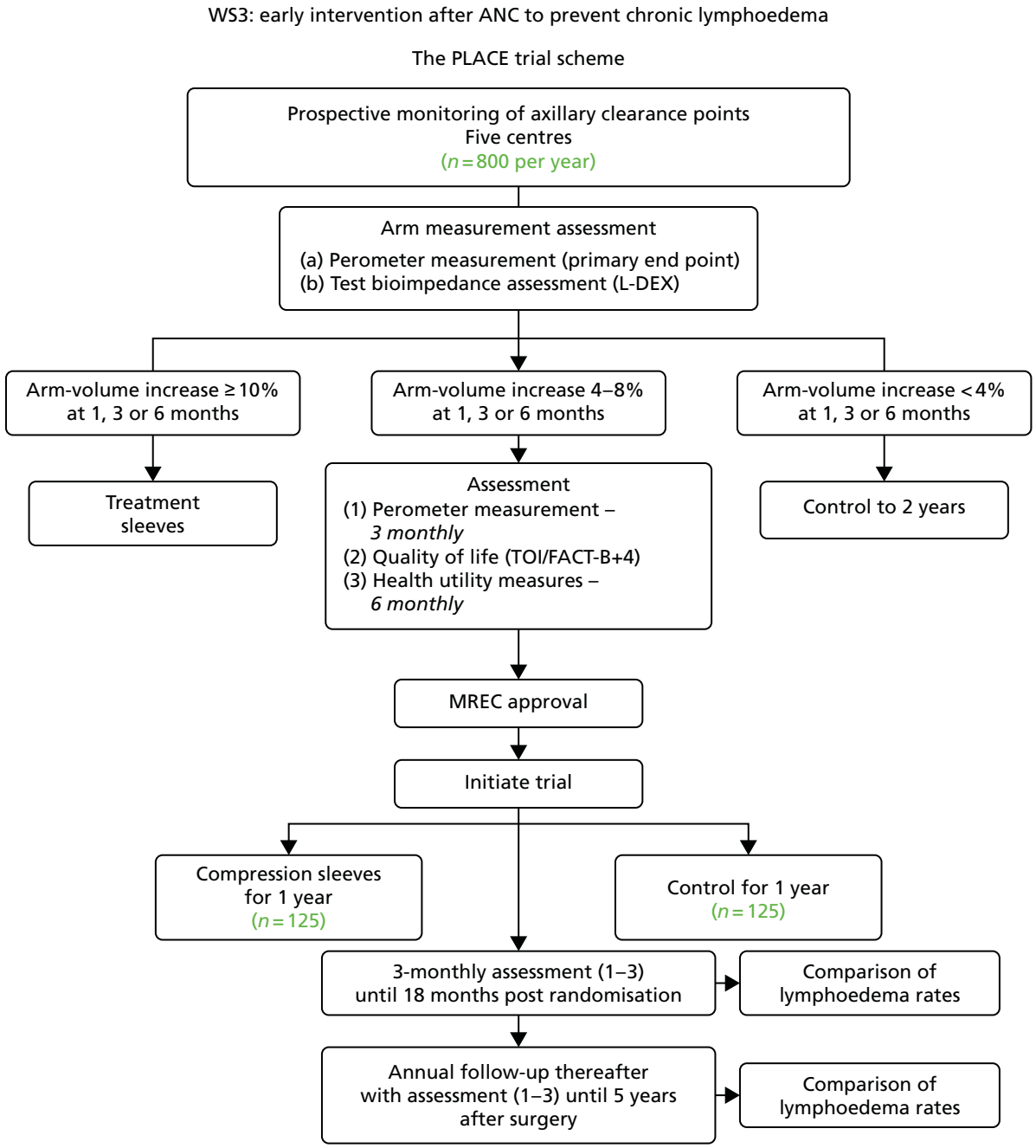


FIGURE 51 Workstream 3: early intervention after ANC to prevent chronic lymphoedema.

Appendix 19 Findings of the PLACE trial's qualitative substudy

Introduction

Low recruitment to RCTs can affect internal and external validity, statistical power and successful completion of trials.[50] A recent systematic review of recruitment activity highlighted how common recruitment problems are in health-care RCTs. Currently, 50% of RCTs fail to recruit to target and only 50% of those that successfully recruit do so in a timely manner.[51]

Maximising and encouraging more patients to take part in health research is one of the main aims of the National Institute for Health Research.[52] In addition, a key recommendation of the government's Life Science Strategy is for health-care organisations to provide adequate support to researchers who are recruiting to studies.[53] Although recruitment failure in RCTs has been extensively studied, there remains a lack of substantive research on initiatives that could improve the recruitment activity of research practitioners to improve patient recruitment.

Successful recruitment into trials generally focuses on the patient/recruiter encounter where the impact of communication skills has an important influence on patients' decision-making processes.[54] Research has highlighted, however, that information conveyed during recruitment varies considerably in quality and content, and that there is little research on actual recruitment encounters.[50] Findings from a qualitative study[55] that interviewed recruiting practitioners across six RCTs found that recruiting staff struggled with explaining the rationale for RCTs to patients; willingness to approach all eligible patients; providing accurate information about the trial; and confidence in eliciting patient preferences and exploring underlying reasons for preferences. Another study[56] found that patient preferences could change after discussions with the recruiting practitioner. Other research[57] has highlighted the importance of shared decision-making between patients and recruiters in obtaining informed consent that is free from coercion.

Predominantly, nurses with a clinical care background are employed as recruiting practitioners within the NHS. However, a number of studies of staff barriers to trial recruitment found that nurses tend to experience conflict between three distinct roles: caring clinical nurse, patient advocate and recruiter/scientist. This conflict leads to discomfort when approaching eligible patients judged as 'too unwell' or 'at the wrong stage of treatment' to participate in a RCT, such as during chemotherapy.[55,58] These studies also found that problematic recruiter behaviour during encounters, such as interruption, digression, inaccurate information-giving, and inattentiveness, made it difficult for patients' voices to be heard.

A survey and workshop on interventions to improve recruitment activity into RCTs recommended training recruiter practitioners in generic communication skills and trial-specific skills, such as explaining randomisation and dealing with patient preferences.[59] A recent systematic review[60] of training programmes for recruiters suggested that training programmes can improve practitioner recruiters' self-confidence and communication of some key RCT concepts to patients.

Research aim

Explore staff recruitment practices and shared decision-making during recruitment to the PLACE UK multisite RCT.

Methods

This qualitative study was conducted alongside the UK nationwide PLACE trial. Data were collected between September 2015 and May 2016 from six hospital recruitment sites. Initially, purposive sampling of key recruiting staff was undertaken. All 16 recruiting staff took part in either a focus group ($n = 8$) or a face-to-face interview ($n = 15$). The job titles of recruiting staff were senior research nurse ($n = 5$), research nurse ($n = 7$) and research practitioner/health-care assistant ($n = 4$). Open-ended interviews were conducted using a topic guide. The topic guide covered the following areas: staff attitudes to recruitment issues, recruitment procedures, research and study knowledge and information sharing, communication with patients, organisational barriers to recruitment, staff support and research training. Interviews were conducted in a private room at their place of work and lasted between 40 and 70 minutes. All interviews were audio recorded with permission from participants; written informed consent was obtained prior to the start of any discussion. A PPI group ($n = 8$) was established at the start of the project, which convened quarterly to inform aspects of the study, such as the design of information and interview guides, and to discuss and refine emerging findings from the interviews.

Interviews were transcribed verbatim and NVivo version 10 software (QSR International, Warrington, UK) was used to facilitate analysis. Data were analysed thematically using a framework analysis approach.[61] Analysis of data involved a five-stage process: (1) familiarisation, (2) identifying a thematic framework, (3) indexing, (4) charting and (5) mapping and interpretation. An iterative and inductive approach to analysis was followed so that analysis started alongside data collection and themes and issues identified and informed further questions and probing. Memos and documents were written about emerging categories, to summarise a point, to critique information, and to relate emergent theories to existing literature. All authors met on a regular basis to discuss the development of codes, themes, categories and theories about the phenomenon being studied.

Results

Role of the PLACE trial recruitment practitioners

Health-care professionals with a background in nursing ($n = 12$), as well as non-clinical staff ($n = 4$), were employed from established breast cancer research centres ($n = 5$) to identify patients who fulfilled the inclusion criteria for the PLACE trial. At post-surgery follow-up checks at 1, 3, 6 and 9 months, recruitment practitioners would conduct arm measurements of patients and compare any increase swelling with baseline data.

Four key themes were identified from the focus group and interviews that reflected the main reasons why recruitment rates were low. These were (1) wait and see culture, (2) conflicting roles, (3) misunderstanding the trial arms and (4) paternalism versus shared decision-making.

Wait and see culture

It became apparent that all recruiters held variable interpretations of who was eligible for the trial. Although a detailed protocol had been developed to help identify eligible patients, the majority of sites varied in their consensus of the way patient's eligibility status was decided. The majority of sites (4 out of 5) never recruited eligible patients at the first 1-month follow-up; usually staff considered that any swelling was mainly due to surgery. Interestingly, recruiters further described that they would provide the standard management arm of the study and defer recruitment into the RCT:

> *So if a patient has 6% increase at month 1 follow-up, that is not indicative of anything yet, she might have had sermonas or any swellings or infections in the breasts. We're not worried with a 6% increase. We reiterate about taking care of the arm, we do skin care, we do massage and send them on their merry way.*
>
> *Clinical nurse*

At 1 month we'd tell the patient it's only been 4 weeks or 6 weeks since your surgery so there might be still post-op swelling, so we leave it at that. But we do say you can do arm exercises that they have been shown by the physio as well. We give people a bit of information from the PLACE [trial] information exercise sheet at the same time as giving good skin care tips, and say see you in 2 months' time.

Clinical nurse

When you measure patients and there has been quite a jump, you know, from their previous measurements and it is just simply to do with the fact that they have been overusing their arm. So it is put down to that and so patients are more than happy to watch and wait. I don't know if that, kind of, stops them I suppose from getting on the trial.

Research practitioner

Conflicting roles

The majority of recruiting staff employed within the five PLACE trial sites were nurses (n = 12). All emphasised their dual roles as a clinician/patient advocate and recruiter and reflected on the conflict between the role of health professional, protecting the needs and vulnerability of their patients, and role of recruiter for a clinical trial. This role conflict was experienced by nurses during subsequent recruitment encounters beyond the 1-month follow-up:

If they were over 4% but very fretful I wouldn't give a PLACE [trial] information sheet and I would let them concentrate on trying to recover from the cancer surgery. But if there's no good reason that that swelling is there, I would possibly give a PLACE [trial] information sheet just as some background information. Keep it very easy, very light, I'll just give you this and the next time you come in if you're over the size again you might want to think about this RCT.

Clinical nurse

I've noticed that some patients might start radiotherapy around the 3-month follow-up appointment and, they'll have the radiotherapy on the same side as well, sometimes that doesn't help with the measurements, they can't get their arm in position due to restrictions. If they've started their radiotherapy they're going to be in and out every day, they might not want to come down for follow-up appointments again because they're quite tired, then the swelling might not go down due to the skin reactions in that area of the body as well. So I think that's a little bit of a tricky point to recruit also.

Clinical nurse

Sometimes people if they had a high measurement at 3 months, we'd sort of say, look . . . you're due to see me again in 3 months. If it's still up then I can recruit you then? I sort of explain that as well, because I think sometimes people don't want to do anything else. There is enough going on when they're at 3 months post surgery. Sometimes it's nice to reassure people that, we are due to see them again at 6 months and 9 months.

Research practitioner

At any stage if a patient seems tearful and a little anxious, that has to be brought into the mix as well, because if you introduce something new to a patient at this point when they've actually gotten better then they might think, oh, well, I've improved so why are you wanting me to possibly start wearing a sleeve. If I saw a 6% increase at 1 month I might say it will probably settle down, but we'll have a look at you next time. If I then saw a 4.1% increase from baseline the next time I would then think well, she's doing well, is there any signs of it [lymphoedema], is she coping well, and I'd kind of leave it, like everyone else, and wait.

Clinical nurse

The 'wait and see' nursing culture that was evident across multiple sites became part the way of working for all recruiters regardless of their clinical or non-clinical background. Recruitment teams (generally headed by more senior nurses) followed unwritten procedures embedded in their recruitment teams' assessment of trial eligibility. The extracts below from research practitioners indicate the powerful way embedded nursing culture affected recruitment rates:

> *I don't know about other sites but here it's not necessarily about recruiting to [the] PLACE [trial]. I'm not saying that, that's not what people are thinking about, but caring for the patient is more important than recruiting to [the] PLACE [trial]. Here if a lady is looking like they are eligible we tend to give them the information leaflets about standard care and say we will see you next time and see how you are getting on. So sometimes it feels a bit like we're making them ineligible for [the] PLACE [trial] by making them better, but that's the paradox of it really. Because of course most of the people I work with, they're nurses and that's what they do.*
>
> *Research practitioner*

> *My view here has been very much that I'm the new person on the team recruiting patients in to the RCT and what will happen is what has always happened. As decided by the people who've been here for an awful lot longer than I have and there isn't a great deal for manoeuvre on that, especially because they are nurses and I am a mere non-nurse.*
>
> *Research practitioner*

Owing to the 'wait and see' culture, as well as the role conflict experienced by recruiters who were reluctant to approach vulnerable patients, for example during chemotherapy treatment, some patients were missed during the whole of their eligibility time period. In addition, if patients presented with an arm swelling towards the upper limit of eligibility for the PLACE trial, recruiters would in some cases make a clinical judgement to refer the patient directly to the lymphoedema service, even if the patient was eligible for the study sleeve:

> *When we had up to 2 years to recruit it was a little bit easier because you had more time to get patients into the study. Now it's quite a short little burst that we have, so I think it's probably a little bit too short now because people will only have finished their chemotherapy and radiotherapy in 9 months. I think if it was maybe open to recruitment until 12 months, recruitment rates might improve.*
>
> *Clinical nurse*

> *At 6 months or even at the 9-month visit if patients swellings have been steadily increasing towards the upper limit of PLACE [trial] eligibility some patients may want something done about it and they don't really want to go into the study as there is only a 50% chance of them getting a sleeve, they just want an assessment with the lymphoedema service. That's what I found anyway, we always do have to say that there's always the referral to the lymphoedema service, because it is part of patient care too. So we can't just say the only solution for you is the study because it's not right to do that.*
>
> *Research practitioner*

Misunderstanding the trial arms and equipoise

A common problem among recruiters was that they misunderstood the trial arms of the study. This generally led to recruiters explaining the RCT incorrectly to patients and/or presenting the trial arms in a positive or negative way. Patients' views and decisions about participating in clinical trials are greatly influenced by how information is presented to them during the recruitment encounter. A number of recruiters inadvertently explained the randomisation process to patients as a 'fifty–fifty chance of getting the sleeve', which may have had a detrimental effect on their decision to take part, especially if patients felt that their treatment preferences would not be met. Other recruiters encouraged patients to follow incorrect procedures, for example wearing the compression garment/sleeve day and night:

> *I think it is very evident, like, it's that the numbers are lagging and to be honest it is a little bit, kind of, it's not baffling though to be honest. You know, so if the study was presented to me, if I had an*

increase in my arm swelling and they give me the option of say fifty, fifty of getting the sleeve or not I personally would want something done about it. So I would take the lymphedema referral. So yeah I get why people haven't gone on to the study.

Research practitioner

We tell them to wear it all day every day especially day time when doing activity stuff. One patient said she found it uncomfortable wearing it at night so she takes it off. But then she noticed that in the mornings her arm was very swollen and it takes time to put it back on. So I said, if the sleeve isn't that uncomfortable for you at night time, wear it. I think the only time patients take it off is to wash it.

Research practitioner

So I usually explain that it's a 50/50 chance of getting either the controller where it's just arm exercises we give you to do or the computer randomises you to have the sleeve.

Research practitioner

Paternalism versus shared decision-making

Recruiter practitioners involved in the PLACE trial made assumptions that taking part in the RCT may be burdensome, intrusive or not beneficial to individual patients who were deemed by some recruiters as being vulnerable:

I suppose, because they are going through chemo, they are quite . . . you know, they've got a lot going on in their lives. You might not want to . . . after discussing about somebody's life outside surgery, they're having a tough time then, it might be the last thing you want to do is recruit them into something. It's our choice it's about clinical care as well as just the research.

Clinical nurse

There's two arms to the study, but I think the prospect of patients potentially having to wear a sleeve when potentially there isn't a benefit for patients, I think that's one of the things that patients pick up on and realise that and I think especially in some of the younger women, we have approached for [the] PLACE [trial], it's not necessarily a nice thing to potentially have to wear.

Research practitioner

I think we get a few occasions where patients are quite visibly put off by the fact of having to wear a sleeve, I don't think that's a very nice prospect for patients in the first instance especially as, you know, we're talking to patients, you know, maybe 6 months, 9 months down the line where they're maybe coming to the end of their treatment, they may have just done the chemotherapy, radiotherapy and then we're coming back to them and saying actually, we think, potentially there could be some early signs of lymphoedema there and we're saying that, you know, normally patients wouldn't necessarily have this treatment, we don't know if there's a benefit or not, but we would like to see if there would be a benefit.

Research practitioner

Conclusion

As highlighted earlier, assumptions made by recruitment staff that taking part in the RCT may be burdensome for patients had a significant impact on recruitment behaviour, which, in turn, led to poor recruitment rates. During recruitment encounters, staff acted as gatekeepers by suggesting taking part in the PLACE trial only to those patients who were deemed suitable for the trial, rather than to all patients who met the inclusion eligibility criteria. Making a clinical judgement not to recruit patients in this way is perceived as paternalistic. For example, the PLACE trial recruiters were making decisions on their patients' behalf with the view that as clinicians they knew what was best for patients. Certain recruiters generally described that their focus was on protecting and caring for patients' needs rather than sharing knowledge and information about the RCT.

Future research

To develop and test a person-centred communication skills training intervention for clinical research nurses and research practitioners recruiting patients into RCTs. Although extensive research exists that explores barriers to patient participation in clinical trials,[62] less work has been untaken that investigates initiatives that could improve the recruiters' encounters with potential participants. The drive to deliver person-centred care across the NHS has been significantly promoted over the past decade as a means of enhancing the quality of care experienced by patients in everyday clinical settings. However, trial recruitment interactions have been largely neglected and little attention has been given to how the concept of person-centred care is relevant to improving trial recruitment. Within the model of person-centred care, person-centred communication involves providing room for the patient's story, exploring emotional cues and showing empathy, providing information and advice, explaining things clearly, and involving patients in shared decision-making. Training research practitioners in how to manage these encounters in a more person-centred way has the potential to help recruiters improve their communication skills, increase recruitment rates and collaborate with patients as partners in the development of evidence-based research.

Appendix 20 Consolidated Standards of Reporting Trials flow diagram (from the 1100 multifrequency bioimpedance cohort) based on the data set used in the analyses of workstream 2

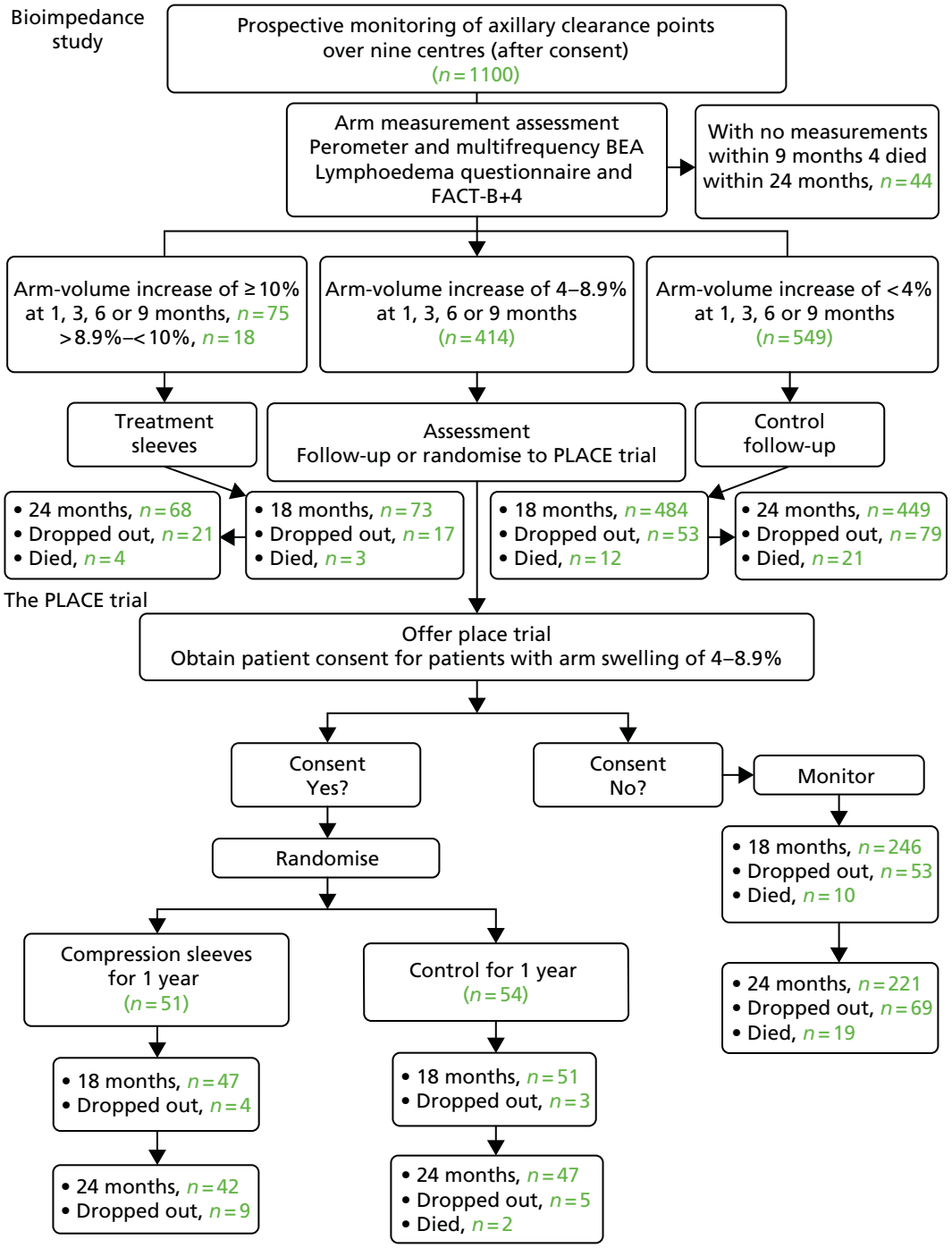


FIGURE 52 Consolidated Standards of Reporting Trials flow diagram. Note that 143 participants were randomised in the PLACE trial (69 to compression sleeves, 74 to control) from the full BEA cohort.

Information from the 600 with final follow-up at 60 months estimated using final perometer measurements:

- dropout by 24 months – 63, of which 28 had happened by 18 months
- deaths by 24 months – 50, of which 28 had happened by 18 months (a further 55 patients died after 24 months).

Appendix 21 Site contact list for Programme Grants for Applied Research studies

Site name	Site type	Site address
South Manchester	Sponsor site BEA, PLACE and PLACE qualitative	Nightingale and Genesis Prevention Centre, Wythenshawe Hospital, Manchester, UK
Pennine	BEA, PLACE and PLACE qualitative	The Pennine Acute Hospitals NHS Trust, Oncology Research, North Manchester General Hospital, Trust Headquarters, Manchester, UK
North Staffordshire	BEA and PLACE	University Hospital of North Staffordshire NHS Trust, The Cancer Centre, City General Site, Stoke-on-Trent, UK
Derby	BEA, PLACE and PLACE qualitative	Derby Hospitals NHS Foundation Trust, Royal Derby Hospital, Nightingale Macmillan Unit, Derby, UK
Guy's	BEA, PLACE and PLACE qualitative	Guy's & St Thomas' NHS Foundation Trust, Guy's Hospital, London, UK
Bournemouth	BEA and PLACE	Royal Bournemouth & Christchurch Hospitals NHS Foundation Trust, The Royal Bournemouth Hospital, Bournemouth, UK
Poole	BEA and PLACE	Poole Hospital NHS Foundation Trust, Oncology Research, Poole, UK
Wolverhampton	BEA and PLACE	The Royal Wolverhampton Hospitals NHS Trust, New Cross Hospital, The McHale Building, New Cross Hospital, Wolverhampton, UK
Stockport	BEA screening site	Stepping Hill Hospital, Room Stepping Hill Hospital, Stockport, UK
Mansfield	PLACE	King's Mill Hospital, Sutton in Ashfield, UK
Hull	PLACE	Castle Hill Hospital, Breast Care Unit, Cottingham, UK
Swansea	PLACE	Singleton Hospital, Swansea, UK
Macclesfield	PLACE and PLACE qualitative	Macclesfield District General Hospital, Cancer Resource Centre, Macclesfield, UK
Peterborough	PLACE	Peterborough and Stamford Hospitals NHS Foundation Trust, Peterborough City Hospital, Peterborough, UK
Dudley	PLACE	Russel Hall Hospital, Dudley, UK
Wigan	PLACE	Royal Albert Edward Infirmary, Wigan, UK
London	PLACE	Homerton University Hospital, London, UK
Nuneaton	PLACE	George Eliot Hospital NHS Trust, Research & Development Office, Nuneaton, UK

Appendix 22 Authors' publications that underpin/emanate from the Programme Grant for Applied Research funding

Professor Nigel Bundred

Book chapters

Turner LE, Bundred NJ. Treatment of Menopausal Symptoms in Women with Breast Cancer. In Robert Leonard, Andreas Polychronis, Andrew Miles, editors. *The Effective Management of Breast Cancer*. 3rd edn. London: Aesculapius Medical Press; 2004. Chapter 21.

Review articles

Holland P, Bundred NJ. Ductal carcinoma in situ. *Surgery* 1994;**12**:55–7.

Hadjiloucas I, Bundred NJ. Axillary surgery: is it necessary? *The Breast* 2000;**9**:1–3.

Chan KC, Bundred NJ. Chapter 16 Classification and Staging of Breast Cancer: Operable, Locally Advanced and Metastatic. In JM Dixon and V Sacchini, editors. *Breast Cancer Diagnosis and Management*. London: Elsevier; 2000.

Bundred NJ. Is radiotherapy necessary for all women with DCIS? *Oncology Times* 2005;**1**:3.

Original refereed papers in academic journals

(Overall H Index 48, cited over 8405 times.)

To 2000

Hawkins RA, White G, Bundred NJ, Dixon JM, Miller WR, Stewart HJ, Forrest AP. Prognostic significance of oestrogen and progestogen receptor activities in breast cancer. *Br J Surg* 1987;**74**:1009–13.

Bundred NJ, Dover MS, Coley S, Morrison JM. Breast abscesses and cigarette smoking. *Br J Surg* 1992;**79**:58–9.

Walls J, Boggis CR, Wilson M, Asbury DL, Roberts JV, Bundred NJ, Mansel RE. Treatment of the axilla in patients with screen-detected breast cancer. *Br J Surg* 1993;**80**:436–8.

Harding C, Knox WF, Faragher EB, Baildam A, Bundred NJ. Hormone replacement therapy and tumour grade in breast cancer: prospective study in screening unit. *BMJ* 1996;**312**:1646–7.

Holland PA, Walls J, Boggis CR, Knox F, Baildam AD, Bundred NJ. A comparison of axillary node status between cancers detected at the prevalence and first incidence breast screening rounds. *Br J Cancer* 1996;**74**:1643–6.

Holland PA, Gandhi A, Knox WF, Wilson M, Baildam AD, Bundred NJ. The importance of complete excision in the prevention of local recurrence of ductal carcinoma in situ. *Br J Cancer* 1998;**77**:110–14.

Abdullah TI, Iddon J, Barr L, Baildam AD, Bundred NJ. Prospective randomised controlled trial to determine the value of preservation of the intercostobrachial nerve during axillary node clearance for breast cancer. *Br J Surg* 1998;**85**:1443–5.

Bundred N, Maguire P, Reynolds J, Grimshaw J, Morris J, Thomson L, *et al*. Randomised controlled trial of effects of early discharge after surgery for breast cancer. *BMJ* 1998;**317**:1275–9.

Hargreaves DF, Knox F, Swindell R, Potten CS, Bundred NJ. Epithelial proliferation and hormone receptor status in the normal post-menopausal breast and the effects of hormone replacement therapy. *Br J Cancer* 1998;**78**:945–9.

Hargreaves DF, Potten CS, Harding C, Shaw LE, Morton MS, Roberts SA, *et al*. Two-week dietary soy supplementation has an estrogenic effect on normal premenopausal breast. *J Clin Endocrinol Metab* 1999;**84**:4017–24. https://doi.org/10.1210/jcem.84.11.6152

2000–10

Chan KC, Knox WF, Sinha G, Gandhi A, Barr L, Baildam AD, Bundred NJ. Extent of excision margin width required in breast conserving surgery for ductal carcinoma in situ. *Cancer* 2001;**91**:9–16.

Bundred NJ. Hormone replacement therapy, breast cancer and the future. *J Br Menopause Soc* 2001;**7**:13–15.

Bundred NJ. Prognostic and predictive factors in breast cancer. *Cancer Treat Rev* 2001;**27**:137–42. https://doi.org/10.1053/ctrv.2000.0207

Dey P, Bundred N, Gibbs A, Hopwood P, Baildam A, Boggis C, *et al.* Costs and benefits of a one stop clinic compared with a dedicated breast clinic: randomised controlled trial. *BMJ* 2002;**324**:507.

Robertson JF, Nicholson RI, Bundred NJ, Anderson E, Rayter Z, Dowsett M, *et al.* Comparison of the short-term biological effects of 7alpha-[9-(4,4,5,5,5-pentafluoropentylsulfinyl)-nonyl]estra-1,3,5,(10)-triene-3,17beta-diol (Faslodex) versus tamoxifen in postmenopausal women with primary breast cancer. *Cancer Res* 2001;**61**:6739–46.

Dowsett M, Bundred NJ, Decensi A, Sainsbury RC, Lu Y, Hills M, *et al.* Effect of Raloxifene on breast cancer cell Ki67 and apoptosis: a double blind, placebo-controlled, randomised clinical trial in postmenopausal patients. *Cancer Epidemiol Biomarkers Prevent* 2001;**10**:961–9.

Chan KC, Knox WF, Gee JM, Morris J, Nicholson RI, Potten CS, Bundred NJ. Effect of epidermal growth factor receptor tyrosine kinase inhibition on epithelial proliferation in normal and premalignant breast. *Cancer Res* 2002;**62**:122–8.

Wärnberg F, Bundred N. Will early detection of non-axillary sentinel nodes affect treatment decisions? *Br J Cancer* 2002;**87**:691–3. https://doi.org/10.1038/sj.bjc.6600557

Bundred NJ, Anderson E, Nicholson RI, Dowsett M, Dixon M, Robertson JF. Fulvestrant, an estrogen receptor downregulator, reduces cell turnover index more effectively than tamoxifen. *Anticancer Res* 2002;**22**:2317–19.

Freeman SR, Washington SJ, Pritchard T, Barr L, Baildam AD, Bundred NJ. Long term results of a randomised prospective study of preservation of the intercostobrachial nerve. *Eur J Surg Oncol* 2003;**29**:213–15.

Boland GP, McKeown A, Chan KC, Prasad R, Knox WF, Bundred NJ. Biological response to hormonal manipulation in oestrogen receptor positive ductal carcinoma in situ of the breast. *Br J Cancer* 2003;**89**:277–83. https://doi.org/10.1038/sj.bjc.6601013

Prasad R, Boland GP, Cramer A, Anderson E, Knox WF, Bundred NJ. Short-term biologic response to withdrawal of hormone replacement therapy in patients with invasive breast carcinoma. *Cancer* 2003;**98**:2539–46. https://doi.org/10.1002/cncr.11836

Warnberg F, Bundred NJ. The relationship between oestrogen and breast cancer. *J RC Physc Edinburgh* 2004;**34**:25–31.

Bundred NJ, Turner LE. Postmenopausal hormone therapy before and after breast cancer: clinical experiences. *Maturitas* 2004;**49**:S22–31. https://doi.org/10.1016/j.maturitas.2004.06.021

Barnes NL, Boland GP, Davenport A, Knox WF, Bundred NJ. Relationship between hormone receptor status and tumour size, grade and comedo necrosis in ductal carcinoma in situ. *Br J Surg* 2005;**92**:429–34. https://doi.org/10.1002/bjs.4878

Wilson GR, Cramer A, Welman A, Knox F, Swindell R, Kawakatsu H, *et al.* Activated c-SRC in ductal carcinoma in situ correlates with high tumour grade, high proliferation and HER2 positivity. *Br J Cancer* 2006;**95**:1410–14.

Howell A, Clarke RB, Evans G, Bundred N, Cuzick J, Santen R, Allred C. Estrogen deprivation for breast cancer prevention. *Recent Results Cancer Res* 2007;**174**:151–67.

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 > or = 65 years. *Br J Cancer* 2007;**96**:1197–203.

Lavelle K, Moran A, Howell A, Bundred N, Campbell M, Todd C. Older women with operable breast cancer are less likely to have surgery. *Br J Surg* 2007;**94**:1209–15. https://doi.org/10.1002/bjs.5834

2011

Cuzick J, Sestak I, Pinder SE, Ellis IO, Forsyth S, Bundred NJ, *et al.* Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial. *Lancet Oncol* 2011;**12**:21–9. https://doi.org/10.1016/S1470-2045(10)70266-7

Davies C, Godwin J, Gray R, Clarke M, Cutter D, Darby S, *et al.* Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet* 2011;**378**:771–84. https://doi.org/10.1016/S0140-6736(11)60993-8

Coleman RE, Marshall H, Cameron D, Dodwell D, Burkinshaw R, Keane M, *et al.*; AZURE Investigators. Breast-cancer adjuvant therapy with zoledronic acid. *N Engl J Med* 2011;**365**:1396–405.

2012

Barnes NL, Ooi JL, Yarnold JR, Bundred NJ. Ductal carcinoma in situ of the breast. *BMJ* 2012;**344**:e797. https://doi.org/10.1136/bmj.e797

Hadji P, Gnant M, Body JJ, Bundred NJ, Brufsky A, Coleman RE, *et al.* Cancer treatment-induced bone loss in premenopausal women: a need for therapeutic intervention? *Cancer Treat Rev* 2012;**38**:798–806. https://doi.org/10.1016/j.ctrv.2012.02.008

2013

Farnie G, Willan PM, Clarke RB, Bundred NJ. Combined inhibition of ErbB1/2 and Notch receptors effectively targets breast ductal carcinoma in situ (DCIS) stem/progenitor cell activity regardless of ErbB2 status. *PLOS ONE* 2013;**8**:e56840. https://doi.org/10.1371/journal.pone.0056840

Singh JK, Farnie G, Bundred NJ, Simões BM, Shergill A, Landberg G, *et al.* Targeting CXCR1/2 significantly reduces breast cancer stem cell activity and increases the efficacy of inhibiting HER2 via HER2-dependent and -independent mechanisms. *Clin Cancer Res* 2013;**19**:643–56. https://doi.org/10.1158/1078-0432.CCR-12-1063

Farnie G, Johnson RL, Williams KE, Clarke RB, Bundred NJ. Lapatinib inhibits stem/progenitor proliferation in preclinical in vitro models of ductal carcinoma in situ (DCIS). *Cell Cycle* 2014;**13**:418–25. https://doi.org/10.4161/cc.27201

Coleman R, de Boer R, Eidtmann H, Llombart A, Davidson N, Neven P, *et al.* Zoledronic acid (zoledronate) for postmenopausal women with early breast cancer receiving adjuvant letrozole (ZO-FAST study): final 60-month results. *Ann Oncol* 2013;**24**:398–405. https://doi.org/10.1093/annonc/mds277

Bundred NJ, Prasad R, Morris J, Knox WF, Byrne G, Cheung S, *et al.* Are symptomatic guidelines for chemotherapy appropriate to ER-positive screen-detected breast cancer (SDBC)? *Breast Cancer Res Treat* 2013;**138**:359–68. https://doi.org/10.1007/s10549-011-1652-6

Bundred N, Gardovskis J, Jaskiewicz J, Eglitis J, Paramonov V, McCormack P, *et al.* Evaluation of the pharmacodynamics and pharmacokinetics of the PARP inhibitor olaparib: a phase I multicentre trial in patients scheduled for elective breast cancer surgery. *Invest New Drugs* 2013;**31**:949–58. https://doi.org/10.1007/s10637-012-9922-7

Eccles SA, Aboagye EO, Ali S, Anderson AS, Armes J, Berditchevski F, *et al.* Critical research gaps and translational priorities for the successful prevention and treatment of breast cancer. *Breast Cancer Res* 2013;**15**:R92. https://doi.org/10.1186/bcr3493

Singh JK, Simões BM, Clarke RB, Bundred NJ. Targeting IL-8 signalling to inhibit breast cancer stem cell activity. *Expert Opin Ther Targets* 2013;**17**:1235–41. https://doi.org/10.1517/14728222.2013.835398

Bundred N, Gardovskis J, Jaskiewicz J, Eglitis J, Paramonov V, McCormack P, *et al.* Evaluation of the pharmacodynamics and pharmacokinetics of the PARP inhibitor olaparib: a phase I multicentre trial in patients scheduled for elective breast cancer surgery. *Invest New Drugs* 2013;**31**:949–58. https://doi.org/10.1007/s10637-012-9922-7

2014

Barnes NL, Dimopoulos N, Williams KE, Howe M, Bundred NJ. The frequency of presentation and clinico-pathological characteristics of symptomatic versus screen detected ductal carcinoma in situ of the breast. *Eur J Surg Oncol* 2014;**40**:249–54. https://doi.org/10.1016/j.ejso.2013.12.013

Bundred SM, Zhou J, Whiteside S, Morris J, Wilson M, Hurley E, Bundred N. Impact of full-field digital mammography on pre-operative diagnosis and surgical treatment of mammographic microcalcification. *Breast Cancer Res Treat* 2014;**143**:359–66. https://doi.org/10.1007/s10549-013-2803-8

Lavelle K, Sowerbutts AM, Bundred N, Pilling M, Degner L, Stockton C, Todd C. Is lack of surgery for older breast cancer patients in the UK explained by patient choice or poor health? A prospective cohort study. *Br J Cancer* 2014;**110**:573–83. https://doi.org/10.1038/bjc.2013.734

Farnie G, Johnson RL, Williams KE, Clarke RB, Bundred NJ. Lapatinib inhibits stem/progenitor proliferation in preclinical in vitro models of ductal carcinoma in situ (DCIS). *Cell Cycle* 2014;**13**:418–25. https://doi.org/10.4161/cc.27201

Cuzick J, Sestak I, Forbes JF, Dowsett M, Knox J, Cawthorn S, *et al.* Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. *Lancet* 2014;**383**:1041–8. https://doi.org/10.1016/S0140-6736(13)62292-8

Topps A, Clay V, Absar M, Howe M, Lim Y, Johnson R, Bundred N. The sensitivity of pre-operative axillary staging in breast cancer: comparison of invasive lobular and ductal carcinoma. *Eur J Surg Oncol* 2014;**40**:813–17. https://doi.org/10.1016/j.ejso.2014.03.026

Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJ, Mansel RE, *et al.* Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol* 2014;**15**:1303–10. https://doi.org/10.1016/S1470-2045(14)70460-7

2015

Bundred NJ, Barnes NL, Rutgers E, Donker M. Is axillary lymph node clearance required in node-positive breast cancer? *Nat Rev Clin Oncol* 2015;**12**:55–61. https://doi.org/10.1038/nrclinonc.2014.188

Williams KE, Bundred NJ, Landberg G, Clarke RB, Farnie G. Focal adhesion kinase and Wnt signaling regulate human ductal carcinoma in situ stem cell activity and response to radiotherapy. *Stem Cells* 2015;**33**:327–41. https://doi.org/10.1002/stem.1843

Williams KE, Barnes NL, Cramer A, Johnson R, Cheema K, Morris J, *et al.* Molecular phenotypes of DCIS predict overall and invasive recurrence. *Ann Oncol* 2015;**26**:1019–25. https://doi.org/10.1093/annonc/mdv062

Bundred NJ, Stockton C, Keeley V, Riches K, Ashcroft L, Evans A, *et al.* Comparison of multi-frequency bioimpedance with perometry for the early detection and intervention of lymphoedema after axillary node clearance for breast cancer. *Breast Cancer Res Treat* 2015;**151**:121–9. https://doi.org/10.1007/s10549-015-3357-8

Lavelle K, Sowerbutts AM, Bundred N, Pilling M, Todd C. Pretreatment health measures and complications after surgical management of elderly women with breast cancer. *Br J Surg* 2015;**102**:653–67. https://doi.org/10.1002/bjs.9796

Leary A, Evans A, Johnston SR, A'Hern R, Bliss JM, Sahoo R, *et al.* Antiproliferative effect of Lapatinib in HER2-positive and HER2-negative/HER3-high breast cancer: results of the presurgical randomized MAPLE trial (CRUK E/06/039). *Clin Cancer Res* 2015;**21**:2932–40. https://doi.org/10.1158/1078-0432.CCR-14-1428

Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Coleman R, Powles T, Paterson A, Gnant M, Anderson S, Diel I, *et al.* Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. *Lancet* 2015;**386**:1353–61.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Dowsett M, Forbes JF, Bradley R, Ingle J, Aihara T, Bliss J, *et al.* Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet* 2015;**386**:1341–52.

Forbes JF, Sestak I, Howell A, Bonanni B, Bundred N, Levy C, *et al.*; IBIS-II investigators. Anastrozole versus tamoxifen for the prevention of locoregional and contralateral breast cancer in postmenopausal women with locally excised ductal carcinoma in situ (IBIS-II DCIS): a double-blind, randomised controlled trial. *Lancet* 2016;**387**:866–73.

2016

Bundred SM, Maxwell AJ, Morris J, Lim YY, Harake MJ, Whiteside S, Bundred NJ. Randomized controlled trial of stereotactic 11-G vacuum-assisted core biopsy for the diagnosis and management of mammographic microcalcification. *Br J Radiol* 2016;**89**:20150504. https://doi.org/10.1259/bjr.20150504

Bundred N, Maxwell AJ, Harvey J, Hunt R, Morris J, Lim YY. A randomised pilot study comparing 13 G vacuum-assisted biopsy and conventional 14 G core needle biopsy of axillary lymph nodes in women with breast cancer. *Clin Radiol* 2016;**71**:551–7.

Forbes JF, Sestak I, Howell A, Bonanni B, Bundred N, Levy C, *et al.* Anastrozole versus tamoxifen for the prevention of locoregional and contralateral breast cancer in postmenopausal women with locally excised ductal carcinoma in situ (IBIS-II DCIS): a double-blind, randomised controlled trial. *Lancet* 2016;**387**:866–73.

Al-Himdani S, Timbrell S, Tan KT, Morris J, Bundred NJ. Prediction of margin involvement and local recurrence after skin-sparing and simple mastectomy. *Eur J Surg Oncol* 2016;**42**:935–41. https://doi.org/10.1016/j.ejso.2016.04.055

Gellert P, Segal CV, Gao Q, López-Knowles E, Martin L, Dodson A, *et al.* Impact of mutational profiles on response of primary oestrogen receptor-positive breast cancers to oestrogen deprivation. *Nature Comm* 2016;**7**:13294.

2017

Pegington M, Adams JE, Bundred NJ, Campbell AM, Howell A, Howell SJ, *et al.* Recruitment to the 'Breast-Activity and Healthy Eating After Diagnosis' (B-AHEAD) randomized controlled trial. *Integr Cancer Ther* 2017;**17**:131–7.

Shaker H, Harrison H, Clarke R, Landberg G, Bundred NJ, Versteeg HH, Kirwan CC. Tissue factor promotes breast cancer stem cell activity in vitro. *Oncotarget* 2017;**8**:25915–27. https://doi.org/10.18632/oncotarget.13928

Loncaster J, Armstrong A, Howell S, Wilson G, Welch R, Chittalia A, *et al.* Impact of Oncotype DX breast Recurrence Score testing on adjuvant chemotherapy use in early breast cancer: real world experience in Greater Manchester, UK. *Eur J Surg Oncol* 2017;**43**:931–7.

Bundred NJ, Thomas J, Dixon JMJ. Whither surgical quality assurance of breast cancer surgery (surgical margins and local recurrence) after Paterson. *Breast Cancer Res Treat* 2017;**165**:473–5. https://doi.org/10.1007/s10549-017-4369-3

Published presentations to learned societies

Bundred NJ, Stewart HJ, Sturgeon C, Hawkins RA, Shaw D. In vitro production of CEA and breast cyst protein by breast carcinomas: relationship to receptor status: prognosis and response to hormonal therapy. *Eur J Surg Oncol* 1987;**13**:281.

Bundred NJ, Stewart HJ, Sturgeon C, Hawkins RA, Shaw D, Forrest APM, Miller WR. Apocrine differentiation: relationship to receptor status: prognosis and hormonal response in breast cancer. *Br J Surg* 1987;**74**:1144–5.

Bundred NJ, Walker RA, White GK, Stewart HJ, Miller WR. The prognosis of apocrine cancer. *Breast Cancer Res Treat* 1988;**12**:145.

Bundred NJ, West RR, O'Dowd J, Mansel RE. Is there an increased risk of breast cancer in women who have had a cyst aspirated? *Br J Surg* 1989;**76**:626.

Bundred NJ, Walker RA, White GK, Stewart HJ, Miller WR. Apocrine differentiation: a new prognostic factor for breast cancer. *Br J Surg* 1989;**76**:625.

Bundred NJ, West RR, Harvey P, Mansel RE. Why do women develop breast cysts? *Br J Surgery* 1989;**76**:1230.

Bundred NJ, Walker RA, Miller WR. Comparison of results of assessing apocrine differentiation in breast carcinoma. *Breast Cancer Res Treat* 1989;**14**:189.

Bundred NJ, Davis SJ, Scott WN, Miller WR, Mansel RE. Is zinc alpha-2 glycoprotein a marker for apocrine activity. *Breast Cancer Res Treat* 1989;**14**:159.

Bundred NJ, Woodhead S, Wheeler MH. Screening for MEN 1. *Eur J Surg Oncol* 1990;**16**:262–3. (Winner Alan Edwards Prize.)

Bundred NJ, Woodhead S, Wheeler MH. Screening for multiple endocrine neoplasia type. *Br J Surg* 1990;**77**:A1312.

Bundred NJ, Walker RA, Botha H, Everson N. The value of breast cancer screening amongst Asians living in Britain.*Br J Cancer* 1990;**62**(Suppl.):26.

Bundred NJ, Ratcliffe WA, Walker RA, Coley S, Morrison JM, Ratcliffe JG. Parathyroid hormone related protein and hypercalcaemia in breast cancer. *BMJ* 1991;**303**:1506–9.

Bundred NJ, Jones CE, Wellington M, Walker RA, Morrison JM, Baker PR. The importance of Laminin in the growth of human breast cancer. *Br J Cancer* 1991;**64**(S XV):9.

Bundred NJ, Wallace DMA, Chan KK, Fielding F. Salvage surgery for recurrent pelvic malignancy. *Br J Cancer* 1991;**64**(S XV):20.

Gateley CA, Bundred NJ, Turkes A, Mansel RE. Electrolyte in gross cystic disease fluid in breast cyst fluid. *Br J Cancer* 1991;**64**(S XV):4.

Walls J, Boggis CRM, Wilson M, Asbury DL, Bundred NJ, Mansel RE. Should the axilla be dissected in screen detected breast cancer? *Br J Surg* 1992;**79**:A1222.

Walls J, Boggis CRM, Wilson M, Asbury DL, Bundred NJ, Mansel RE. Treatment of the axilla in patients with screen-detected breast cancer. *Br J Surg* 1993;**80**:436–8.

Walls J, Ratcliffe WA, Hughes S, McIlwrath A, Howell A, Bundred NJ. A new approach to the diagnosis of hypercalcaemia in a screened population. *Eur J Surg Oncol* 1993;**19**:214.

Walls J, Hughes S, McIlwrath A, Ratcliffe WA, Howell A, Bundred NJ. Mechanisms of action of parathyroid hormone related protein (PTHrP) in hypercalcaemia. *Br J Surg* 1993;**80**:A648.

Walls J, Ratcliffe WA, Howell A, Bundred NJ. The interaction of parathyroid hormone related protein, hypercalcaemia and bisphosphonate therapy. *Br J Cancer* 1993; Supplement April.

Edwards RC, Bundred NJ, Ratcliffe WA, Walls J, Morrison M, Ratcliffe JG. Expression of parathyroid hormone related protein (PTHrP) in primary breast cancers. *J Endocr* 1993;**137**:30.

Mawer EB, Davies M, Gargan P, Walls J, Howell A, Ratcliffe WA, Bundred NJ. 1,25 Dihydroxyvitamin D (1,25 (OH)2D) and parathyroid hormone related protein (PTHrP) in plasma of patients with breast cancer. *J Endocr* 1993;**137**:38.

Walls J, Ratcliffe WA, Hughes S, Howell A, Bundred NJ. The role of parathyroid hormone related protein in the diagnosis of hypercalcaemia in a screened population. *Br J Surg* 1993;**80**:1207.

Walls J, Donne A, Knox F, Redford J, Swindell R, Howell A, Bundred NJ. The contribution of full axillary dissection to a prognostic index. *The Breast* 1993;**2**:205–6.

Walls J, Mawer EB, Davies M, Gargan P, Ratcliffe WA, Howell A, Bundred NJ. Interaction of Vitamin D and parathyroid hormone related protein in patients with breast cancer. *The Breast* 1993;**2**:203.

Bundred NJ, Walls J, Ratcliffe W, Edwards R, O'Donoghue D, Hopkins L, Morrison JM. Cytosol extraction of PTHrP in breast cancer and normal breast tissue. *The Breast* 1993;**2**:203.

Walls J, Boggis CRM, Wilson M, Asbury DL, Knox F, Mansel RE, Baildam AD, Bundred NJ. Can mammographic microcalcification predict resection margin involvement in screening breast biopsies. *Br J Surg* 1993;**80**:1483.

Baildam AD, Wilson M, Boggis CRM, Walls J, Bundred NJ, Asbury DL. Ultrasound guided biopsy of the breast: an alternative to needle localisation for screen detected impalpable lesions. *Breast Cancer Res Treat* 1993;**26**:187.

Walls J, Boggis CRM, Wilson M, Asbury DL, Knox, F, Coyne J, Baildam AD, Bundred NJ, Mansel. Can mammographic microcalcification predict resection margin involvement in screening breast biopsies? *Eur J Surg Oncol* 1993;**19**:491.

Walls J, Mawer EB, Davies M, Gargan P, Ratcliffe WA, Howell A, Bundred NJ. The interaction of Vitamin D and parathyroid hormone-related protein in patients with breast cancer. *Eur J Surg Oncol* 1993;**19**:495.

Knox F, Walls J, Donne A, Wallis NT, Redford J, Swindell R, Howell A, Bundred NJ. The prognostic value of axillary clearance. *J Pathol* 1993;**170**:S384A.

Walls J, Donne A, Knox F, Redford J, Swindell R, Howell A, Bundred NJ. Does axillary node status provide additional information? *Breast Cancer Res Treat* 1993;**27**:143.

Walls J, Mawer EB, Davies M, Gargan P, Ratcliffe WA, Howell A, Bundred NJ. The effect of parathyroid hormone-related protein on 1,25(OH)2 vitamin D in patients with breast cancer. *Breast Cancer Res Treat* 1993;**27**:168.

Walls J, Ratcliffe W, Edwards R, O'Donoghue D, Hopkins L, Morrison JM, Bundred NJ. Parathyroid hormone-related protein; cytosol extraction in breast cancer, and normal breast tissue. *Breast Cancer Res Treat* 1993;**27**:168.

Baildam AD, Higgins RM, Hurley E, Furlong A, Walls J, Venning MC, *et al.* Cyclosporin A-induced fibroadenomas: a potential model for tumour genesis. *Breast Cancer Res Treat* 1993;**27**:185.

Baildam AD, Wilson M, Boggis CRM, Walls J, Bundred NJ, Asbury D, Mansel RE. Ultrasound-guided biopsy of the breast: an alternative to needle-localisation for screen detected impalpable lesions. *Breast Cancer Res Treat* 1993;**27**:187.

Walls J, Mawer EB, Davies M, Howell A, Ratcliffe WA, Bundred NJ. The interaction of vitamin D and parathyroid hormone related protein in patients with breast cancer. *Br J Surg* 1993;**80**:A1467.

Walls J, Donne A, Knox F, Redford J, Swindell R, Howell A, Bundred NJ. Does axillary node status provide additional prognostic information? *Br J Surg* 1993;**80**:1468.

Bowcott M, Ratcliffe WA, Hill-Wilson G, Bundred NJ. Parathyroid hormone-related protein is a growth factor for prostate cancer. *Br J Surg* 1994;**81**:767.

Walls J, Assiri AMA, Eastell R, Howell A, Ratcliffe WA, Bundred NJ. Urinary pyridinolines identify bone resorption in humoral hypercalcaemia. *Br J Surg* 1994;**81**:767.

Walls J, Assiri AMA, Ratcliffe WA, Howell A, Eastell R, Bundred NJ. Urinary cross links: mechanisms of hypercalcaemia in women with breast cancer. *Br J Surg* 1994;**81**:755.

Anderson P, Hoyland J, Knox F, Bowcott M, Freemont AJ, Bundred NJ. A role for Interleukin 6 and IL6 receptor in breast cancer. *Eur J Cancer* 1994;**30A**(Suppl. 2):25.

Umaar R, Thomas C, Tetlow L, Harding C, Greenhalgh R, Howell A, Bundred NJ. Does the protein composition of breast secretions alter in malignant breast disease? *Eur J Cancer* 1994;**30A**(Suppl. 2):52.

Gateley C, Holland P, El-Teraifi, Baildam AD, Bundred NJ. Prediction of axillary lymph node metastases by cytology in patients with breast cancer. *Eur J Cancer* 1994;**30A**(Suppl. 2):73.

Holland PA, Walls J, Wilson M, Boggis C, Asbury DL, Knox F, *et al.* Incidence screen detected breast cancers require axillary node clearance. *Eur J Cancer* 1994;**30A**(Suppl. 2):30.

Holland PA, Walls J, Wilson M, Boggis C, Asbury DL, Knox WF, *et al.* Incidence screen detected breast cancers require axillary node clearance. *Breast Cancer Res Treat* 1994;**32**(Suppl.):40.

Holland PA, Knox F, Howell A, Baildam AD, Bundred NJ. Factors affecting relapse of ductal carcinoma in situ after surgical excision. *Breast Cancer Res Treat* 1994;**32**(Suppl.):44.

Bundred NJ, Anderson P, Hoyland J, Knox F, Bowcott M, Freemont AJ. A role for interleukin 6 and its receptor in breast cancer. *Breast Cancer Res Treat* 1994;**32**(Suppl.):56.

Bundred NJ, Walls J, Assiri AMA, Ratcliffe WA, Howell A. Eastell R. Urinary cross-links: mechanisms of hypercalcaemia in women with breast cancer. *Breast Cancer Res Treat* 1994;**32**(Suppl.):59.

Bundred NJ, Bhatia RK, Bowcott M, Knox F, Walls J. Thrombospondin expression on human breast cancers. *Breast Cancer Res Treat* 1994;**32**(Suppl.):60.

Holland PA, Knox WF, Potten CS, Howell A, Baildam AD, Bundred NJ. An in vivo model for human ductal carcinoma in situ of the breast. *Br J Surg* 1995;**82**:698.

Downey SE, Bowcott M, Ratcliffe WA, Fraser WD, Bundred NJ. Vitamin D inhibits prostate cancer growth by down-regulating production of PTHrP. *Br J Surg* 1995;**82**:704.

Harding C, Knox W, Baildam AD, Bundred NJ. Tumours developing on HRT have a better grade. *Eur J Surg Oncol* 1995;**21**:111.

Holland PA, Shah A, Howell A, Baildam AD, Bundred NJ. Lobular carcinoma of the breast can be managed with conserving therapy. *Eur J Surg Oncol* 1995;**21**:118.

Howell A, Knox E, Swindell R, Bundred N, Galea M, Blamey RW, *et al.* Comparability of prognostic indices. *The Breast* 1995;**4**:237.

Harding C, Rogers E, Margison J, Faragher B, Howell A, Bundred NJ. Is increased target organ sensitivity of the breast responsible for breast cancer development? *The Breast* 1995;**4**:241.

Downey SE, Hoyland JA, Walls J, Ratcliffe WA, Edwards R, Freemont AJ, Bundred NJ. Parathyroid hormone receptor protein and its receptor expression in primary breast carcinomas – prognostic significance. *The Breast* 1995;**4**:242.

Holland PA, Knox WF, Baildam AD, Howell A, Bundred NJ. Nuclear grade of DCIS does not predict for early local relapse. *The Breast* 1995;**4**:244.

Holland PA, Knox WF, Potten CS, Anderson E, Howell A, Baildam AD, Bundred NJ. Comedo DCIS is hormone independent and will not benefit from antioestrogen therapy. *The Breast* 1995;**4**:245.

Harding C, Margison J, Howell A, Bundred NJ. Is increased target organ sensitivity to oestrogen responsible for breast cancer development? *Breast Cancer Res Treat* 1996;**37**(Suppl.):109.

Downey SE, Hoyland JA, Walls J, Freemont AJ, Bundred NJ. Primary breast cancers express the receptor for parathyroid hormone related protein. Breast Cancer Research and Treatment. *Breast Cancer Res Treat* 1996;**37**(Suppl.):109.

Harding C, Knox WF, Baildam AD, Bundred NJ. Does the use of hormone replacement therapy influence breast cancer prognosis? *Breast Cancer Res Treat* 1996;**37**(Suppl.):98.

Harding C, Osudenko S, Tetlow L, Faragher B, Howell A, Bundred NJ. Apolipoprotein D, a new anitoestrogen marker in the breast. *Br J Surg* 1996;**83**(Suppl. 1):11.

Harding C, Harvey J, Kirkman R, Bundred NJ. Hormone replacement therapy-induced mastalgia responds to evening primrose oil. *Br J Surg* 1996;**83**(Suppl. 1):24.

Gandhi A, Coyne J, Baildam AD, Bundred NJ. The treatment of mammary fistulas. *Br J Surg* 1996;**83**(Suppl. 1):25.

Harding C, Osudenko O, Tetlow L, Howell A, Bundred NJ. Non invasive measurement of antioestrogen activity in the breast. *Eur J Cancer* 1996;**32A**(Suppl. 2):13.

Dey P, Bundred N, Baildam A, Asbury D, Hopwood P, Readman L, *et al.* Randomised controlled trial comparing the effectiveness of rapid diagnosis and routine out-patient clinics. *Eur J Cancer* 1996;**32A**(Suppl. 2):31.

Bundred NJ, Naylor K, Walls J, Evans G, Eastell R, Howell A. Does tamoxifen (tam) increase bone resorption in premenopausal women? *Eur J Cancer* 1996;**32A**(Suppl. 2):35.

Bundred NJ, Naylor K, Walls J, Evans G, Eastell R, Howell A. Does tamoxifen increase bone resorption in premenopausal women? *Eur J Surg Oncol* 1996;**22**:553.

Gandhi A, Holland PA, Knox WF, Potten CS, Bundred NJ. Epithelial proliferation and expression of apoptotic genes in human breast ductal carcinoma in situ. *Eur J Surg Oncol* 1997;**23**:92.

Michael Phillips D, Harding C, Morton M, Howell A, Potten C, Bundred NJ. The effects of soy supplementation on epithelial proliferation in the normal human breast. *Eur J Surg Oncol* 1997;**23**:97.

Downey SE, Hoyland JA, Iddon J, Freemont AJ, Bundred NJ. Expression of Interleukin-6 and its receptor in primary and secondary breast tumours. *Eur J Surg Oncol* 1997;**23**:99.

McMichael-Phillips D, Harding C, Morton M, Howell A, Potten C, Bundred NJ. The effects of soy supplementation on epithelial proliferation in the normal human breast. *Br Cancer Res Treat* 1996;**41**:263.

Dey P, Hopwood P, Bundred NJ, Baildam A, Asbury D, Woodman CBJ. *Randomised Controlled Trial of the Effectiveness of Rapid Diagnosis Clinics – Preliminary Results of Psychological Morbidity*. Proceedings of the 7th International Symposium on Benign Breast Disease, London, May 1997.

Gandhi A, Baildam AD, Bundred NJ. *Total Duct Excision is the Treatment of Choice for Periareolar Sepsis and Nipple Discharge.* Proceedings of the 7th International Symposium on Benign Breast Disease, London, May 1997.

Gandhi A, Holland PA, Knox WF, Baildam AD, Potten CS, Bundred NJ. Antioestrogen therapy does not affect apoptosis or mitosis in comedo ductal carcinoma in situ (DCIS). *The Breast* 1997;**6**:229.

Gandhi A, Holland PA, Knox WF, Baildam AD, Bundred NJ. Breast conserving surgery is appropriate for localised ductal carcinoma in situ. *The Breast* 1997;**6**:230.

Iddon J, Abdullah K, Knox WF, Baildam AD, Barr L, Bundred NJ. Can mastectomy prevent breast cancer? *The Breast* 1997;**6**:230.

Hargreaves DF, Sarwar S, Knox F, Potten CS, Bundred NJ. Epithelial proliferation and hormone receptor status in the normal postmenopausal breast and the effects of HRT use. *The Breast* 1997;**6**:238.

Shrestha S, Knox WF, Boggis CRM, Howell A, Bundred NJ. Factors influencing local recurrence following breast conservation therapy. *The Breast* 1997;**6**:240.

Abdullah TI, Iddon J, Walls J, Baildam AD, Bundred NJ. A randomised prospective study of preservation of the intercostobrachial nerve in axillary node clearance. *The Breast* 1997;**6**:247.

Downey SE, Hoyland JA, Freemont AJ, Bundred NJ. Differential expression of growth factors in metastases to different sites. *The Breast* 1997;**6**:247.

Bundred NJ, Reynolds J, Allen D, Rees J, Grimshaw J, Barr L, Baildam AD, Maguire P. A randomised controlled trial of early versus standard discharge after breast cancer surgery. *The Breast* 1997;**6**:249.

Iddon J, Downey SE, Freemont A, Hoyland J, Bundred NJ. Expression of parathyroid hormone related protein in prostate cancer. *Br J Surg* 1997;**84**:1594.

Iddon J, Downey SE, Freemont A, Hoyland J, Bundred NJ. The expression of parathyroid hormone related protein in prostate cancer. *Eur J Surg Oncol* 1997;**23**:376.

Abdullah TI, Iddon J, Walls J, Baildam AD, Bundred NJ. A randomised prospective study of preservation of the intercostobrachial nerve in axillary node clearance. *Eur J Surg Oncol* 1997;**23**:379.

Gandhi A, Holland PA, Knox WF, Baildam AD, Bundred NJ. Breast conserving surgery (BCS) is appropriate for localised ductal carcinoma in situ (DCIS). *Breast Cancer Res Treat* 1997;**46**:35.

Bronder CS, Byrne GJ, Swindell R, Ashcroft L, Howell A, Bundred NJ. Factors predicting survival after mastectomy and flap recurrence. *Breast Cancer Res Treat* 1997;**46**:106.

Pontefract DR, Harding C, Skrimshire K, Tetlow L, Bundred NJ. Why do women develop breast cysts? *Breast* 1997;**6**:396.

Gandhi A, Baildam AD, Bundred NJ. Total duct excision is the treatment of choice for peri-areolar sepsis and nipple discharge. *Breast* 1997;**6**:397.

Iddon J, Harding C, Baildam AD, Barr L, Bundred NJ. The effect of hormone replacement therapy (HRT) on screen detected breast cancers. *Eur Jr Surg Oncol* 1998;**24-4**:350.

Byrne GJ, Hayden KE, Tetlow L, Aggarwal R, Sinha G, Howell AH, Bundred NJ. Plasma thrombospondin (pTSP) in early and advanced breast cancer. *Eur Jr Surg Oncol* 1998;**24-4**:355.

Byrne GJ, Agarwal R, Sinha G, Bundred NJ. Circulating VEGF in pre- and post-menopausal women and women with early breast cancer. *Eur Jr Surg Oncol* 1998;**24-4**:356.

Bundred NJ, Reynolds J, Allen D, Rees J, Grimshaw J, Barr L, Baildam AD, Maguire P. A randomised controlled trial of early versus standard discharge after breast cancer surgery. *Eur J Surg Oncol* 1998;**24-4**.

Byrne GJ, Hayden KE, Tetlow L, Aggarwal R, Sinha G, Howell A, Bundred NJ. Plasma thrombospondin in early and advanced breast cancer. *BJS* 1998;**85**:1570.

Iddon J, Harding C, Boggis C, Baildam AD, Barr L, Bundred NJ. Effect of hormone replacement therapy on screen-detected breast cancers. *BJS* 1998;**85**:1570.

Bramley MD, Harake J, Boggis CRM, Howell A, Bundred NJ. Neoadjuvant chemotherapy for primary breast cancer – how many breasts are saved? *Eur J Cancer* 1998;**34**:S53.

Anderson E, Cramer A, Taylor P, Clarke RB, Baildam AD, Bundred NJ, Howell A. Prognostic value of proliferation steroid receptor and epidermal growth factor receptor content determined immunohistochemically in a large series of primary breast tumours. *Breast Cancer Res Treat* 1998;**50**:276.

Iddon J, Harding C, Boggis C, Baildam AC, Barr L, Bundred NJ. Breast cancers developing in women taking HRT are of a lower grade. *Breast Cancer Res Treat* 1998;**50**:300.

Shaw LE, Hargreaves DF, Knox F, Bundred NJ, Potten CS. The effects of androgen therapy on normal premenopausal female breast. *Breast Cancer Res Treat* 1998;**50**:312.

Chan KC, Knox WF, Woodburn JR, Potten CS, Bundred NJ. An Epidermal growth factor receptor (EGFR) Tyrosine kinase inhibitor (ZD1839) inhibits proliferation in normal and preinvasive epithelia. *Breast Cancer Res Treat* 1999;**57**:27.

Dowsett M, Lu Y, Hills M, Bundred NJ, Costa A, Decensi A, Sainsbury R, O'Brien M, Scott T, Muchmore DB. Effect of Raloxifene on Ki67 and apoptosis. *Breast Cancer Res Treat* 1999;**57**:31.

Robertson JFR, Dixon M, Bundred N, Anderson E, Dowsett M, Nicholson R, Ellis I. A partially-blind randomised multicentre study comparing the anti-tumour effects of single doses (50, 125 and 250 mg) of long-acting (LA) Faslodex (ICI 182,780) with tamoxifen in postmenopausal women with primary breast cancer prior to surgery. *Breast Cancer Res Treat* 1999;**57**:31.

Seward J, Byrne GJ, Howell A, Bundred NJ, McCollum CN. Does Cytotoxic chemotherapy precipitate venous thromboembolism in patients with cancer? *Breast Cancer Res Treat* 1999;**57**:57.

Byrne GJ, Stringfellow J, Hawnaur JM, Chan KC. Boggis CRM, Bundred NJ. Breast magnetic resonance imaging (MRI): a useful investigation in patients with primary breast cancer? *Breast Cancer Res Treat* 1999;**57**:58.

Chan KC, Knox WF, Sinha G, Barr L, Baildam AD, Bundred NJ. Extent of excision margin required in breast conserving surgery (BCS) for ductal carcinoma in situ (DCIS). *Breast Cancer Res Treat* 1999;**57**:70.

Byrne GJ, Hayden KE, Tetlow L, Aggarwal R, Howell AH, Bundred NJ. Plasma thrombospondin (PTSP) in early and advanced breast cancer: a marker for metastasis. *Breast Cancer Res Treat* 1999;**57**:121.

Hadjiloucas I, Anderson NG, Salem RJ, Garrod DR, Bundred NJ. The expression of desmosomal proteins in invasive breast cancer. *Eur J Surg Oncol* 1999;**25**:658.

Chan KC, Knox WF, Sinha G, Gandhi A and Bundred NJ. Extent of excision margin required for ductal carcinoma in situ (DCIS) breast conservation surgery. *Br J Surg* 1999;**86**:86.

Iddon J, Byrne G, Baird P, Hoyland J, Freemont AJ, Howell A, Bundred NJ. Macrophage colony stimulating factor and its role in metastatic breast cancer. *Br J Surg* 1999;**86**:35.

Chan KC, Knox WF, Sinha G, Gandhi A, Bundred NJ. What is the optimal excision margin distance for ductal carcinoma in situ (DCIS) breast conservation surgery. *Breast* 1999;**8**:217.

Iddon J, Byrne G, Baird P, Hoyland J, Freemont AJ, Howell A, Bundred NJ. Macrophage colony-stimulating factor (MCSF) and its role in metastatic breast cancer. *Breast* 1999;**8**:222.

Bundred NJ, Reynolds J, Allen D, Rees J, Grimshaw J, Barr L, Baildam AD, Maguire P. A randomised controlled trial of early versus standard discharge after breast cancer surgery. *Breast* 1999;**8**:232.

Hargreaves DF, Roberts SA, Howell A, Morton M, Potten CS, Bundred NJ. Effect of phyto-oestrogens on epithelial proliferation in the breast. *Breast* 1999;**8**:236.

Chan KC, Knox WF, Woodburn JR, Slamon D, Potten CS, Bundred NJ. Epidermal growth factor receptor inhibition decreases epithelial proliferation in ductal carcinoma in situ of the breast, whereas c-erbB2 blocking does not. *Br J Surg* 2000;**87**:628.

Chan KC, Knox WF, Woodburn JR, Potten CS, Bundred NJ. Proliferation in normal breast epithelium is decreased by epidermal growth factor receptor inhibition. *Br J Surg* 2000;**87**:679.

Anderson NG, Hoey RP, Linforth RA, Bundred NJ. Characterization of the mitogenic actions of parathyroid hormone-related protein in MCF-7 breast carcinoma cells. *Br J Surg* 2000;**87**:26.

Linforth RA, Morris J, Bundred NJ. Cigarette smoking is an aetiological factor in hidradenitis suppurativa. *Br J Surg* 2000;**87**:34.

Dobson RRH, Chan CK, Knox F, Potten CS, Bundred NJ. The effects of prolonged HRT treatment in normal postmenopausal breast epithelium. *Breast Cancer Res Treat* 2000;**64**:106.

Hurley E, Reaney S, Bundred N. Randomized controlled trial comparing 14g core biopsy with minimally invasive breast biopsy (MIBB) in pre-operative diagnosis of mammographically detected breast lesions. *The Breast* 2001;**10**:361.

Down S, Barr L, Baildam A, Bundred N. Axillary accessory breast tissue: incidence, surgical excision and operative complications. *The Breast* 2001;**10**:362.

Dey P, Arnold D, Ellen E, Hindmarsh P, Bundred N. Survey of the management of thyroid cancer in the north west. *Br J Surg* 2001;**88**:66.

Boland GP, Chan KC, Knox WF, Bundred NJ. Comparison of margin status with the Van Nuys Prognostic Index to predict recurrence of Ductal carcinoma in situ (DCIS) after breast conserving surgery. *Br J Surg* 2001;**88**(Suppl. 1):41.

Boland GP, McKeown A, Chan KC, Knox WK, Potten CS, Bundred NJ. Oestrogen withdrawal reduces cell proliferation in Oestrogen receptor positive but not in Oestrogen receptor negative DCIS. *Eur J Cancer* 2001;**37**(Suppl. 5):29.

Boland GP, Chan KC, Knox WF, Bundred NJ. Comparison of margin status with the Van Nuys Prognostic Index to predict recurrence of Ductal carcinoma in situ (DCIS) after breast conserving surgery. *Eur J Cancer* 2001;**37**(Suppl.):15.

Boland GP, Brown I, Can KC, Baildam AD, Barr L, Bundred NJ. Reliability of stereotactic core biopsy diagnosed ductal carcinoma in situ (DCIS) for screen detected disease. *Eur J Cancer* 2001;**37**(Suppl.):13–14.

Bundred NJ. Hormone replacement therapy, breast cancer, and the future. *J Br Menopause Soc* 2001;**7**(Suppl. 2):13–15.

Bundred NJ, Chan K, Anderson NG. Studies of epidermal growth factor receptor inhibition in breast cancer. *Endocr Relat Cancer* 2001;**8**:183–9.

Boland GP, IS Butt, WF Knox & NJ Bundred. Cox-2 Expression in Breast Neoplasia. *Eur J Surg Oncol* 2001;**27**:775.

Baildam A, Keeling F, Noblet M, Thomson L, Bundred N, Hopwood P. Nurse led follow-up for women treated for breast cancer: a randomised controlled trial. *EJSO* 2001;**27**:792.

Prasad R, Boland GP, Cramer A, Anderson E, Bundred NJ. Stopping of hormone replacement therapy (HRT) leads to decreased epithelial proliferation in estrogen receptor positive breast cancer. *EJSO* 2001;**27**:797.

Boland GP, McKeown A, Chan KC, Knox WF, Potten CS, Bundred NJ. *Oestrogen Withdrawal Reduces Cell Proliferation in Oestrogen Receptor (ER) Positive Ductal Carcinoma In Situ (DCIS*). 24th Annual San Antonio Breast Cancer Symposium poster presentation, 2001.

Elangovan AE, Wilson M, Knox FW, Barr L, Bundred NJ. *Predicting Sentinel Node Involvement: Manchester Experience.* 24th Annual San Antonio Breast Cancer Symposium poster presentation, 2001.

Boland GP, Holland PA, Knox WF, Epstein M, Slamon DJ. Potten CS, Bundred NJ. *Receptor Expression in Ductal Carcinoma In Situ (DCIS).* 24th San Antonio Breast Cancer Symposium poster presentation, 2001.

Boland GP, Brown I, Prasad R, Knox WF, Wilson M, Bundred NJ. Preoperative factors do not predict which patients require reoperation for ductal carcinoma in situ (DCIS). *Br J Surg* 2002;**89**:9.

Boland GP, Brown I, Prasad R, Knox WF, Wilson M, Bundred NJ. Impact of preoperative core biopsy on reoperation rates for screen-detected ductal carcinoma in situ (DCIS). *Br J Surg* 2002;**89**:9.

Moran T, Gibbs A, Woodman C, Bundred NJ. Do older women get poorer treatment after breast conserving surgery? *BJS* 2002;**89**:75.

Prasad R, Boland GP, Cramer A, Anderson E, Bundred NJ. Expression of cerbB-2 does not prevent the withdrawal response to hormone replacement therapy (HRT) in breast cancers. *BJS* 2002;**89**:74.

Boland G, Davenport A, Barnes N, Knox WF, Bundred NJ. Prospective study of hormone receptor status is ductal carcinoma in situ (DCIS). Implications for therapy. *Br J Surg* 2003;S1.

Prasad R, Byrne G, Wilson M, Barr L, Baildam A, Morris J, Bundred NJ. Which women with screen detected breast cancers (SDBC) require chemotherapy? (new index predicting recurrence and mortality). *Br J Surg* 2003;(90):S1.

Prasad R, Byrne G, Wilson M, Barr L, Baildam AD, Morris J, Bundred NJ. Comparison of 5 year survival of screen detected breast cancers (SDBC) with symptomatic ones of same age (50–60 years) in one unit. *Br J Surg* 2003;(90):S1.

Warnberg F, White D, Anderson E, Peristerakis I, Knox F, Clarke RB, Bundred NJ. Effect of a RAS farnesyl transferase inhibitor on DCIS and HER-2 positive tumours *in vivo*. *Br J Surg* 2003;(90):S1.

Absar M, Prasad R, Wicks P, Burke M, Byrne G, Bundred NJ. Does radiotherapy (DXT) affect survival after breast conserving surgery in elderly patients? *Br J Surg* 2003;**90**(Suppl. 1):27.

Warnberg F, White D, Anderson E, Peristerakis I, Kox F, Clarke RB, Bundred NJ. Effect of a ras farnesyl transferase inhibitor on DCIS and HER-2 positive tumours in vivo. *Br J Surg* 2003;**90**(Suppl. 1):29.

Prasad R, Byrne G, Wilson M, Barr L, Baildam A, Morris J, Bundred NJ. Which women with screen detected breast cancers (SDBC) require chemotherapy? (New index predicting recurrence and mortality.) *Br J Surg* 2003;**90**(Suppl. 1):99.

Prasad R, Byrne G, Wilson M, Barr L, Baildam AD, Morris J, Bundred NJ. Comparison of 5 year survival of screen detected breast cancers (SDBC) with symptomatic ones of same age (50-66 years) in one unit. *Br J Surg* 2003;**90**(Suppl. 1):101

Byrne GJ, Kirwan C, Kumar S, Bundred NJ. High levels of serum VEGF and VCAM-1 predict recurrence in women with early breast cancer. *Br J Surg* 2003;**90**(Suppl. 1):107.

Barnes NLP, Boland G, Davenport A, Knox WF, Bundred NJ. A prospective study of oestrogen and progesterone receptor status in ductal carcinoma in situ. *Breast Cancer Res Treat* 2003;**82**:Abstract No. 150.

Burke MM, Pravica V, Hutchinson IV, Bundred NJ. Association between EGFR ligand gene polymorphisms and the risk and severity of breast cancer. *Breast Cancer Res Treat* 2003;**82**:Abstract No. 269.

Warnberg F, White D, Anderson E, Knox F, Clarke RB, Bundred NJ. Effect of a farnesyl transferase inhibitor on HER2 positive tumours and ductal carcinoma in situ of the breast. *Breast Cancer Res Treat* 2003;**82**:Abstract No. 347.

Prasad R, Wilson M, Morris J, Byrne G, Bundred NJ. Current HRT (hormone replacement therapy) use at diagnosis of breast cancer does not adversely affect survival from symptomatic or screen detected breast cancers in postmenopausal women. *Breast Cancer Res Treat* 2003;**82**:Abstract No. 542.

Barnes NLP, Warnberg F, White D, Anderson E, Bundred NJ. Cyclooxygenase-2 inhibition and tumour growth:celecoxib increases apoptosis in HER2 positive cell lines. *Breast Cancer Res Treat* 2003;**82**:Abstract No. 667.

Moore HA, Anderson E, Clarke RB, Warnberg F, Barnes NL, Wakeling AE, Bundred NJ. The effects of fulvestrant and gefitinib on proliferation, progesterone-receptor and pS2 expression in normal human breast epithelium in vivo. *Breast Cancer Res Treat* 2003;**82**:Abstract No. 672.

Barnes N, Boland G, Davenport A, Knox WF, Bundred NJ. Hormone Receptor status in ductal carcinoma in situ (DCIS): implications for therapy. *EJC* 2003;**1**:14 abstract No. O-43.

Barnes N, Warnberg F, White D, Anderson E, Bundred NJ. The effect of cyclooxygenase-2 (COX-2) inhibition on tumour growth in a xenograft model. *EJC* 2003;**1**:14 abstract No. O-141.

Barnes NLP, Warnberg F, White D, Anderson E, Bundred NJ. Cyclooxygenase-2 inhibition: effects on tumour growth and apoptosis in HER2 positive cell lines. *EJSO* 2003;**29**:791 abstract No. 29.

Barnes NLP, Boland GP, Khavari S, Cramer A, Knox WF, Bundred NJ. Type 1 Tyrosine kinase receptor co-expression is a predictor of recurrence in ductal carcinoma in situ of the breast. *BJS* 2004;**91**:1214.

Barnes NLP, Boland GP, Cramer A, Knox WF, Bundred NJ. Recurrence of ductal carcinoma in situ: the role of COX-2 expression. *BJS* 2004;**91**(S1):37 abstract No. 02.

Boland GP, Prasad R, Barnes N, Knox WF, Bundred NJ. HRT use leads to development of oestrogen receptor positive DCIS. *BJS* 2004;**91**(S1):135 abstract No. 27.

Barnes NLP, Warnberg F, White D, Anderson E, Bundred NJ. Celecoxib treatment leads to decreased cyclooxygenase-2 (COX-2) expression in a xenograft model of breast cancer. *BJC* 2004;**91**(S1):S9 abstract No. 1.8.

Prasad R, Morris J, Wilson M, Knox F, Byrne G, Bundred NJ. The lower proliferation rate of screen detected breast cancers underlies their better survival. *BJS* 2005;**92**:1032–327.

Barnes NLP, Haywood PB, Flint PJ, Knox WF, Bundred NJ. Survivin is related to COX-2 expression and recurrence in DCIS. *BJS* 2005;**92**:31.

Farnie G, Clarke RB, Bundred NJ. The influence of tumour grade on DCIS stem cell growth. Nottingham Meeting September 2005. *Eur J Cancer* 2005;**3**:37.

Prasad R, Knox WF, Morris J, Wilson M, Bundred NJ. Comparison of local recurrence between screen detected and symptomatic breast cancer. Nottingham Meeting. *Eur J Cancer* 2005;**3**(S1):14.

Barnes NLP, Flint P, Clarke R, Bundred NJ. Cox-2 inhibition increases apoptosis in human ductal carcinoma in situ of the breast (DCIS) in a xenograft model. Nottingham Meeting. *Eur J Cancer* 2005;**3**(S1):16.

Wilson G, Barnes NLP, Knox F, Swindell R, Kawakatsu H, Dive C, Bundred NJ. Activated c-src in dcis correlates with high grade and HER2 expression. Nottingham Meeting. *Eur J Cancer* 2005;**3**(S1):17.

Wilson G, Remoush F, Barnes NLP, Knox F, Swindell R, Bundred NJ. Factors predicting recurrence in DCIS after breast conserving surgery with clear margins. Nottingham Meeting. *Eur J Cancer* 2005;**3**(S1):17.

Farnie G, Brennan K, Clarke RB, Bundred NJ. *Ductal Carcinoma in Situ (DCIS) mammosphere formation; Effect of EGF and NOTCH signalling pathways on self renewal capacity*. San Antonio Breast Cancer Conference, 2005.

Pegington M, Adams JE, Bundred NJ, Campbell AM, Howell A, Howell SJ, *et al.* Recruitment to the 'Breast-Activity and Healthy Eating After Diagnosis' (B-AHEAD) randomized controlled trial. *Integr Cancer Ther* 2018;**17**:131–7. https://doi.org/10.1177/1534735416687850

Professor Chris Todd

Author/co-author of more than 240 peer-reviewed papers (45% first/last author). Lifetime citation Google 17,795, h-index = 71; WoS = 9477, h-index = 52. Scopus 10,900, h-index = 55.

To 2000

Hollingworth W, Todd CJ, Bell MI, Arafat Q, Girling S, Karia KR, Dixon AK. The diagnostic and therapeutic impact of MRI: an observational multi-centre study. *Clin Radiol* 2000;**55**:825–31. https://doi.org/10.1053/crad.2000.0546

Hobby JL, Tom BD, Todd C, Bearcroft PW, Dixon AK. Communication of doubt and certainty in radiological reports. *Br J Radiol* 2000;**73**:999–1001. https://doi.org/10.1259/bjr.73.873.11064655

Grande GE, Todd CJ, Barclay SI, Farquhar MC. A randomized controlled trial of a hospital at home service for the terminally ill. *Palliat Med* 2000;**14**:375–85. https://doi.org/10.1191/026921600701536200

Sharples LD, Todd CJ, Caine N, Tait S. Measurement properties of the Nottingham Health Profile and the Short Form 36 health status measures in a population sample of elderly people living at home: results from ELPHS. *Br J Health Psychol* 2000;**5**:217–34.

Rogers MS, Todd CJ. The 'right kind' of pain: talking about symptoms in outpatient oncology consultations. *Palliat Med* 2000;**14**:299–307. https://doi.org/10.1191/026921600669288537

Farquhar M, Camilleri-Ferrante C, Todd C. Continuity of care in maternity services: women's views of one team midwifery scheme. *Midwifery* 2000;**16**:35–47.

Farquhar M, Camilleri-Ferrante C, Todd C. General practitioners' views of working with team midwifery. *Br J Gen Pract* 2000;**50**:211–13.

Grande GE, Todd CJ. Why are trials in palliative care so difficult? *Palliat Med* 2000;**14**:69–74. https://doi.org/10.1191/026921600677940614

Ismail AA, O'Neill TW, Cooper C, Silman AJ. Risk factors for vertebral deformities in men: relationship to number of vertebral deformities. European Vertebral Osteoporosis Study Group. *J Bone Miner Res* 2000;**15**:278–83. https://doi.org/10.1359/jbmr.2000.15.2.278

Ismail AA, O'Neill TW, Cockerill W, Finn JD, Cannata JB, Hoszowski K, *et al.* Validity of self-report of fractures: results from a prospective study in men and women across Europe. EPOS Study Group. European Prospective Osteoporosis Study Group. *Osteoporos Int* 2000;**11**:248–54.

Cockerill W *et al* (including Todd) on behalf of the EPOS group. Does location of vertebral deformity within the spine influence back pain and disability? *Ann Rheumatic Dis* 2000;**59**:368–71.

Grande GE, Todd CJ, Barclay SI, Farquhar MC. Does hospital at home for palliative care facilitate death at home? Randomised controlled trial. *BMJ* 1999;**319**:1472–5.

Lips P, Cooper C, Agnusdei D, Caulin F, Egger P, Johnell O, *et al.* Quality of life in patients with vertebral fractures: validation of the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO). Working Party for Quality of Life of the European Foundation for Osteoporosis. *Osteoporos Int* 1999;**10**:150–60.

Bradley C, Todd C, Gorton T, Symonds E, Martin A, Plowright R. The development of an individualized questionnaire measure of perceived impact of diabetes on quality of life: the ADDQoL. *Qual Life Res* 1999;**8**:79–91.

O'Neill TW, McCloskey EV, Kanis JA, Bhalla AK, Reeve J, Reid DM, *et al.* The distribution, determinants, and clinical correlates of vertebral osteophytosis: a population based survey. *J Rheumatol* 1999;**26**:842–8.

Barclay S, Todd C, McCabe J, Hunt T. Primary care group commissioning of services: the differing priorities of general practitioners and district nurses for palliative care services. *Br J Gen Pract* 1999;**49**:181–6.

Ismail AA, O'Neill TW, Cooper C, Finn JD, Bhalla AK, Cannata JB, *et al.* Mortality associated with vertebral deformity in men and women: results from the European Prospective Osteoporosis Study (EPOS). *Osteoporos Int* 1998;**8**:291–7.

Hollingworth W, Dixon AK, Todd CJ, Bell MI, Antoun NM, Arafat Q, *et al.* Self reported health status and magnetic resonance imaging findings in patients with low back pain. *Eur Spine J* 1998;**7**:369–75.

Todd CJ, Farquhar MC, Camilleri-Ferrante C. Team midwifery: the views and job satisfaction of midwives. *Midwifery* 1998;**14**:214–24.

Hollingworth W, Bell MI, Dixon AK, Antoun NM, Moffat DA, Todd CJ. Measuring the effects of medical imaging in patients with possible cerebellopontine angle lesions: a four centre study. *Acad Radiol* 1998;**5**:S306–9.

Grande GE, Addington-Hall JM, Todd CJ. Place of death and access to home care services: are certain patient groups at a disadvantage? *Soc Sci Med* 1998;**47**:565–79.

Parker M, Todd C, Palmer C, Camilleri-Ferrante C, Freeman C, Laxton C, Payne B, Rushton N. Inter-hospital variations in length of hospital stay following hip fracture. *Age Ageing* 1998;**27**:333–7.

Rogers MS, Barclay SI, Todd CJ. Developing the Cambridge palliative audit schedule (CAMPAS): a palliative care audit for primary health care teams. *Br J Gen Pract* 1998;**48**:1224–7.

Farquhar M, Camilleri-Ferrante C, Todd C. Working with team midwifery: health visitors' views of one team midwifery scheme. *J Adv Nurs* 1998;**27**:546–52.

Still A, Todd C. When technical rationality fails: thinking about terminally ill patients. *J Health Psychol* 1998;**3**:137–48. https://doi.org/10.1177/135910539800300111

Ismail AA, Cooper C, Felsenberg D, Varlow J, Kanis JA, Silman AJ, O'Neill TW. Number and type of vertebral deformities: epidemiological characteristics and relation to back pain and height loss. European Vertebral Osteoporosis Study Group. *Osteoporos Int* 1999;**9**:206–13.

Matthis C and the EVOS group. (Including Todd) Health impact of vertebral deformities: Results from the European Vertebral Osteoporosis Study. *Osteoporosis Int* 1998;**8**:364–72.

Barclay S, Todd C, Grande G, Lipscombe J. How common is medical training in palliative care? A postal survey of general practitioners. *Br J Gen Pract* 1997;**47**:800–4.

Laxton C, Freeman C, Todd C, Payne B, Camilleri-Ferrante C, Palmer C, Parker M, Rushton N. Morbidity at 3 months after hip fracture: data from the East Anglian audit. *Health Trends* 1997;**29**:55–60.

Grande GE, Barclay SI, Todd CJ. Difficulty of symptom control and general practitioners' knowledge of patients' symptoms. *Palliat Med* 1997;**11**:399–406. https://doi.org/10.1177/026921639701100511

Grande GE, Todd CJ, Barclay SI. Support needs in the last year of life: patient and carer dilemmas. *Palliat Med* 1997;**11**:202–8. https://doi.org/10.1177/026921639701100304

Silman A and the EVOS group (including Todd). Influence of physical activity on vertebral deformity in men and women: results from the European Vertebral Osteoporosis Study. *J Bone Mineral Res* 1997;**12**:813–19.

Reeve J, Silman A, EPOS Study Group. Epidemiology of osteoporotic fractures in Europe: towards biologic mechanisms, The European Prospective Osteoporosis Study. *Osteoporosis Int* 1997;**7**(S3):78–83.

O'Neill TW, Silman AJ, Naves Diaz M, Cooper C, Kanis J, Felsenberg D. Influence of hormonal and reproductive factors on the risk of vertebral deformity in European women. European Vertebral Osteoporosis Study Group. *Osteoporos Int* 1997;**7**:72–8.

Naves Diaz M, O'Neill TW, Silman AJ. The influence of alcohol consumption on the risk of vertebral deformity. European Vertebral Osteoporosis Study Group. *Osteoporos Int* 1997;**7**:65–71.

Diaz MN, O'Neill TW, Silman AJ. The influence of family history of hip fracture on the risk of vertebral deformity in men and women: the European Vertebral Osteoporosis Study. *Bone* 1997;**20**:145–9.

Johnell O, the EVOS study group. Anthropometric measurements and vertebral deformities. *Am J Epidemiol* 1997;**146**:287–93.

Bedford S, Melzer D, Dening T, Lawton C, Todd C, Badger G, Brayne C. Carers and the monitoring of psychogeriatric community teams. *Int J Geriatr Psychiatry* 1996;**11**:1057–61.

Bedford S, Melzer D, Dening T, Lawton C, Todd C, Badger G, Brayne C. What becomes of people with dementia referred to community psychogeriatric teams? *Int J Geriatr Psychiatry* 1996;**11**:1051–56.

Hollingworth W, Todd CJ, Parker MJ. The cost of treating hip fractures in the twenty-first century: short report. *Osteoporos Int* 1996;**6**(Suppl. 2):13–15.

Grande GE, Todd CJ, Barclay SI, Doyle JH. What terminally ill patients value in the support provided by GPs, district and Macmillan nurses. *Int J Palliat Nurs* 1996;**2**:138–43. https://doi.org/10.12968/ijpn.1996.2.3.138

O'Neill TW, the EVOS group. The prevalence of vertebral deformity in European men and women – The European Vertebral Osteoporosis Study. *J Bone Mineral Res* 1996;**11**:1010–18.

Hollingworth W, Mackenzie R, Todd CJ, Dixon AK. Measuring changes in quality of life following magnetic resonance imaging of the knee: SF-36, EuroQol or Rosser index? *Qual Life Res* 1995;**4**:325–34.

Chi LY, Brayne C, Todd CJ, O'Connor DW, Pollitt PA. Predictors of hospital contact by very elderly people: a pilot study from a cohort of people aged 75 years and over. *Age Ageing* 1995;**24**:382–8.

Hollingworth W, Todd CJ, Parker MJ. The cost of treating hip fractures in the twenty-first century. *J Public Health Med* 1995;**17**:269–76.

Todd CJ, Freeman CJ, Camilleri-Ferrante C, Palmer CR, Hyder A, Laxton CE, *et al.* Differences in mortality after fracture of hip: the east Anglian audit. *BMJ* 1995;**310**:904–8.

O'Neill TW, Marsden D, Silman AJ. Differences in the characteristics of responders and non-responders in a prevalence survey of vertebral osteoporosis. European Vertebral Osteoporosis Study Group. *Osteoporos Int* 1995;**5**:327–34.

O'Neill TW, the EVOS group. Survey response rates – national and regional differences in a European multicenter study of vertebral osteoporosis. *J Epidemiol Community Health* 1995;**49**:87–93.

Meyer HE, Falch JA, O'Neill T, Tverdal A, Varlow J. Height and body mass index in Oslo, Norway, compared to other regions of Europe: do they explain differences in the incidence of hip fracture? European Vertebral Osteoporosis Study Group. *Bone* 1995;**17**:347–50.

O'Neill TW, the EVOS group. Design and development of a questionnaire for use in a multicentre survey of vertebral osteoporosis in Europe: The European Vertebral Osteoporosis Study. *Rheumatology in Europe* 1995;**24**:75–81.

Vaughan NJA, Bradshaw C, Bradley C, Brown F, Cleary R, Clements D, *et al.* Measuring the outcomes of diabetes care. *Diabetic Med* 1994;**11**:418–23.

Reid N, Robinson G, Todd C. The 12-hour shift: the views of nurse educators and students. *J Adv Nurs* 1994;**19**:938–46.

O'Neill TW, Varlow J, Felsenberg D, Johnell O, Weber K. Marchant F, *et al.* Variation in vertebral height ratios in population studies. European Vertebral Osteoporosis Study Group. *J Bone Mineral Res* 1994;**9**:1895–907.

O'Neill TW, Cooper C, Cannata JB, Diaz Lopez JB, Hoszowski K, Johnell O, *et al.* Reproducibility of a questionnaire on risk factors for osteoporosis in a multicentre prevalence survey: the European Vertebral Osteoporosis Study. *Int J Epidemiol* 1994;**23**:559–65.

Hollingworth W, Todd C, Parker M, Roberts JA, Williams R. Cost analysis of early discharge after hip fracture. *BMJ* 1993;**307**:903–6.

Todd C, Robinson G, Reid N. 12-hour shifts: job satisfaction of nurses. *J Nurs Manag* 1993;**1**:215–20.

Reid N, Robinson G, Todd C. The quantity of nursing care on wards working eight hour and twelve hour shifts. *Int J Nurs Stud* 1993;**30**:403–13.

Todd C, Still A. General practitioners' strategies and tactics of communication with the terminally ill. *Fam Pract* 1993;**10**:268–76.

Wilson AE, Home PD. A dataset to allow exchange of information for monitoring continuing diabetes care. The Diabetes Audit Working Group. *Diabetic Med* 1993;**10**:378–90.

Working Group of the Research Unit of the Royal College of Physicians and the British Diabetic Association. A proposal for continuing audit of diabetes services. *Diabetic Med* 1992;**9**:759–64.

Todd CJ. Reduction in the incidence of suicide: a health gain objective for the NHS. *J Psychopharmacol* 1992;**6**(Suppl. 2):318–24. https://doi.org/10.1177/026988119200600206l

Reid N, Todd C, Robinson G. Educational activities on wards under 12 hour shifts. *Int J Nurs Stud* 1991;**28**:47–54.

Todd C, Reid N, Robinson G. The quality of nursing care on wards working eight and twelve hour shifts: a repeated measures study using the MONITOR index of quality of care. *Int J Nurs Stud* 1989;**26**:359–68.

Still AW, Todd CJ. Role ambiguity in general practice: the care of patients dying at home. *Soc Sci Med* 1986;**23**:519–25.

Still A, Todd C. Differences between terminally ill patients who know, and those who do not know, that they are dying. *J Clin Psychol* 1986;**42**:287–96.

Todd CJ, Still AW. Communication between general practitioners and patients dying at home. *Soc Sci Med* 1984;**18**:667–72.

2001

O'Leary D, Paykel E, Todd C, Vardulaki K. Suicide in primary affective disorders revisited: a systematic review by treatment era. *J Clin Psychiatry* 2001;**62**:804–11.

Walter FM, Kinmonth AL, Hyland F, Murrell P, Marteau TM, Todd C. Experiences and expectations of the new genetics in relation to familial risk of breast cancer: a comparison of the views of GPs and practice nurses. *Fam Pract* 2001;**18**:491–4.

Murrell P, Todd CJ, Martin A, Walton J, Lips P, Reeve J, Working Party for Quality of Life of the International Osteoporosis Foundation. Postal administration compared with nurse-supported administration of the QUALEFFO-41 in a population sample: comparison of results and assessment of psychometric properties. *Osteoporos Int* 2001;**12**:672–9.

The Women's Concerns Study Group. Raising concerns about family history of breast cancer in primary care consultations: prospective, population based study. *BMJ* 2001;**322**:27–8.

Ismail AA, Cockerill W, Cooper C, Finn JD, Abendroth K, Parisi G, *et al.* Prevalent vertebral deformity predicts incident hip though not distal forearm fracture: results from the European Prospective Osteoporosis Study. *Osteoporosis Int* 2001;**12**:85–90.

2002

Coomber S, Todd C, Park G, Baxter P, Firth-Cozens J, Shore S. Stress in UK intensive care unit doctors. *Br J Anaesth* 2002;**89**:873–81.

Freeman C, Todd C, Camilleri-Ferrante C, Laxton C, Murrell P, Palmer CR, *et al.* Quality improvement for patients with hip fracture: experience from a multi-site audit. *Qual Saf Health Care* 2002;**11**:239–45.

Rogers M, Todd C. Information exchange in oncology outpatient clinics: source, valence and uncertainty. *Psycho-Oncology* 2002;**11**:336–45. https://doi.org/10.1002/pon.575

Barrett J, Goh S, Todd C, Barclay S, Daza-Ramirez P, Vardulaki K. A description of an intermediate care service using routinely collected data. *J Nurs Manag* 2002;**10**:221–7.

Canoy DS, Hart AR, Todd CJ. Epidemiology of duodenal ulcer perforation: a study on hospital admissions in Norfolk, United Kingdom. *Dig Liver Dis* 2002;**34**:322–7.

Barclay S, Todd C, Grande G, Lipscombe J. Controlling cancer pain in primary care: the prescribing habits and knowledge base of general practitioners. *J Pain Symptom Manage* 2002;**23**:383–92.

Hollingworth W, Todd CJ, King H, Males T, Dixon AK, Karia KR, Kinmonth AL. Primary care referrals for lumbar spine radiography: diagnostic yield and clinical guidelines. *Br J Gen Pract* 2002;**52**:475–80.

Burbeck R, Coomber S, Robinson SM, Todd C. Occupational stress in consultants in accident and emergency medicine: a national survey of levels of stress at work. *Emerg Med J* 2002;**19**:234–8.

Barclay S, Todd C, Finlay I, Grande G, Wyatt P. Not another questionnaire! Maximizing the response rate, predicting non-response and assessing non-response bias in postal questionnaire studies of GPs. *Fam Pract* 2002;**19**:105–11.

Todd CJ, Grande GE, Barclay SI, Farquhar MC. General practitioners' and district nurses' views of hospital at home for palliative care. *Palliat Med* 2002;**16**:251–4. https://doi.org/10.1191/0269216302pm513oa

Farquhar M, Grande G, Todd C, Barclay S. Defining patients as palliative: hospital doctors' versus general practitioners' perceptions. *Palliat Med* 2002;**16**:247–50. https://doi.org/10.1191/0269216302pm520oa

Grande GE, McKerral A, Todd CJ. Which cancer patients are referred to Hospital at Home for palliative care? *Palliat Med* 2002;**16**:115–23. https://doi.org/10.1191/0269216302pm519oa

European Prospective Osteoporosis Study (EPOS) Group, Felsenberg D, Silman AJ, Lunt M, Armbrecht G, Ismail AA, *et al.* Incidence of vertebral fractures in Europe: results from the European Prospective Osteoporosis Study (EPOS). *J Bone Mineral Res* 2002;**17**:716–24.

Lunt M, Ismail AA, Felsenberg D, Cooper C, Kanis JA, Reeve J, *et al.*; the EPOS Study Group (including Todd). Defining incident vertebral deformities in population studies: a comparison of morphometric criteria. *Osteoporosis Int* 2002;**13**:809–15.

The European Prospective Osteoporosis Study (EPOS) Group, O'Neill TW. The relationship between bone density and incident vertebral fracture in men and women. *J Bone Mineral Res* 2002;**17**:2214–21.

Ismail AA, Pye SR, Cockerill WC, Lunt M, Silman AJ, Reeve J, *et al.* Incidence of limb fracture across Europe: results from the European Prospective Osteoporosis Study (EPOS). *Osteoporos Int* 2002;**13**:565–71. https://doi.org/10.1007/s001980200074

Canoy DS, Hart AR, Todd CJ. Epidemiology of duodenal ulcer perforation: a study on hospital admissions in Norfolk, United Kingdom. *Dig Liver Dis* 2002;**34**:322–7.

2003

Booth S, Silvester S, Todd C. Breathlessness in cancer and chronic obstructive pulmonary disease: using a qualitative approach to describe the experience of patients and carers. *Palliat Support Care* 2003;**1**:337–44.

Grande GE, McKerral A, Addington-Hall JM, Todd CJ. Place of death and use of health services in the last year of life. *J Palliat Care* 2003;**19**:263–70.

Boyle A, Todd C. Incidence and prevalence of domestic violence in a UK emergency department. *Emerg Med J* 2003;**20**:438–42.

Barclay S, Wyatt P, Shore S, Finlay I, Grande G, Todd C. Caring for the dying: how well prepared are general practitioners? A questionnaire study in Wales. *Palliat Med* 2003;**17**:27–39. https://doi.org/10.1191/0269216303pm665oa

Cullum S, Nandhra H, Darley J, Todd C. Screening for depression in older people on medical wards: which cut off should we use? *Int J Geriatr Psychiatry* 2003;**18**:358–9.

Roy DK, O'Neill TW, Finn JD, Lunt M, Silman AJ, Felsenberg D, *et al.* Determinants of incident vertebral fracture in men and women: results from the European Prospective Osteoporosis Study (EPOS). *Osteoporos Int* 2003;**14**:19–26. https://doi.org/10.1007/s00198-002-1317-8

Reeve J, Lunt M, Felsenberg D, Silman AJ, Scheidt-Nave A, Poor G, *et al.* Determinants of the size of incident vertebral deformities in European men and women in the 6th–9th decades of age: the European Prospective Osteoporosis Study (EPOS). *J Bone Mineral Res* 2003;**18**:1664–73.

2004

Walshe CE, Caress AL, Chew-Graham C, Todd CJ. Case studies: a research strategy appropriate for palliative care? *Palliat Med* 2004;**18**:677–84. https://doi.org/10.1191/0269216304pm962ra

Grande GE, Farquhar MC, Barclay SI, Todd CJ. Valued aspects of primary palliative care: content analysis of bereaved carers' descriptions. *Br J Gen Pract* 2004;**54**:772–8.

Ewing G, Rogers M, Barclay S, McCabe J, Martin A, Todd C. Recruiting patients into a primary care based study of palliative care: why is it so difficult? *Palliat Med* 2004;**18**:452–9. https://doi.org/10.1191/0269216304pm905oa

Grande GE, Farquhar MC, Barclay SI, Todd CJ. Caregiver bereavement outcome: relationship with hospice at home, satisfaction with care, and home death. *J Palliat Care* 2004;**20**:69–77.

Ewing G, Todd C, Rogers M, Barclay S, McCabe J, Martin A. Validation of a symptom measure suitable for use among palliative care patients in the community: CAMPAS-R. *J Pain Symptom Manage* 2004;**27**:287–99. https://doi.org/10.1016/j.jpainsymman.2003.12.012

Todd C, Griffiths J. Commentary on Gallagher LP, Truglio-Londrigan M. Community support: older adults' perceptions. *Clin Nurs Res* 2004;**13**:24–32.

Raspe H, Matthis C, Croft P, O'Neill T, European Vertebral Osteoporosis Study Group. Variation in back pain between countries: the example of Britain and Germany. *Spine* 2004;**29**:1017–21.

O'Neill T, Cockerill W, Matthis C, Raspe HH, Lunt M, Cooper C, *et al.* Back pain, disability and prevalent vertebral fracture: a prospective study. *Osteoporosis Int* 2004;**15**:760–5.

Cockerill W, Lunt M, Silman A, Cooper C, Lips P, Bhalla AK, *et al.* Health related quality of life and radiographic vertebral fracture. *Osteoporosis Int* 2004;**15**:113–19.

European Prospective Osteoporosis Study Group. Risk factors for Colles' fracture in men and women: results from the European Prospective Osteoporosis Study. *Osteoporosis Int* 2003;**14**:213–18. [Erratum published in *Osteoporosis Int* 2004;**15**:927.]

2005

Burden ST, Stoppard E, Shaffer J, Makin A, Todd C. Can we use mid upper arm anthropometry to detect malnutrition in medical inpatients? A validation study. *J Hum Nutr Diet* 2005;**18**:287–94.

Coventry PA, Grande GE, Richards DA, Todd CJ. Prediction of appropriate timing of palliative care for older adults with non-malignant life-threatening disease: a systematic review. *Age Ageing* 2005;**34**:218–27.

2006

Uitterlinden AG, Ralston SH, Brandi ML, Carey AH, Grinberg D, Langdahl BL, *et al.*; APOSS Investigators; EPOS Investigators; EPOLOS Investigators; FAMOS Investigators; LASA Investigators; Rotterdam Study Investigators; GENOMOS Study. The association between common vitamin D receptor gene variations and osteoporosis: a participant-level meta-analysis. *Ann Intern Med* 2006;**145**:255–64.

Grande GE, Farquhar MC, Barclay SI, Todd CJ. The influence of patient and carer age in access to palliative care services. *Age Ageing* 2006;**35**:267–73.

Ewing G, Rogers M, Barclay S, McCabe J, Martin A, Campbell M, Todd C. Palliative care in primary care: a study to determine whether patients and professionals agree on symptoms. *Br J Gen Pract* 2006;**56**:27–34.

Kaptoge S, Armbrecht G, Felsenberg D, Lunt M, Weber K, Boonen S, *et al.* Whom to treat? The contribution of vertebral X-rays to risk-based algorithms for fracture prediction. Results from the European Prospective Osteoporosis Study. *Osteoporos Int* 2006;**17**:1369–81. https://doi.org/10.1007/s00198-005-0067-9

2007

Lavelle K, Moran A, Howell A, Bundred N, Campbell M, Todd C. Older women with operable breast cancer are less likely to have surgery. *Br J Surg* 2007;**94**:1209–15. https://doi.org/10.1002/bjs.5834

Cullum S, Tucker S, Todd C, Brayne C. Effectiveness of liaison psychiatric nursing in older medical inpatients with depression: a randomised controlled trial. *Age Ageing* 2007;**36**:436–42.

Yardley L, Donovan-Hall M, Francis K, Todd C. Attitudes and beliefs that predict older people's intention to undertake strength and balance training. *J Gerontol B Psychol Sci Soc Sci* 2007;**62**:P119–25.

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 > or = 65 years. *Br J Cancer* 2007;**96**:1197–203.

Berman R, Campbell M, Makin W, Todd C. Occupational stress in palliative medicine, medical oncology and clinical oncology specialist registrars. *Clin Med* 2007;**7**:235–42.

Walshe C, Caress A, Chew-Graham C, Todd C. Evaluating partnership working: lessons for palliative care. *Eur J Cancer Care* 2007;**16**:48–54.

2008

Walshe C, Caress A, Chew-Graham C, Todd C. Implementation and impact of the Gold Standards Framework in community palliative care: a qualitative study of three primary care trusts. *Palliat Med* 2008;**22**:736–43. https://doi.org/10.1177/0269216308094103

2009

Preston N, Payne S, Todd C. Conducting research in palliative care patients: a burden or an opportunity? *Int J Palliat Nurs* 2009;**15**:524–5.

Grande G, Stajduhar K, Aoun S, Toye C, Funk L, Addington-Hall J, *et al.* Supporting lay carers in end of life care: current gaps and future priorities. *Palliat Med* 2009;**23**:339–44. https://doi.org/10.1177/0269216309104875

Mackereth P, Carter A, Parkin S, Stringer J, Caress A, Todd C, *et al.* Complementary therapists' training and cancer care: a multi-site study. *Eur J Oncol Nurs* 2009;**13**:330–5. https://doi.org/10.1016/j.ejon.2009.04.009

Mackereth P, Carter A, Parkin S, Stringer J, Roberts D, Long A, *et al.* Complementary therapists' motivation to work in cancer/supportive and palliative care: a multi-centre case study. *Complement Ther Clin Pract* 2009;**15**:161–5.

Pye SR, Tobias J, Silman AJ, Reeve J, O'Neill; EPOS Study Group. Childhood fractures do not predict future fractures: results from the European Prospective Osteoporosis Study. *J Bone Mineral Res* 2009;**24**:1314–18.

2011

Walshe C, Caress A, Chew-Graham C, Todd C. Equity, choice or chance? Community palliative care. *J Community Nurs* 2011;**25**:4–7.

McAllister M, Wood AM, Dunn G, Shiloh S, Todd C. The Genetic Counseling Outcome Scale: a new patient-reported outcome measure for clinical genetics services. *Clin Genet* 2011;**79**:413–24. https://doi.org/10.1111/j.1399-0004.2011.01636.x

2012

Burden S, Todd C, Hill J, Lal S. Pre-operative nutrition support in patients undergoing gastrointestinal surgery. *Cochrane Database Syst Rev* 2012;**11**:CD008879. https://doi.org/10.1002/14651858.CD008879.pub2

Stone P, Gwilliam B, Keeley V, Todd C, Gittins M, Kelly L, *et al.* Patients' reports or clinicians' assessments: which are better for prognosticating? *BMJ Support Palliat Care* 2012;**2**:219–23. https://doi.org/10.1136/bmjspcare-2012-000216

Hawley, H. Skelton, D.A. Campbell, M. Todd. C. Are the attitudes of exercise instructors who work with older adults influenced by training and personal characteristics? *J Ageing Physical Activity* 2012;**20**:47–63.

McAllister M, Wood AM, Dunn G, Shiloh S, Todd C. The Perceived Personal Control (PPC) Questionnaire: reliability and validity in a UK sample. *Am J Med Genet A* 2012;**158A**:367–72.

2013

Lavelle K, Sowerbutts AM, Bundred N, Pilling M, Degner L, Stockton C, Todd C. Is lack of surgery for older breast cancer patients in the UK explained by patient choice or poor health? A prospective cohort study. *Br J Cancer* 2014;**110**:573–83.

Evans CJ, Harding R, Higginson IJ, MORECare. 'Best practice' in developing and evaluating palliative and end-of-life care services: a meta-synthesis of research methods for the MORECare project. *Palliat Med* 2013;**27**:885–98. https://doi.org/10.1177/0269216312467489

Preston NJ, Fayers P, Walters SJ, Pilling M, Grande GE, Short V, *et al.* Recommendations for managing missing data, attrition and response shift in palliative and end-of-life care research: part of the MORECare research method guidance on statistical issues. *Palliat Med* 2013;**27**:899–907. https://doi.org/10.1177/0269216313486952

Roberts D, Wilson C, Todd C, Long AF, Mackereth P, Stringer J, *et al.* Complementary therapies in cancer: patients' views on their purposes and value pre and post receipt of complementary therapy – a multi-centre case study. *Eur J Integr Med* 2013;**5**:443–9.

2015

Lavelle K, Sowerbutts AM, Bundred N, Pilling M, Todd, C. Pre-treatment health measures and complications after surgical management of elderly women with breast cancer. *Br J Surg* 2015;**102**:653–67.

Sowerbutts AM, Griffiths, J, Todd C, Lavelle K. Why are older women not having surgery for breast cancer? *Psychooncology* 2015;**24**:1036–42.

2016

Hawley-Hague H, Horne M, Skelton DA, Todd C. Review of how we should define (and measure) adherence in studies examining older adults' participation in exercise classes. *BMJ Open* 2016;**6**:e011560. https://doi.org/10.1136/bmjopen-2016-011560

Farquhar MC, Prevost AT, McCrone P, Brafman-Price B, Bentley A, Higginson IJ, *et al.* The clinical and cost effectiveness of a Breathlessness Intervention Service for patients with advanced non-malignant disease and their informal carers: mixed findings of a mixed method randomised controlled trial. *Trials* 2016;**17**:185. https://doi.org/10.1186/s13063-016-1304-6

Preston NJ, Farquhar MC, Walshe CE, Stevinson C, Ewing G, Calman LA, *et al.* Strategies designed to help healthcare professionals to recruit participants to research studies. *Cochrane Database Syst Rev* 2016;**2**:MR000036.

Hawley-Hague H, Horne M, Skelton DA, Todd C. Older adults' uptake and adherence to exercise classes: instructors' perspectives. *J Aging Phys Act* 2016;**24**:119–28. https://doi.org/10.1123/japa.2014-0108

2017

Helbostad JL, Vereijken B, Becker C, Todd C, Taraldsen K, Pijnappels M, *et al.* Mobile Health Applications to Promote Active and Healthy Ageing. *Sensors* 2017;**17**:E622.

Bundred N, Lavelle K, Sowerbutts AM, Pilling M, Todd C. Impact of primary surgery on short-term survival of older breast cancer patients in the UK. Feb 2017. *Cancer Res* (4 suppl.) ed. American Association for Cancer Research, Vol. 77, p. P3-13-021.

Boulton E, Horne M, Todd C. Multiple influences on participating in physical activity in older age: developing a social ecological approach. *Health Expect* 2018;**21**:239–48.

Julie Morris

2015

Williams KE, Barnes NL, Cramer A, Johnson R, Cheema K, Morris J, *et al.* Molecular phenotypes of DCIS predict overall and invasive recurrence. *Ann Oncol* 2015;**26**:1019–25. https://doi.org/10.1093/annonc/mdv062

Jayanti A, Foden P, Wearden A, Morris J, Brenchley P, Mitra S, BASIC-HHD Study Group. Self-cannulation for haemodialysis: patient attributes, clinical correlates and self-cannulation predilection models. *PLOS ONE* 2015;**10**:e0125606. https://doi.org/10.1371/journal.pone.0125606

2016

Al-Himdani S, Timbrell S, Tan KT, Morris J, Bundred NJ. Prediction of margin involvement and local recurrence after skin-sparing and simple mastectomy. *Eur J Surg Oncol* 2016;**42**:935–41. https://doi.org/10.1016/j.ejso.2016.04.055

Dr Vaughan Keeley

2003

Hunt J, Cobb M, Keeley VL, Ahmedzai SH. The quality of spiritual care – developing a standard. *Int J Palliat Nurs* 2003;**9**:208–15. https://doi.org/10.12968/ijpn.2003.9.5.11493

2004

Hunt J, Keeley VL, Cobb M, Ahmedzai SH. A new quality assurance package for hospital palliative care teams: the Trent Hospice Audit Group model. *Br J Cancer* 2004;**91**:248–53. https://doi.org/10.1038/sj.bjc.6601945

2008

Keeley V. Pharmacological treatment for chronic oedema. *Br J Community Nurs* 2008;**13**:S4, S6, S8–10. https://doi.org/10.12968/bjcn.2008.13.Sup2.29394

Keeley V. Quality of life assessment tools in chronic oedema. *Br J Community Nurs* 2008;**13**:S22–7. https://doi.org/10.12968/bjcn.2008.13.Sup5.31193

Keeley VL. Lymphoedema and cellulitis: chicken or egg? *Br J Dermatol* 2008;**158**:1175–6. https://doi.org/10.1111/j.1365-2133.2008.08590.x

2010

Connell F, Brice G, Jeffery S, Keeley V, Mortimer P, Mansour S. A new classification system for primary lymphatic dysplasias based on phenotype. *Clin Genet* 2010;**77**:438–52. https://doi.org/10.1111/j.1399-0004.2010.01394.x

2012

Gwilliam B, Keeley V, Todd C, Gittins M, Roberts C, Kelly L, *et al.* Development of Prognosis in Palliative care Study (PiPS) predictor models to improve prognostication in advanced cancer: prospective cohort study. *BMJ Support Palliat Care* 2012;**2**:63–71. https://doi.org/10.1136/bmjspcare.2012.d4920rep

Stone P, Gwilliam B, Keeley V, Todd C, Gittins M, Kelly L, *et al.* Patients' reports or clinicians' assessments: which are better for prognosticating? *BMJ Support Palliat Care* 2012;**2**:219–23. https://doi.org/10.1136/bmjspcare-2012-000216

2013

Connell FC, Gordon K, Brice G, Keeley V, Jeffery S, Mortimer PS, *et al.* The classification and diagnostic algorithm for primary lymphatic dysplasia: an update from 2010 to include molecular findings. *Clin Genet* 2013;**84**:303–14. https://doi.org/10.1111/cge.12173

Connell F, Brice G, Jeffery S, Keeley V, Mortimer P, Mansour S. A new classification system for primary lymphatic dysplasias based on phenotype. *Clin Genet* 2010;**77**:438–52. https://doi.org/10.1111/j.1399-0004.2010.01394.x

Stone PC, Gwilliam B, Keeley V, Todd C, Kelly LC, Barclay S. Factors affecting recruitment to an observational multicentre palliative care study. *BMJ Support Palliat Care* 2013;**3**:318–23. https://doi.org/10.1136/bmjspcare-2012-000396

Gwilliam B, Keeley V, Todd C, Roberts C, Gittins M, Kelly L, *et al.* Prognosticating in patients with advanced cancer – observational study comparing the accuracy of clinicians' and patients' estimates of survival. *Ann Oncol* 2013;**24**:482–8. https://doi.org/10.1093/annonc/mds341

2015

Atton G, Gordon K, Brice G, Keeley V, Riches K, Ostergaard P, *et al.* The lymphatic phenotype in Turner syndrome: an evaluation of nineteen patients and literature review. *Eur J Hum Genet* 2015;**23**:1634–9. https://doi.org/10.1038/ejhg.2015.41

Bundred NJ, Stockton C, Keeley V, Riches K, Ashcroft L, Evans A, *et al.* Comparison of multi-frequency bioimpedance with perometry for the early detection and intervention of lymphoedema after axillary node clearance for breast cancer. *Breast Cancer Res Treat* 2015;**151**:121–9. https://doi.org/10.1007/s10549-015-3357-8

2017

Narahari SR, Aggithaya MG, Moffatt C, Ryan TJ, Keeley V, Vijaya B, *et al.* Future research priorities for morbidity control of lymphedema. *Indian J Dermatol* 2017;**62**:33–40. https://doi.org/10.4103/0019-5154.198039

Moffatt CJ, Keeley V, Franks PJ, Rich A, Pinnington LL. Chronic oedema: a prevalent health care problem for UK health services. *Int Wound J* 2017;**14**:772–81. https://doi.org/10.1111/iwj.12694

Keeley V. Advances in understanding and management of lymphoedema (cancer, primary). *Curr Opin Support Palliat Care* 2017;**11**:355–60. https://doi.org/10.1097/SPC.0000000000000311

Professor Arnie Purushotham

2004

Evans JR, Helmy AE, Cluroe A, Purushotham AD. Lymphoma of the breast - case report and review of the literature. *J BUON* 2004;**9**:307–11.

Lynch MD, Jones AE, Marker A, Grant JW, Purushotham AD. Malignant eccrine poroma in breast cancer-related lymphoedema. *Ann R Coll Surg Engl* 2004;**86**:W32–5. https://doi.org/10.1308/147870804155

2005

Tait R, Pinder SE, Ellis IO, Purushotham AD. Adenomyoepithelioma of the breast; a case report and literature review. *J BUON* 2005;**10**:393–5.

De Silva NK, Pinder S, Purushotham AD. Invasive micropapillary carcinoma of breast: case report with literature review. *J BUON* 2005;**10**:271–5.

Lynch MD, Cariati M, Purushotham AD. Breast cancer, stem cells and prospects for therapy. *Breast Cancer Res* 2006;**8**:211.

Pain SJ, Barber RW, Solanki CK, Ballinger JR, Britton TB, Mortimer PS, *et al.* Short-term effects of axillary lymph node clearance surgery on lymphatic physiology of the arm in breast cancer. *J Appl Physiol* 2005;**99**:2345–51.

2006

Patkar V, Hurt C, Steele R, Love S, Purushotham A, Williams M, *et al.* Evidence-based guidelines and decision support services: a discussion and evaluation in triple assessment of suspected breast cancer. *Br J Cancer* 2006;**95**:1490–6.

O'Mahony S, Solanki CK, Barber RW, Mortimer PS, Purushotham AD, Peters AM. Imaging of lymphatic vessels in breast cancer-related lymphedema: intradermal versus subcutaneous injection of 99mTc-immunoglobulin. *AJR Am J Roentgenol* 2006;**186**:1349–55.

2007

Cash CJ, Coles CE, Treece GM, Purushotham AD, Britton P, Sinnatamby R, *et al.* Breast cancers: noninvasive method of preoperative localization with three-dimensional US and surface contour mapping. *Radiology* 2007;**245**:556–66.

Purushotham AD, Bennett Britton TM, Klevesath MB, Chou P, Agbaje OF, Duffy SW. Lymph node status and breast cancer-related lymphedema. *Ann Surg* 2007;**246**:42–5. https://doi.org/10.1097/01.sla.0000259390.51203.7b

O'Mahony S, Britton TM, Solanki CK, Ballinger JR, Pain SJ, Mortimer PS, *et al.* Lymphatic transfer studies with immunoglobulin scintigraphy after axillary surgery. *Eur J Surg Oncol* 2007;**33**:1052–60.

Bennett Britton TM, Buczacki SJ, Turner CL, Vowler SL, Pain SJ, Purushotham AD. Venous changes and lymphoedema 4 years after axillary surgery for breast cancer. *Br J Surg* 2007;**94**:833–4. https://doi.org/10.1002/bjs.5711

2008

Wishart GC, Greenberg DC, Britton PD, Chou P, Brown CH, Purushotham AD, Duffy SW. Screen-detected vs symptomatic breast cancer: is improved survival due to stage migration alone? *Br J Cancer* 2008;**98**:1741-4.

Pal A, Provenzano E, Duffy SW, Pinder SE, Purushotham AD. A model for predicting non-sentinel lymph node metastatic disease when the sentinel lymph node is positive. *Br J Surg* 2008;**95**:302–9. https://doi.org/10.1002/bjs.5943

2009

Peters AM, Fowler JC, Britton TB, Solanki CK, Ballinger JR, Ravichandran D, *et al.* Functional variation in lymph node arrangements within the axilla. *Lymphat Res Biol* 2009;**7**:139–44. https://doi.org/10.1089/lrb.2008.1021

Bennett Britton TM, Wallace SM, Wilkinson IB, Mortimer PS, Peters AM, Purushotham AD. Sympathetic nerve damage as a potential cause of lymphoedema after axillary dissection for breast cancer. *Br J Surg* 2009;**96**:865–9. https://doi.org/10.1002/bjs.6660

Britton TB, Solanki CK, Pinder SE, Mortimer PS, Peters AM, Purushotham AD. Lymphatic drainage pathways of the breast and the upper limb. *Nucl Med Commun* 2009;**30**:427–30. https://doi.org/10.1097/MNM.0b013e328315a6c6

Bennett Britton TM, Purushotham AD. Understanding breast cancer-related lymphoedema. *Surgeon* 2009;**7**:120–4.

Fowler JC, Solanki CK, Guenther I, Barber R, Miller F, Bobrow L, *et al.* A pilot study of dual-isotope lymphoscintigraphy for breast sentinel node biopsy comparing intradermal and intraparenchymal injection. *Eur J Surg Oncol* 2009;**35**:1041–7. https://doi.org/10.1016/j.ejso.2009.02.018

2010

Purushotham A, Pinder S, Cariati M, Harries M, Goldhirsch A. Neoadjuvant chemotherapy: not the best option in estrogen receptor-positive, HER2-negative, invasive classical lobular carcinoma of the breast? *J Clin Oncol* 2010;**28**:3552-4.

Fowler JC, Britton TB, Provenzano E, Ravichandran D, Lawrence D, Solanki CK, *et al.* Measurement of lymph node function from the extraction of immunoglobulin in lymph. *Scand J Clin Lab Invest* 2010;**70**:112–15. https://doi.org/10.3109/00365510903572040

Lewison G, Purushotham A, Mason M, McVie G, Sullivan R. Understanding the impact of public policy on cancer research: a bibliometric approach. *Eur J Cancer* 2010;**46**:912–19. https://doi.org/10.1016/j.ejca.2009.12.020

O'Mahony S, Britton TB, Ballinger JR, Solanki CK, Barber RW, Mortimer PS, *et al.* Delivery of radiolabelled blood cells to lymphatic vessels by intradermal injection: a means of investigating lymphovenous communications in the upper limb. *Nucl Med Commun* 2010;**31**:121–7. https://doi.org/10.1097/MNM.0b013e328330dd14

2011

Sullivan R, Purushotham AD. Avoiding the zero sum game in global cancer policy: beyond 2011 UN high level summit. *Eur J Cancer* 2011;**47**:2375–80. https://doi.org/10.1016/j.ejca.2011.08.017

Sullivan R, Peppercorn J, Sikora K, Zalcberg J, Meropol NJ, Amir E, *et al.* Delivering affordable cancer care in high-income countries. *Lancet Oncol* 2011;**12**:933–80. https://doi.org/10.1016/S1470-2045(11)70141-3

2012

Sullivan R, Homberg L, Purushotham AD. Cancer risk and prevention in a globalised world: solving the public policy mismatch. *Eur J Cancer* 2012;**48**:2043–5. https://doi.org/10.1016/j.ejca.2012.01.019

Purushotham AD, Lewison G, Sullivan R. The state of research and development in global cancer surgery. *Ann Surg* 2012;**255**:427–32. https://doi.org/10.1097/SLA.0b013e318246591f

Haire K, Burton C, Park R, Reynolds J, Stewart D, Purushotham AD. Integrated Cancer System: a perspective on developing an integrated system for cancer services in London. *London J Prim Care* 2012;**5**:29–34.

2013

Purushotham A, Bains S, Lewison G, Szmukler G, Sullivan R. Cancer and mental health – a clinical and research unmet need. *Ann Oncol* 2013;**24**:2274–8. https://doi.org/10.1093/annonc/mdt214

Klevesath MB, Pantel K, Agbaje O, Provenzano E, Wishart GC, Gough P, *et al.* Patterns of metastatic spread in early breast cancer. *Breast* 2013;**22**:449–54. https://doi.org/10.1016/j.breast.2013.04.017

Enfield L, Cantanhede G, Douek M, Ramalingam V, Purushotham A, Hebden J, Gibson A. Monitoring the response to neoadjuvant hormone therapy for locally advanced breast cancer using three-dimensional time-resolved optical mammography. *J Biomed Opt* 2013;**18**:56012. https://doi.org/10.1117/1.JBO.18.5.056012

Purushotham A, Cornwell J, Burton C, Stewart D, Sullivan R. What really matters in cancer?: Putting people back into the heart of cancer policy. *Eur J Cancer* 2013;**49**:1669–72. https://doi.org/10.1016/j.ejca.2013.01.004

2014

Ahmed M, Purushotham AD, Douek M. Novel techniques for sentinel lymph node biopsy in breast. *Ann Surg Oncol* 2014;**21**:1237–45. https://doi.org/10.1245/s10434-013-3379-6

Ahmed M, Purushotham AD, Douek M. Novel techniques for sentinel lymph node biopsy in breast cancer: a systematic review. *Lancet Oncol* 2014;**15**:e351–62. https://doi.org/10.1016/S1470-2045(13)70590-4

Honeth G, Lombardi S, Ginestier C, Hur M, Marlow R, Buchupalli B, *et al.* Aldehyde dehydrogenase and estrogen receptor define a hierarchy of cellular differentiation in the normal human mammary epithelium. *Breast Cancer Res* 2014;**16**:R52. https://doi.org/10.1186/bcr3663

Purushotham A, Shamil E, Cariati M, Agbaje O, Muhidin A, Gillett C, *et al.* Age at diagnosis and distant metastasis in breast cancer – a surprising inverse relationship. *Eur J Cancer* 2014;**50**:1697–705. https://doi.org/10.1016/j.ejca.2014.04.002

Suyoi A, Bains SK, Kothari A, Douek M, Agbaje O, Hamed H, *et al.* When is a completion axillary lymph node dissection necessary in the presence of a positive sentinel lymph node? *Eur J Cancer* 2014;**50**:690–7. https://doi.org/10.1016/j.ejca.2013.11.024

Douek M, Klaase J, Monypenny I, Kothari A, Zechmeister K, Brown D, *et al.* Sentinel node biopsy using a magnetic tracer versus standard technique: the SentiMAG Multicentre Trial. *Ann Surg Oncol* 2014;**21**:1237–45.

2015

Bains SK, Peters AM, Zammit C, Ryan N, Ballinger J, Glass DM, *et al.* Global abnormalities in lymphatic function following systemic therapy in patients with breast cancer. *Br J Surg* 2015;**102**:534–40. https://doi.org/10.1002/bjs.9766

Bains SK, Ballinger J, Allen S, Stanton AW, Levick JR, Mortimer PS, *et al.* An investigation of lymphovenous communications in the upper limbs of breast cancer patients. *Eur J Surg Oncol* 2015;**41**:433–8. https://doi.org/10.1016/j.ejso.2014.11.036

Sullivan R, Alatise OI, Anderson BO, Audisio R, Autier P, Aggarwal A, *et al.* Global cancer surgery: delivering safe, affordable, and timely cancer surgery. *Lancet Oncol* 2015;**16**:1193–224. https://doi.org/10.1016/S1470-2045(15)00223-5

Bundred NJ, Stockton C, Keeley V, Riches K, Ashcroft L, Evans A, *et al.* Comparison of multi-frequency bioimpedance with perometry for the early detection and intervention of lymphoedema after axillary node clearance for breast cancer. *Breast Cancer Res Treat* 2015;**151**:121–9. https://doi.org/10.1007/s10549-015-3357-8

Cariati M, Bains SK, Grootendorst MR, Suyoi A, Peters AM, Mortimer P, *et al.* Adjuvant taxanes and the development of breast cancer-related arm lymphoedema. *Br J Surg* 2015;**102**:1071–8. https://doi.org/10.1002/bjs.9846

Harris J, Tsianakas V, Ream E, Van Hemelrijck M, Purushotham A, Mucci L, *et al.* CanWalk: study protocol for a randomized feasibility trial of a walking intervention for people with recurrent or metastatic cancer. *Pilot Feasibility Stud* 2015;**1**:7. https://doi.org/10.1186/s40814-015-0003-5

Robert G, Cornwell J, Locock L, Purushotham A, Sturmey G, Gager M. Patients and staff as codesigners of healthcare services. *BMJ* 2015;**350**:g7714. https://doi.org/10.1136/bmj.g7714

Ahmed M, Purushotham AD, Horgan K, Klaase JM, Douek M. Meta-analysis of superficial versus deep injection of radioactive tracer and blue dye for lymphatic mapping and detection of sentinel lymph nodes in breast cancer. *Br J Surg* 2015;**102**:169–81. https://doi.org/10.1002/bjs.9673

Vollan HK, Rueda OM, Chin SF, Curtis C, Turashvili G, Shah S, *et al.* A tumor DNA complex aberration index is an independent predictor of survival in breast and ovarian cancer. *Mol Oncol* 2015;**9**:115–27. https://doi.org/10.1016/j.molonc.2014.07.019

2016

Møller H, Henson K, Lüchtenborg M, Broggio J, Charman J, Coupland VH, *et al.* Short-term breast cancer survival in relation to ethnicity, stage, grade and receptor status: national cohort study in England. *Br J Cancer* 2016;**115**:1408–15. https://doi.org/10.1038/bjc.2016.335

Weitsman G, Barber PR, Nguyen LK, Lawler K, Patel G, Woodman N, *et al.* HER2-HER3 dimer quantification by FLIM-FRET predicts breast cancer metastatic relapse independently of HER2 IHC status. *Oncotarget* 2016;**7**:51012–51026. https://doi.org/10.18632/oncotarget.9963

Cintolesi V, Stanton AW, Bains SK, Cousins E, Peters AM, Purushotham AD, *et al.* Constitutively Enhanced Lymphatic Pumping in the Upper Limbs of Women Who Later Develop Breast Cancer-Related Lymphedema. *Lymphat Res Biol* 2016;**14**:50–61. https://doi.org/10.1089/lrb.2016.0005

Melvin JC, Wulaningsih W, Hana Z, Purushotham AD, Pinder SE, Fentiman I, *et al.* Family history of breast cancer and its association with disease severity and mortality. *Cancer Med* 2016;**5**:942–9. https://doi.org/10.1002/cam4.648

Jeffs E, Purushotham A. The prevalence of lymphoedema in women who attended an information and exercise class to reduce the risk of breast cancer-related upper limb lymphoedema. *Springerplus* 2016;**5**:21. https://doi.org/10.1186/s40064-015-1629-8

2017

Lawler K, Papouli E, Naceur-Lombardelli C, Mera A, Ougham K, Tutt A, *et al.* Gene expression modules in primary breast cancers as risk factors for organotropic patterns of first metastatic spread: a case control study. *Breast Cancer Res* 2017;**19**:113. https://doi.org/10.1186/s13058-017-0881-y

Aggarwal A, Lewis D, Mason M, Purushotham A, Sullivan R, van der Meulen J. Effect of patient choice and hospital competition on service configuration and technology adoption within cancer surgery: a national, population-based study. *Lancet Oncol* 2017;**18**:1445–53.

Tsianakas V, Harris J, Ream E, Van Hemelrijck M, Purushotham A, Mucci L, *et al.* CanWalk: a feasibility study with embedded randomised controlled trial pilot of a walking intervention for people with recurrent or metastatic cancer. *BMJ Open* 2017;**7**:e013719. https://doi.org/10.1136/bmjopen-2016-013719

Professor Adrian Bagust

Up to 2000

Bagust A, Burrows J, Oakley J. Quality or quantity. *Health Serv J* 1992;**102**:23–5.

Haycox A, Bagust A, Walley T. Importance of health economics must be recognised when trials are designed. *BMJ* 1999;**318**:1696–7.

2010

Sacco JJ, Botten J, Macbeth F, Bagust A, Clark P. The average body surface area of adult cancer patients in the UK: a multicentre retrospective study. *PLOS ONE* 2010;**5**:e8933. https://doi.org/10.1371/journal.pone.0008933

Maria Bramley

2015

Bundred NJ, Stockton C, Keeley V, Riches K, Ashcroft L, Evans A, *et al.* Comparison of multi-frequency bioimpedance with perometry for the early detection and intervention of lymphoedema after axillary node clearance for breast cancer. *Breast Cancer Res Treat* 2015;**151**:121–9. https://doi.org/10.1007/s10549-015-3357-8

Katie Riches

2015

Bundred NJ, Stockton C, Keeley V, Riches K, Ashcroft L, Evans A, *et al.* Comparison of multi-frequency bioimpedance with perometry for the early detection and intervention of lymphoedema after axillary node clearance for breast cancer. *Breast Cancer Res Treat* 2015;**151**:121–9. https://doi.org/10.1007/s10549-015-3357-8

EME
HS&DR
HTA
PGfAR
PHR

Part of the NIHR Journals Library
www.journalslibrary.nihr.ac.uk

Published by the NIHR Journals Library