Omission of surgery in older women with early breast cancer has an adverse impact on breast cancer-specific survival

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Key Words

Breast cancer; elderly; surgery; primary endocrine therapy; comorbidity; retrospective study

Abstract.

Background: Primary endocrine therapy (PET) is used as an alternative to surgery in up to 40% of UK women with early breast cancer over age 70. This study has investigated the impact of surgery versus PET on breast cancer specific survival (BCSS) in older women.

Methods: Cancer registration data were obtained from two English regions from 2002 to 2010 (n=23,961). A retrospective analysis was performed for women with ER positive disease, using statistical modelling to show the effect of treatment (surgery or PET) and age/health status on BCSS. Missing data was handled using multiple imputation.

Results: After data pre-processing, 18,730 (78.5%) were identified as having ER positive disease; of these, 10,087 (54%) had surgery and 8,643 (46%) had PET. BCSS was worse in the PET group compared with the surgical group (5 year BCSS: 69% v 90% respectively). This was true for all strata considered, though the differential was lessened in the cohort with the greatest degree of comorbidity. For older, frailer patients the hazard of breast cancer death has less relative impact on overall survival. Selection for surgery on the basis of predicted life expectancy may permit selection of women for whom surgery confers little benefit. This model is being used to develop an on-line algorithm to aid management of older women with early breast cancer (Age Gap Risk Prediction Tool).

Conclusion: BCSS in older women with ER positive disease is worse if surgery is omitted. This treatment choice may, therefore, contribute to inferior cancer outcomes.

INTRODUCTION

In the UK, women over the age of 70 account for more than 30% of all diagnoses of breast cancer(1). Treatment of older breast cancer patients in the UK differs from that recommended by National guidelines across the spectrum of therapy (2, 3). Rates of breast surgery for operable disease are lower in women aged over 70 than for younger patients (3, 4). In addition, practice varies by UK health region, with rates of surgery varying between 60% and 88%: a difference that cannot be accounted for by case mix (5).

Older women in other developed nations, such as the Netherlands and the Republic of Ireland are less likely to receive surgery for breast cancer than their younger counterparts, but the discrepancy is lower than that observed in the UK(6, 7). In the USA rates of surgical treatment for stage I-II disease remain over 90% for patients aged 90 and over (8).

Relative survival for breast cancer in the UK is inferior to that seen in a number of other developed nations, particularly in this older age group (9). This pattern persists after accounting for stage at diagnosis, suggesting that some of the discrepancy is due to suboptimal management rather than late presentation.

For women with oestrogen receptor positive (ER+) operable breast cancer, primary endocrine therapy (PET) is the main alternative to surgery. Primary endocrine therapy in this context is defined as treatment with an anti-oestrogen, such as tamoxifen or an aromatase inhibitor, without surgical intent. Historic randomized trials of PET compared with surgery, both with and without adjuvant tamoxifen, suggested that in women aged 75 or over there was no evidence of a difference either in terms of overall (OS) or breast cancer specific survival (BCSS) between the two approaches at 5 year median follow up (10). On very long term follow up, survival outcomes in the non-surgical group were inferior(11), as would be expected considering that secondary anti-oestrogen resistance develops with time. Evidence suggests, that women in the 70-75 year age range may benefit from surgery even at 5 year follow-up (12). Local disease control was considerably worse with PET even

on short and medium term follow up (11-13), with a significantly greater number of patients requiring a change of management on disease progression. The trials were flawed by modern standards: patients with co-morbidities were excluded and the surgical arm therapies were often substandard with no adjuvant chemotherapy, and no chest wall or breast radiotherapy. As a result, the trial populations did not reflect the heterogeneity in health states typical of the older population nor the sophistication of modern breast cancer care. Furthermore, these trials do not reflect the advances in surgical and anaesthetic techniques, the introduction of third generation aromatase inhibitors or the increase in life expectancy over the last four decades (from 75.3 years in 1971 to 83.2 years in 2012-14)(14). Rates of mortality and morbidity from modern day breast cancer surgery were very low in a recent National UK audit, suggesting that surgery is safe in the majority of older woman (15). These historic trials may no longer fully represent modern practice and outcomes.

A recent review of evidence from non-randomised cohort studies has suggested that surgery may be more effective than PET in terms of BCSS (10). Cohort studies are often better able to include representative populations, and provide information on outcomes of treatment in a "real world" clinical setting. However, the studies included in this review did not attempt to account for the differing patient characteristics between women treated with surgery and those with PET. On average, women are more likely to receive PET if they are older and have chronic comorbidities (16, 17). This confounds overall survival estimates and will increase non-breast cancer mortality in the non-surgically treated patients. Similarly, disease characteristics such as stage at diagnosis and tumour grade are associated with treatment choice. Bates and colleagues (2014) found that large tumour size (>5cm) and node positivity were associated with non-surgical treatments suggesting that selection bias by stage of disease may confound the outcomes of observational studies in favour of surgery (17). In addition women who have surgery are usually those with early stage disease as surgery is not appropriate or possible in advanced breast cancer. Outcomes in the non-surgical group may appear worse if women with advanced disease remain under-staged and are

mistakenly categorised as having early stage disease. This causes confounding in estimates of breast cancer specific survival. Observed differences in outcomes seen in these cohort studies cannot, therefore, be assumed to be solely due to treatment. Another issue in observational data is that cause of death may be misclassified as due to breast cancer whereas in a randomised trial efforts to establish the actual cause of death may be more rigorous.

There are significant barriers to conducting sufficiently powered randomised clinical trials in older breast cancer patients (18). The Endocrine+/- Surgical Therapy for Elderly women with Mammary Cancer trial (ESTEeM) was a recent attempt to conduct an age and fitness stratified randomised trial to compare these treatment approaches. It failed, with the study closing in 2009, due to slow recruitment (18). In light of this, it is necessary to make use of observational evidence, combined with mathematical modelling, to adjust for issues such as confounding, in order to assess how treatment choices impact on outcomes.

The aim of this study was to investigate how current UK practice in the surgical treatment of older women (age >70 years) with breast cancer affects breast cancer survival at the population level. A retrospective cohort analysis was conducted using UK Cancer Registry data. The data were routinely collected from two English cancer registration regions which are demographically representative of the wider UK population (West Midlands and Northern & Yorkshire). The effect of PET versus surgical treatment on survival outcomes was assessed using exploratory data analysis and survival analysis methods.

METHODS

Data

Data on all first diagnoses of invasive breast cancer in women aged 70 and over between the years of 2002 and 2010 were acquired from two UK cancer registry regions (West Midlands, Northern & Yorkshire). Variables provided for analysis are shown in Table 1. The patient and disease variables are representative of wider UK National data in terms of the age distribution, deprivation pattern, tumour stage and biological sub-type distributions. Survival data was derived from death certifications from the Office for National Statistics. Time to death was defined as the difference in days between the date of diagnosis and the date of death. Patients who remain alive were censored. Cause of death was recorded by the registry as either "breast cancer", "other (cancer)", "other (non-cancer)", "other (unknown)" or "unknown". For the purposes of this analysis, deaths were classified dichotomously as either "breast cancer" or "not breast cancer".

The data presented in Table 1 had been pre-processed as described in Supplemental Materials. In particular, oestrogen receptor (ER) status was not completely recorded for all patients, predominantly in the Northern and Yorkshire region. In the West Midlands 14.5% of patients had missing ER status data over the 2002-2010 period; in the Northern & Yorkshire region ER status was not available for patients diagnosed before 2010; in 2010 35% of patients had missing data. Patients with missing ER status who had received hormone therapy were assumed to have had ER+ disease. This was justified by the fact that hormone therapy is only effective for and offered to ER+ patients, which was routinely tested for throughout this time period and therefore it is reasonable to suppose that hormone therapy would not have been given to women with ER negative tumours. Previous internal data quality audits by the cancer registry have shown that hormone therapy data is reliable for the Northern & Yorkshire region.

Data on surgical procedures were available from linked records of treatment episodes. These include the OPCS4 code of the procedure(s) received along with the date of the episode. A patient was

classed as receiving primary surgery if they had an episode including a procedure indicating breast surgery recorded within 6 months of diagnosis. Comorbidity was derived from linked records in the Hospital Episode Statistics dataset and aggregated using the Charlson Co-morbidity Index (CCI)(19) by counting diagnostic codes recorded in episodes in the 18 months prior to diagnosis, an approach used in other studies using routine registration data(20).

[INSERT TABLE 1]

Statistical analysis

Exploratory survival analysis consisted of plotting cumulative incidence curves for breast cancer and other cause mortality for patients treated surgically and non-surgically. The effect of treatment and other covariates on breast cancer specific survival were estimated using two models. The first was the commonly used Cox proportional hazards model (21), which estimates the effects of covariates on survival outcomes but makes no assumptions about the shape of the underlying survival curve. The second was the Royston-Parmar model,(22) which relaxes the proportional hazards assumption, allowing the effect of a covariate to vary over time. On the basis of exploratory analysis, the effects of age at diagnosis and treatment options (surgery or PET) were modelled as time varying and the others were modelled as time invariant. It also specifies a flexible functional form for the underlying hazard, making it easier to extrapolate to predictions of future outcomes.

The registry data contained a number of variables with a non-negligible proportion of missing values (Table 1). If every patient with any missing data had been excluded from analysis, a lot of useful information would have been lost. Also, because the 'missingness' is often dependent on patient characteristics, results would be biased by the exclusions. To mitigate these issues, the method of multiple imputation was used prior to fitting the models. For each patient where one or more

variables were missing, the distribution of those variables in patients with similar characteristics was used to impute values for the missing variables. In this way the dataset was completed in a probabilistically plausible way. In order to account for the randomness in completing the dataset in this way, the multiple imputation was repeated to create a collection of 1000 completed datasets. The modelling was carried out on each of these complete datasets and the results combined to produce a final result which makes maximal use of the information in the data but avoids the bias of being based on any individual imputed dataset. Further details of the imputation process are included in supplemental materials.

Exploratory analysis and derivation of the final models were carried out using the open-source statistical package R (version 3.0.1)(23). The user-contributed CRAN R package "mi" was used to implement the method of multiple imputation with chained equations (24). The Royston Parmar model was implemented using Stata 13 (StataCorp. 2013), via the module "stpm2"(25).

RESULTS

The cumulative incidence of breast cancer and other cause mortality for patients treated surgically and non-surgically were derived, after removing patients with ER negative disease and early deaths (within 91 days) (Figure 1). Non-breast cancer causes of death predominate in the PET group, due to frailer, less fit women being less likely to have surgery.

[INSERT FIGURE 1]

Five year breast cancer specific survival (BCSS) in the PET and surgery arms was 69% and 90% respectively. Figures 2 and 3 shows the Kaplan Meier estimates for BCSS by stage and for unknown

stage at diagnosis (Figure 2), by age group (Figure 3, left) and by number of co-morbidities (Figure 3, right). The curves by stage demonstrate that BCSS was inferior in patients treated with PET compared to those who received surgery, regardless of stage at diagnosis. Figure 2 shows that for patients with missing stage at diagnosis (bottom right) there was a sharp drop in BCSS in the first few months for patients who are treated with PET. This may reflect the fact that some patients in this group had undiagnosed advanced disease at diagnosis as mentioned above. The curves in Figure 3 demonstrate that BCSS remained inferior for patients receiving PET despite increasing age. The same is true for increasing numbers of co-morbidities, except for those in the highest comorbidities category. Here the degree of separation between outcomes and the width of the confidence intervals is less distinct. It is less clear that the PET choice had a detrimental effect in this group.

[INSERT FIGURE 2]

[INSERT FIGURE 3]

The survival models were fit to the datasets following multiple imputation. The results of the Cox proportional hazards (Table SM3) and Royston Parmar model (Table 2 and Figures 4 and SM1) demonstrate the effect of treatment and other covariates on BCSS. The estimates from the Cox model indicate that the hazard of BC mortality is lower in patients treated surgically. Tumour grade, nodal involvement and method of detection also have a strong influence on this outcome, with grade 3 disease and node positivity associated with inferior BCSS and screen detection being associated with better BCSS. Similar results are seen in the Royston Parmar model. The hazard ratio for surgical treatment on breast cancer specific survival, from the Royston Parmar model is shown in

Figure 4. The hazard ratio is approximately constant at around 0.37 from year 3 onwards. Hazard ratios for other covariates from the Royston Parmar model (Table 2) show that, as would be expected, patients with higher grade, larger tumour size, and nodal involvement have a higher hazard of breast cancer mortality. Screen detection is associated with a considerably lower hazard of breast cancer mortality. There are also small increases in breast cancer mortality associated with increased numbers of comorbidities and with income deprivation.

[INSERT TABLE 2]

[INSERT FIGURE 4]

DISCUSSION

The results of this analysis show that in a retrospective cohort of older breast cancer patients with ER+ disease in the UK, the hazard of breast cancer death was greater in patients treated with PET than those who received surgery. Assuming this reflects a true underlying difference in the hazard between the two treatment approaches, this will translate into a difference in overall survival. This difference is greatest in patients who would otherwise have a high underlying life expectancy, i.e. younger and healthier patients. For older, frailer patients, the high risk of death from non-breast cancer causes means that the hazard of breast cancer death would have less relative impact on overall survival, so the effect of non-surgical treatment on survival outcomes would be smaller. In some patients, the difference may be so small that PET would be the preferred treatment option in order to avoid any potential morbidity associated with surgery. Given that the registry data contains only limited data on underlying health status, it is unsafe to compare the groups in terms of overall

survival since many of the observed differences may be explained by unobserved confounding variables. Comparisons of BCSS should be less prone to this issue as the observed disease characteristics would be expected to have a more significant effect on this outcome. Higher rates of PET treatment in the UK than in many other developed countries could explain, at least in part, the inferior relative survival for breast cancer in the UK compared with a number of other developed nations in this age group.

The findings of this analysis show similar findings to that of another UK cohort study. This large study (n= 1065) looked at outcomes for a cohort of patients aged 70+ recruited between 1973 and 2009 at a single specialist centre in Nottingham, England(26). This study also demonstrated that at a population level there was a difference in BCSS between patients treated with PET and surgery. However, the magnitude of the difference was smaller than that observed in our registry cohort and estimates of BCSS were also higher in both the surgery and PET arms (95% and 84% respectively) compared with the registry cohort (90% and 69% respectively). Our data are from a larger cohort from multiple sites, rather than one single site and may therefore be more representative of practice across the whole country. In addition, the Nottingham cohort included very ER rich early operable cancer; a subgroup analysis suggested that for women with strongly ER+ tumours (H Score >250) there was no difference in the effectiveness of the two approaches. The H score was not available for the registry cohort so an equivalent analysis was not possible. The historical clinical trials comparing these treatment options suggested there was limited difference in effectiveness between the two approaches, however ER status was not measured in the majority of the trials. These trials are perhaps no longer fully representative of modern practice and outcomes, as detailed above. Even well conducted randomised trials are prone to external biases owing to issues of generalisability; due, for example, to exclusion of patients with certain characteristics or deviations from everyday clinical practice. Routine registration datasets reflects outcomes as observed in real life clinical practice; for example, compliance and adherence to endocrine therapy is likely to be worse in everyday practice than in a clinical study where treatment is more closely monitored.

Routinely collected data has the advantage of reflecting outcomes observed in clinical practice; registry data do, however, have some quality issues. There are a high proportion of missing values for a number of covariates, especially for patients in the non-surgical group. For example, tumour size and clinical node status is not always recorded from imaging reports in these patients. Missing data was addressed using multiple imputation. This approach helps to mitigate against biases which can occur if patients with missing data are excluded and the missing data is connected to the characteristics of the individuals. This contrasts with the complete case analysis approach taken by other models in the breast cancer field, for example PREDICT(27). However missing data was less of an issue for the PREDICT model, which is based only on women treated surgically and includes younger patients who are more likely to have complete data. In the present study, staging data is missing for a number of patients; patients treated non-surgically are more likely to have incomplete staging information as non-pathological staging information has historically not always been recorded. Exclusion of all patients with missing stage at diagnosis would bias results as the remaining sample would not be representative of the population as a whole. Inclusion of all patients with missing stage would also be expected to bias results; poorer survival outcomes in the PET group may result due to the inability to identify all patients who were treated non-surgically due to the presence of advanced stage disease. For this reason, multiple imputation was performed using the whole dataset. In each imputation, patients with actual or imputed Stage IV disease were excluded. The technique of multiple imputation used in this study has the advantage of propagating the uncertainty due to missing data into the estimates of covariate effects.. This is an attempt to avoid the biases which may occur when patients with missing data are excluded from analysis (and the missing data is connected to the characteristics of the data). This method is less prone to bias than other approaches to analysing registry data such as complete case analysis or treating “missing” as a category in a factor variable. There is, however, no perfect method for accounting for missing data and it may not have accounted for all biases. Analysis of the multiple imputed datasets did not raise

any concerns about the validity of the imputation approach. However, by definition it is not possible to compare against the true underlying values.

Observational studies are at risk of confounding between treatment allocation and outcomes, which leads to bias in estimates of treatment effects. The statistical techniques used in our study mitigate against confounding that is due to factors observed in the dataset. However, these techniques will not fully account for the effects of confounders which are not observed in our dataset, especially if there are confounders which are uncorrelated to observed covariates. With respect to BCSS, it was hypothesized *a priori* that disease characteristics and age were primary confounders between the outcome and treatment choice. On the other hand, unobserved characteristics such as frailty, which is not routinely collected by the registry may be accounted for in part due to its correlation with age and comorbidity and so are partially adjusted for in the various models. As a result, the key finding in the present study are unlikely to be explained as being primarily due to confounding. By contrast, it is clear that these (health) factors could have a strong confounding effect with respect to death from non-breast cancer causes, and so overall survival was not considered.

The Kaplan-Meier curves for BCSS suggest a sharper drop in the survival curve in the early part of the curve for the PET group, reflecting a number of early breast cancer deaths in this group. This pattern is not observed in comparable studies; for example, in the Nottingham cohort the difference in BCSS grows slowly over time for both groups. One possible explanation for this is potential inaccuracy in recording of metastatic disease in the cancer registration data; for example it may not be updated if stage IV cancer is detected as a result of follow up staging tests. This may also be due to avoidance of surgery in the very frail and ill, who die of other causes soon after diagnosis. Cause of death may be reported inaccurately. It is difficult to attribute death to a single cause, especially in the frail elderly, and in routine data breast cancer may be listed as the primary cause of death in cases when in fact other causes were the primary contributor. Further research is needed to determine the extent to which routine data can be used to accurately model survival outcomes in this population;

for example by collecting routine registration data alongside data collected specifically for a clinical study.

CONCLUSION

Our analysis suggests that for older breast cancer patients with ER+ disease, the hazard of breast cancer death was greater in patients treated with PET than those who received surgery. This appears to contrast with RCT data from historic trials although a trend in favour of surgery was shown on meta analysis (5, 28) and a significant advantage for surgery was shown on long term follow up of these studies (11), so the outcome is not discordant. Our findings suggest that surgery should be recommended for the majority of women, with PET being reserved for women with limited life expectancy (due to age, frailty or co-morbidity) or those who express a preference not to undergo surgery. Findings from this analysis have been used to develop a web-based clinical management algorithm to help clinical teams decide on best practice for an individual older woman. Evaluation of this tool is ongoing and the data from this study are of value in predicting what may be expected for individuals where different treatment options are being considered even though a causal effect can not be ascertained due to the non randomised nature of the data. An ongoing prospective cohort study, part of the Bridging the Age Gap in Breast Cancer (BTAG) project(29), will provide a more detailed dataset to help assess the effects of surgery in older women on survival and recurrence. The research programme is also developing and evaluating a series of decision support instruments, tailored to older women, to support them in deciding between surgery and PET. This will be targeted at those women where both options are likely to give good outcomes.

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References

1. UK CR. Breast cancer incidence statistics 2014 [Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive#age.
2. Lavelle K, Sowerbutts AM, 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. Br J Cancer. 2014;110(3):573-83.
3. Lavelle K, Downing A, Thomas J, Lawrence G, Forman D, Oliver SE. Are lower rates of surgery amongst older women with breast cancer in the UK explained by co-morbidity? Br J Cancer. 2012;107(7):1175-80.
4. (BCCOM) BCCOMP. Analysis of the management of symptomatic breast cancer diagnosed in 2004, 3rd Year Report.; 2007 December 2007.
5. Morgan J, Richards P, Ward S, Francis M, Lawrence G, Collins K, et al. Case-mix analysis and variation in rates of non-surgical treatment of older women with operable breast cancer. Br J Surg. 2015;102(9):1056-63.
6. Kiderlen M, Bastiaannet E, Walsh PM, Keating NL, Schrodi S, Engel J, et al. Surgical treatment of early stage breast cancer in elderly: an international comparison. Breast Cancer Res Tr. 2012;132(2):675-82.
7. Bastiaannet E, Liefers GJ, de Craen AJ, Kuppen PJ, van de Water W, Portielje JE, et al. Breast cancer in elderly compared to younger patients in the Netherlands: stage at diagnosis, treatment and survival in 127,805 unselected patients. Breast Cancer Res Treat. 2010;124(3):801-7.
8. Schonberg MA, Marcantonio ER, Li D, Silliman RA, Ngo L, McCarthy EP. Breast cancer among the oldest old: tumor characteristics, treatment choices, and survival. J Clin Oncol. 2010;28(12):2038-45.
9. Walters S, Maringe C, Butler J, Rachet B, Barrett-Lee P, Bergh J, et al. Breast cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK, 2000-2007: a population-based study. Br J Cancer. 2013;108(5):1195-208.
10. Morgan JL, Reed MW, Wyld L. Primary endocrine therapy as a treatment for older women with operable breast cancer - a comparison of randomised controlled trial and cohort study findings. Eur J Surg Oncol. 2014;40(6):676-84.
11. Fennessy M, Bates T, MacRae K, Riley D, Houghton J, Baum M, et al. Late follow-up of a randomized trial of surgery plus tamoxifen versus tamoxifen alone in women aged over 70 years with operable breast cancer. Brit J Surg. 2004;91(6):699-704.
12. Mustacchi G, Cazzaniga M, Pronzato P, De Matteis A, Di Costanzo F, Porcu L. Diagnosis and treatment variations in old women with early breast cancer (BC): results from the "NORA" Study. Annals of Oncology. 2004;15:59-60.
13. Gazet JC, Ford HT, Bland JM, Markopoulos C, Coombes RC, Dixon RC. Prospective Randomized Trial of Tamoxifen Versus Surgery in Elderly Patients with Breast-Cancer. Lancet. 1988;1(8587):679-81.
14. Statistics OfN. English Life Tables No.17: 2010 to 2012 2016 [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/englishlifetablesno17/2015-09-01#english-life-tables-no-17.
15. 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(6):653-67.
16. Richards P, Ward S, Morgan J, Lagord C, Reed M, Collins K, et al. The use of surgery in the treatment of ER+ early stage breast cancer in England: Variation by time, age and patient characteristics. Eur J Surg Oncol. 2016;42(4):489-96.

17. Bates T, Evans T, Lagord C, Monypenny I, Kearins O, Lawrence G. A population based study of variations in operation rates for breast cancer, of comorbidity and prognosis at diagnosis: failure to operate for early breast cancer in older women. Eur J Surg Oncol. 2014;40(10):1230-6.
18. Reed MW, Audisio RA, Wyld L. The role of surgery in the treatment of older women with breast cancer. Clin Oncol (R Coll Radiol). 2009;21(2):103-10.
19. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.
20. Morris EJ, Taylor EF, Thomas JD, Quirke P, Finan PJ, Coleman MP, et al. Thirty-day postoperative mortality after colorectal cancer surgery in England. Gut. 2011;60(6):806-13.
21. Cox Dr. Regression Models and life tables (with discussion) Journal of the Royal Statistical Society. 1972;Series B (34):187-220.
22. Royston P, Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Stat Med. 2002;21(15):2175-97.
23. R Core team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, . Vienna, Austria
24. van Buuren S G-OK. mice: Multivariate Imputation by Chained Equations in R. Journal of Statistical Software. 2011;45(3):1-67.
25. Lambert PCaR, P. Further development of flexible parametric models for survival analysis The Stata Journal. 2009;9:265-90.
26. Syed BM, Al-Khyatt W, Johnston SJ, Wong DW, Winterbottom L, Kennedy H, et al. Long-term clinical outcome of oestrogen receptor-positive operable primary breast cancer in older women: a large series from a single centre. Br J Cancer. 2011;104(9):1393-400.
27. Wishart GC, Azzato EM, Greenberg DC, Rashbass J, Kearins O, Lawrence G, et al. PREDICT: a new UK prognostic model that predicts survival following surgery for invasive breast cancer. Breast Cancer Res. 2010;12(1):R1.
28. 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(7):1025-9.
29. Collins K LK, Burton M , Reed M , Edwards A, Ring A , et al Evaluation of decision support interventions for older women with operable breast cancer: protocol for a cluster randomised controlled trial. . BMJ Open (in press) 2017.

TABLES & FIGURES

Table 1. Variables provided for analysis after pre-processing as described above and in Supplemental Materials. ER Status is shown for completeness but ER- tumours were excluded from further analysis. Missing values for grade, size, nodal status and comorbidities were addressed, prior to modelling, using multiple imputation as described in Statistical Analysis. Patients with stage IV disease or who died within 91 days of diagnosis were excluded after the multiple imputation (as likely to have had advanced disease or be unlikely to benefit from breast cancer treatment).

	n=23849	100.0%
Region		
North Yorkshire	12916	54.2%
West Midlands	10933	45.8%
Age at diagnosis		
70 - 74	6401	26.8%
75 - 79	6328	26.5%
80 - 84	5513	23.1%
85 - 89	3662	15.4%
90 - 94	1483	6.2%
95+	462	1.9%
Deprivation quintile		
1 (least deprived)	3861	16.2%
2	4868	20.4%
3	4761	19.9%
4	5060	21.2%
5	5299	22.2%
Detection route		
Screen detected	1345	5.6%
Symptomatic	22504	94.4%

Tumour stage		
I	5142	21.6%
II	8445	35.4%
III	1872	7.8%
IV	1511	6.3%
Missing	6879	28.8%
Tumour diameter (mm, invasive component)		
[0,10)	972	4.1%
[10,20)	4584	19.2%
[20,50)	8487	35.6%
50+	1370	5.7%
Missing	8436	35.4%
Grade		
1	3120	13.1%
2	10482	44.0%
3	5746	24.1%
Missing	4501	18.9%
Nodal status		
Negative	6549	27.5%
Positive	5581	23.4%
Missing	11719	49.1%
ER status		
Negative	5119	21.5%
Positive	18730	78.5%

HER2 status		
Negative	4758	20.0%
Positive	850	3.6%
Missing	18241	76.5%
Comorbidity score		
0	16688	70.0%
1	1882	7.9%
2	979	4.1%
3+	550	1.8%
Missing	3750	15.7%
Breast surgery		
No	10475	43.9%
Yes	13374	56.1%
Chemotherapy		
No	22675	95.1%
Yes	1174	4.9%
Radiotherapy		
No	15759	66.1%
Yes	8090	33.9%
Hormone therapy		
No	8558	35.9%
Yes	15291	64.1%

Table 2. Estimate of non-time-varying hazard ratios for breast cancer mortality from the Royston Parmar restricted cubic spline model

	Hazard ratio	Lower 95% CI	Upper 95% CI	p value
Comorbidity (per Charlson index point)	1.091	1.02	1.168	0.010
Symptomatic detection v screened	2.691	1.84	3.896	<0.001
Deprivation quintile 2 v 1	1.116	0.961	1.297	0.170
Deprivation quintile 3 v 1	1.105	0.951	1.297	0.213
Deprivation quintile 4 v 1	1.094	0.942	1.271	0.264
Deprivation quintile 5 v 1	1.259	1.094	1.448	0.001
Grade 2 v 1	1.391	1.185	1.632	<0.001
Grade 3 v 1	2.886	2.46	3.421	<0.001
Node positive v node negative	2.014	1.804	2.248	<0.001
Tumour size (per mm diameter)	1.011	1.008	1.013	<0.001

Figure 1: Cumulative incidence of breast cancer and other cause mortality for surgery and primary endocrine therapy(PET) treatment arms. Non-breast cancer causes of death predominate in the non-surgical group, due to the frailer, less fit women being less likely to have surgery. Five year breast cancer specific survival in the PET and surgery arms were 69% and 90% respectively.

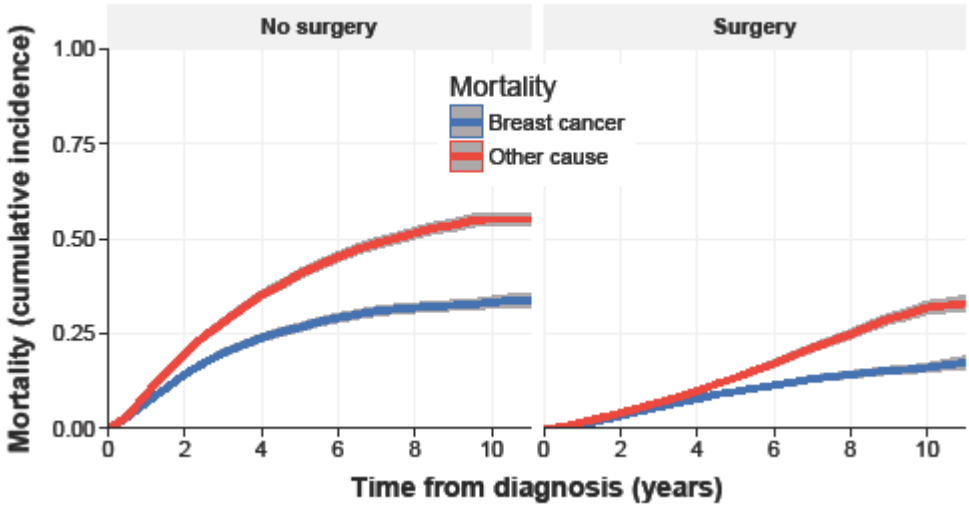

Figure 2: Kaplan Meier estimates for breast cancer specific survival (BCSS) by stage at diagnosis and for unknown stage for surgery and PET treatment arms. These curves demonstrate that BCSS is inferior in patients treated with PET compared to those receiving surgery, regardless of stage at diagnosis. The sharp drop in BCSS in the first few months for patients with missing stage (bottom right) who are treated with PET may reflect the fact that some patients in this group have advanced disease at diagnosis.

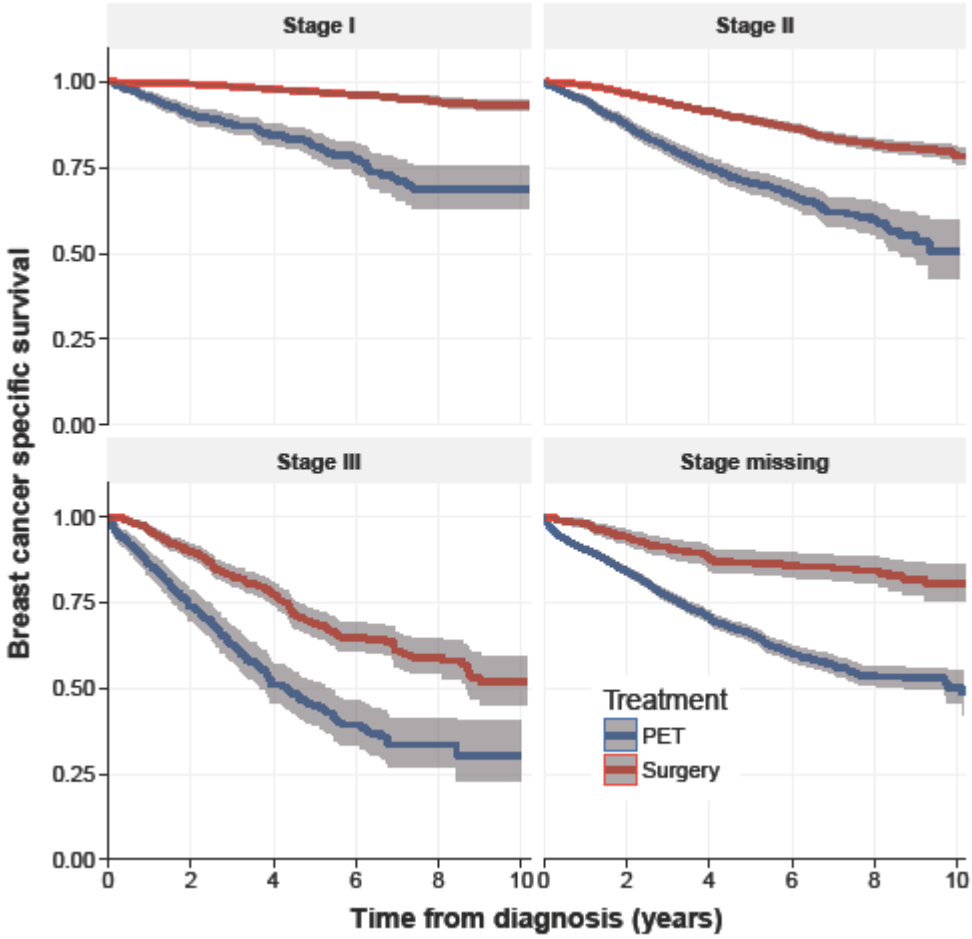

Figure 3: Breast cancer specific survival (BCSS) by age group (left) and by comorbidity score (right) for surgery and PET treatment arms. These curves demonstrate that BCSS remains inferior for patients receiving PET despite older age or increasing numbers of co-morbidities.

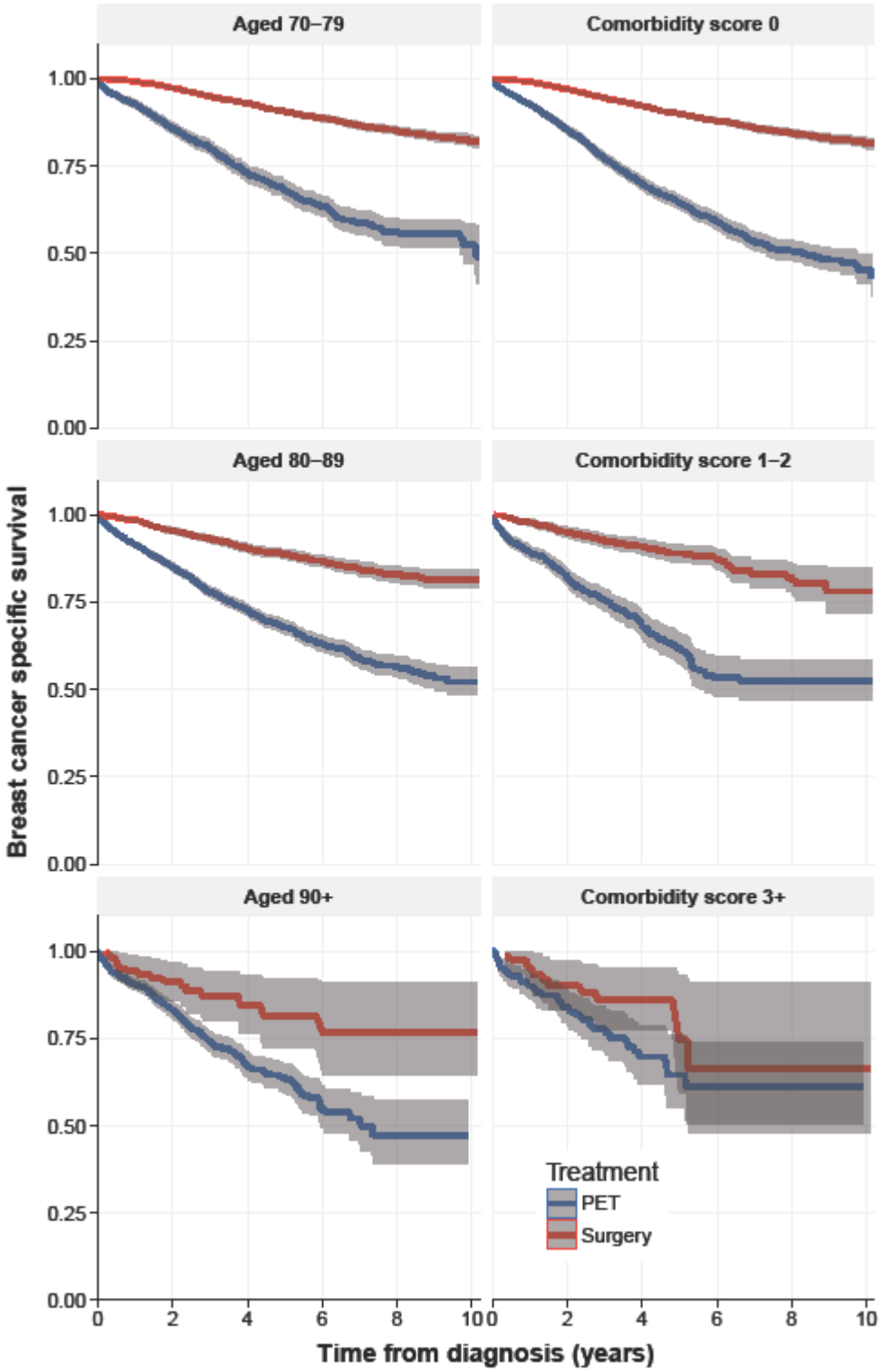

Figure 4: Time varying hazard ratio for breast cancer specific mortality for surgery versus PET treatment arms from Royston-Parmar model. The hazard ratio is approximately constant at around 0.37 from year 3 onwards