


# Survival outcomes after breast cancer surgery among older women with early invasive breast cancer in England: population-based cohort study

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## Abstract

**Background:** This study assessed the influence of age, co-morbidity and frailty on 5-year survival outcomes after breast conservation surgery (BCS) with radiotherapy (RT) *versus* mastectomy (with or without RT) in women with early invasive breast cancer.

**Methods:** Women aged over 50 years with early invasive breast cancer diagnosed in England (2014–2019) who had breast surgery were identified from Cancer Registry data. Survival estimates were calculated from a flexible parametric survival model. A competing risk approach was used for breast cancer-specific survival (BCSS). Standardized survival probabilities and cumulative incidence functions for breast cancer death were calculated for each treatment by age.

**Results:** Among 101 654 women, 72.2% received BCS + RT and 27.8% received mastectomy. Age, co-morbidity and frailty were associated with overall survival (OS), but only age and co-morbidity were associated with BCSS. Survival probabilities for OS were greater for BCS + RT (90.3%) *versus* mastectomy (87.0%), and the difference between treatments varied by age (50 years: 1.9% *versus* 80 years: 6.5%). Cumulative incidence functions for breast cancer death were higher after mastectomy (5.1%) *versus* BCS + RT (3.9%), but there was little change in the difference by age (50 years: 0.9% *versus* 80 years: 1.2%). The results highlight the change in baseline mortality risk by age for OS compared to the stable baseline for BCSS.

**Conclusion:** For OS, the difference in survival probabilities for BCS + RT and mastectomy increased slightly with age. The difference in cumulative incidence functions for breast cancer death by surgery type was small regardless of age. Evidence on real-world survival outcomes among older populations with breast cancer is informative for treatment decision-making.

## Introduction

Patient, tumour and healthcare factors influence the decision-making process between breast-conserving surgery (BCS) or mastectomy, for patients with primary early invasive breast cancer (EIBC). A mastectomy is indicated for patients with a larger tumour volume in relation to breast size, tumour multifocality, individual patient preference, unsuitability for oncoplastic breast preservation, and contraindication for adjuvant radiotherapy<sup>1</sup>. Breast preservation has become the more common approach, and in England around two-thirds (68.5%) of women who undergo breast cancer surgery receive BCS as their initial operation<sup>2</sup>. There is variation by age, as older women are more likely to receive a mastectomy compared with younger women<sup>3–5</sup>.

Randomized controlled trials demonstrated that patients who received BCS with adjuvant radiotherapy had equivalent rates of overall survival (OS) compared to women who received a mastectomy<sup>6–9</sup>. An individual patient meta-analysis of these

trials demonstrated no difference in survival between BCS with radiotherapy compared to mastectomy<sup>10</sup>. However, women aged 70+ years<sup>6,8,9</sup> and patients with co-morbidities<sup>8</sup> were excluded from these studies, suggesting the straightforward application of the trial results to the management of older women in modern clinical practice cannot be assumed.

Several subsequent observational studies have examined survival rates of women who had BCS and radiotherapy or mastectomy for EIBC<sup>11–23</sup>. Although these studies had less-restrictive inclusion criteria than RCTs and represent a more contemporary clinical setting, few of them explored whether there were age-specific differences in survival, and information on co-morbidities was often not available<sup>12,14,16,18,19,23</sup>. None included a measure of frailty, a distinct and valuable concept of ageing. Consequently, clinicians still have limited evidence on the impact of age, frailty and co-morbidity on survival outcomes after breast cancer surgery.

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Seven observational studies have reported more favourable OS or breast cancer-specific survival (BCSS) after BCS with radiotherapy compared to mastectomy<sup>12,17–20,22,23</sup>. Owing to methodological limitations of the published observational literature, uncertainty remains as to the standing of these findings, especially among older patients, in clinical practice. For example, there are shortcomings with using HRs as the only reported outcome measure in observational research, as some studies present a single estimate for the entire study follow-up. This assumes proportional hazards over time, which is often impractical<sup>24</sup>. Translating traditional HRs to measures that are applicable to clinical practice and aid understanding (such as survival probabilities) would provide a more valuable addition to traditional survival analysis methods.

The objective of this paper was to evaluate the impact of age at diagnosis, number of co-morbidities and degree of frailty on OS/BCSS after locoregional treatment (BCS and radiotherapy or mastectomy with or without radiotherapy) for EIBC.

## Methods

### Data sources

This population-based cohort study was performed alongside the work of the National Audit of Breast Cancer in Older Patients (NABCOP; [www.nabcop.org.uk](http://www.nabcop.org.uk)). The NABCOP was a national clinical audit that investigated disparities in the diagnosis and treatment of older women with breast cancer compared to younger women. Further information on the NABCOP cohort is described in the Annual Reports and methodology documents<sup>3,25</sup>.

The NABCOP received pseudonymized national cancer registration data (patient- and tumour-level information) on women with breast cancer diagnosed in English NHS trusts between 1 January 2014 and 31 December 2019 from the National Cancer Registration and Analysis Service. Patient registration records were then linked to their corresponding records from the Cancer Outcomes and Services Data set and other national data sets that provided information on in-patient hospital admissions (Hospital Episode Statistics [HES]), chemotherapy (Systemic Anti-Cancer Therapy data set), radiotherapy (National Radiotherapy Data set) and endocrine therapy prescriptions (Primary Care Prescription Database). Mortality information (cause/date of death and vital status) was provided by the Office for National Statistics death register.

This study was exempt from NHS Research Ethics Committee approval because it involved analysis of pseudonymized linked data collated for the purpose of service evaluation as part of the NABCOP. The NABCOP has approval for processing healthcare information under Section 251 (reference number: 16/CAG/0079).

### Cohort population

The study included women aged 50+ years with EIBC (stages I–IIIA) where the date of breast surgery was within 12 months (and was at least 7 days) from the date of diagnosis. Exclusion criteria were women recorded with metastatic disease, individual tumour/nodal stage values incompatible with EIBC, women who received BCS without radiotherapy or missing values in key variables (Fig. S1).

### Variable definitions

Locoregional treatment was categorized into BCS with radiotherapy or mastectomy with or without radiotherapy. Type of breast surgery was defined as the ultimate type of surgery received; women who received BCS followed by mastectomy (which was within

3 months) were therefore recorded as receiving a mastectomy. The OPCS Classification of Interventions and Procedures codes within the HES data set were used to define type of breast and axillary surgery. Radiotherapy was recorded as received if a radiotherapy date existed within 6 months from the date of surgery (or 12 months if adjuvant chemotherapy was received). Women were categorized as receiving neoadjuvant chemotherapy if it began within 6 months of diagnosis and before the date of initial surgery, and adjuvant chemotherapy was defined as beginning within 6 months from the date of ultimate surgery.

Patient demographics included age at diagnosis, route to diagnosis (screened, non-screened), co-morbidity index, degree of frailty and deprivation level. Tumour characteristics included tumour stage (T1–T3), nodal stage (N0–N2), invasive grade (G1–G3), oestrogen receptor (ER) status (positive (including borderline), negative) and human epidermal growth factor receptor 2 (HER2) status (positive, borderline, negative).

Co-morbidities were defined with the Royal College of Surgeons Charlson co-morbidity index<sup>26</sup>. ICD-10 codes for specific conditions were identified from in-patient admissions within HES up to 2 years prior to diagnosis, and grouped by number of co-morbidities (0, 1, 2, 3+). Frailty was measured using the Secondary Care Administrative Records Frailty index<sup>27</sup>. Frailty deficits (such as social vulnerability) were identified from ICD-10 codes within HES, with a 2-year lookback from diagnosis, and grouped into level of frailty (fit, mild, moderate, severe). Deprivation was assessed using the Index for Multiple Deprivation (IMD), a measure of deprivation at a local area level. Each geographical area was assigned their quintile value based on their IMD rank, with 1 corresponding to the most deprived and 5 the least deprived<sup>28</sup>.

### Statistical analysis

Analysis was performed using Stata V17. Descriptive statistics summarized unadjusted percentages of locoregional treatment stratified by patient, tumour and treatment characteristics.

Study outcomes were 5-year OS and BCSS. A landmark approach was used to mitigate against immortal time bias, given the difference in treatment duration between BCS with radiotherapy and mastectomy. A landmark time of 6 months after initial surgery was selected, and patients who died or were censored during this time were excluded from the survival analysis. Follow-up ended at date of death or censoring. Patients who were alive at the end of the follow-up period were censored on the last date of vital status (October 2021). Median follow-up was calculated using reverse Kaplan–Meier estimates.

Initially, the association between patient, tumour and treatment factors with survival were estimated from a Cox proportional hazards model, to explore relevant variables for inclusion. Proportional hazards for each variable were assessed by plotting observed Kaplan–Meier survival curves and comparing them with predicted curves. Model discrimination was assessed using the Royston D statistic and calibration was assessed using receiver operating characteristic analysis. Variables were included if they were deemed clinically relevant or improved model fit based on Akaike's Information Criteria and Bayesian Information Criteria (BIC).

For OS, estimates of the proportion of patients alive at 5 years for different patient subgroups were derived using the Kaplan–Meier method. For BCSS, these estimates were derived using a competing-risks approach that distinguished between breast cancer (outcome of interest) and non-breast cancer deaths (the competing risk). BCSS was derived as 1 minus the cumulative incidence of death from breast cancer.

Unadjusted and adjusted HRs with their 95% confidence intervals for age, co-morbidity index, frailty level and type of locoregional treatment were obtained from a multivariable flexible parametric survival model. The model estimating the adjusted HRs included the additional explanatory variables: IMD quintile, tumour stage, nodal stage, referral source, ER status, HER2 status, grade, axillary surgery, chemotherapy, post-mastectomy radiotherapy and endocrine therapy prescription. The hazards for the different values of ER status and endocrine treatment were found to be non-proportional, and these were included as time-varying components within the model. Initially, age at diagnosis was grouped into categories, to understand how the HR changed with increasing age, and after adjusting for other covariates.

For OS and BCSS, the survival models were then extended by including interaction terms in order to examine whether the effect of receiving a mastectomy (versus BCS with radiotherapy) varied by age, co-morbidity and frailty<sup>29</sup>. In these models, age was included as a continuous variable and, for both outcomes, a spline with 2 degrees of freedom was used to allow for any non-linear association between age and survival. A decrease in the BIC was used as the rule to judge the value of the interaction terms. The BIC is a common method to aid in model selection, and favours the model which is deemed 'most plausible' according to the data<sup>30</sup>.

To aid interpretation of the survival model results, standardized survival probabilities and standardized cumulative incidence functions were estimated for both BCS with radiotherapy and for mastectomy. For OS, standardized survival probabilities were predicted for each individual and then averaged across the study population<sup>31,32</sup>. For BCSS, standardized cumulative incidence functions for the event of death from breast cancer were estimated, to account for the competing events of death due to other causes<sup>31</sup>.

All statistical tests were two-sided and  $P < 0.001$  was considered to demonstrate strong evidence of an association. A smaller than typical  $P$  was selected given the large sample size of the study.

## Results

The study consisted of 101 654 women with EIBC who received surgery within 12 months from diagnosis: 34 329 (33.8%) were aged 50–59 years, 36 685 (36.1%) were 60–69 years, 22 753 (22.4%) were 70–79 years and 7887 (7.8%) were 80+ years (Fig. S1).

Table 1 describes the cohort characteristics, stratified by locoregional treatment. A total of 72.2% (73 360) of patients received BCS with radiotherapy and 27.8% ( $N = 28\,294$ ) received a mastectomy. Compared with women who had a mastectomy, a greater percentage of women who received BCS with radiotherapy were younger (50–59 years: 35.0% versus 30.5%), had no co-morbidities (no co-morbidities: 89.6% versus 86.1%) or were not frail (83.4% versus 79.0%). A greater percentage of patients who had a mastectomy received chemotherapy compared with women who had BCS with radiotherapy, although the percentage of women who had a record of an endocrine therapy prescription was similar (Table 2). Some 41.4% (11 705) of patients who had a mastectomy received radiotherapy.

### Association between survival and age, co-morbidity, frailty and type of locoregional treatment

Median follow-up was 4.5 years (i.q.r. 3.1 years–6.0 years) and comparable for BCS with radiotherapy and mastectomy. Among all women, 5-year OS was 89.2% (95% c.i. 88.9 to 89.4) and BCSS

was 95.3%. As expected, OS was worse among women as age, the number of co-morbidities, and the degree of frailty increased, as shown by the unadjusted HR in Table 3. The addition of the other patient and tumour characteristics reduced the estimated effect size for age, number of co-morbidities and levels of frailty (Table 3). In addition, after adjusting for other key variables, there was strong evidence that all three factors remained associated with OS ( $P < 0.001$ ). The adjusted HR for mastectomy (versus BCS with radiotherapy) was also smaller than the unadjusted HR after the additional patient and tumour characteristics were added to the model.

The cumulative incidences of death at 5 years from breast cancer and non-breast cancer causes were 4.7% and 6.1% respectively. There was a similar pattern of associations between BCSS and age, number of co-morbidities, frailty level and type of locoregional treatment (Table S1). As before, the adjusted HRs were smaller than the unadjusted. However, there was no evidence of an association between BCSS and frailty ( $P = 0.540$ ). The adjusted HRs for mastectomy (versus BCS with radiotherapy) were similar for OS (adjusted HR 1.41, 95% c.i. 1.33 to 1.49) and BCSS (adjusted HR 1.39, 95% c.i. 1.27 to 1.52).

### Association between survival and age, co-morbidity and frailty by type of locoregional treatment

The models for OS and BCSS were extended to include interaction terms, to examine whether there was evidence that the adjusted HRs for age, co-morbidity and frailty differed by type of locoregional treatment. For co-morbidity and frailty, adding the interaction terms did not decrease the BIC for either OS or BCSS. It was therefore judged that there was insufficient evidence to suggest the association between survival and patient fitness differed by locoregional treatment.

Adding the interaction term for age and locoregional treatment also did not decrease the BIC for either the OS or BCSS models, and it was again concluded that there was insufficient evidence to suggest the HR for mastectomy changed with age. For completeness, Fig. S2 shows how the HR for mastectomy was estimated to change with age for the OS and BCSS models. For OS, the HR for mastectomy was estimated to be highest for women aged 50 at approximately 1.8 before falling to around 1.3 for women aged 80+ years. For BCSS, the HR for mastectomy exhibited a different pattern for age, starting at a value of approximately 1.4 for women aged 50, increasing to a peak of 1.5 when age reached 65, before falling towards a value of 1 as age increased to 90 years. The inconsistency between the two patterns was considered to be another reason for caution and deciding there was insufficient evidence to conclude the HR for mastectomy changed with age.

### Translation of the model results to survival probabilities

Figure 1 describes the standardized survival probabilities for OS, and Fig. 2 the standardized cumulative incidence functions for BCSS, among women who had BCS with radiotherapy and who had a mastectomy (as well as the difference). Although the HRs for mastectomy were similar for both OS and BCSS, the different baseline hazards produced a smaller difference for the BCSS estimates. At 5 years after surgery, the standardized survival probabilities for OS were 90.3% (95% c.i. 90.0 to 90.6) for BCS with radiotherapy and 87.0% (95% c.i. 86.6 to 87.4) for mastectomy, a difference of –3.3% (95% c.i. 2.7 to 3.8). At 5 years, the standardized cumulative incidence functions for breast cancer death under BCS

**Table 1 Patient and tumour characteristics among women with early invasive breast cancer who received breast surgery in England, diagnosed from 2014 to 2019, overall and according to locoregional treatment**

	Total	Locoregional treatment	
		BCS + RT	Mastectomy ± RT
Total (n)	101 654	73 360	28 294
<b>Age (years)</b>			
50–59	34 329 (33.8)	25 704 (35.0)	8625 (30.5)
60–69	36 685 (36.1)	28 788 (39.2)	7897 (27.9)
70–79	22 753 (22.4)	15 389 (21.0)	7364 (26.0)
80+	7887 (7.8)	3479 (4.7)	4408 (15.6)
<b>IMD</b>			
1—Most deprived	15 512 (15.3)	10 859 (14.8)	4653 (16.4)
2	17 980 (17.7)	12 876 (17.6)	5104 (18.0)
3	21 279 (20.9)	15 547 (21.2)	5732 (20.3)
4	23 160 (22.8)	16 790 (22.9)	6370 (22.5)
5—Least deprived	23 723 (23.3)	17 288 (23.6)	6435 (22.7)
<b>Referral source</b>			
Screened	50 859 (50.0)	42 772 (58.3)	8087 (28.6)
Non-screened	50 795 (50.0)	30 588 (41.7)	20 207 (71.4)
<b>Charlson Index</b>			
0	90 127 (88.7)	65 759 (89.6)	24 368 (86.1)
1	8292 (8.2)	5635 (7.7)	2657 (9.4)
2	2387 (2.3)	1500 (2.0)	887 (3.1)
3+	848 (0.8)	466 (0.6)	382 (1.4)
<b>SCARF Index</b>			
Fit	83 570 (82.2)	61 206 (83.4)	22 364 (79.0)
Mild	10 661 (10.5)	7545 (10.3)	3116 (11.0)
Moderate	5772 (5.7)	3766 (5.1)	2006 (7.1)
Severe	1651 (1.6)	843 (1.1)	808 (2.9)
<b>T stage</b>			
T1	59 725 (58.8)	50 734 (69.2)	8991 (31.8)
T2	37 372 (36.8)	21 884 (29.8)	15 488 (54.7)
T3	4557 (4.5)	742 (1.0)	3815 (13.5)
<b>N stage</b>			
N0	72 797 (71.6)	57 491 (78.4)	15 306 (54.1)
N1	24 769 (24.4)	14 325 (19.5)	10 444 (36.9)
N2	4088 (4.0)	1544 (2.1)	2544 (9.0)
<b>ER status</b>			
Positive	87 640 (86.2)	64 339 (87.7)	23 301 (82.4)
Negative	14 014 (13.8)	9021 (12.3)	4993 (17.6)
<b>HER2 status</b>			
Positive	11 530 (11.3)	6975 (9.5)	4555 (16.1)
Negative	80 199 (78.9)	59 126 (80.6)	21 073 (74.5)
Borderline	9925 (9.8)	7259 (9.9)	2666 (9.4)
<b>Grade</b>			
G1	16 552 (16.3)	14 264 (19.4)	2288 (8.1)
G2	56 607 (55.7)	40 431 (55.1)	16 176 (57.2)
G3	28 495 (28.0)	18 665 (25.4)	9830 (34.7)

Values are n (%). BCS, breast-conserving surgery; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; IMD, Index for Multiple Deprivation; RT, radiotherapy; SCARF index, Secondary Care Administrative Records Frailty index.

with radiotherapy were 3.9% (95% c.i. 3.7 to 4.2) and 5.1% (95% c.i. 4.9 to 5.4) for mastectomy, a difference of 1.2% (95% c.i. 0.8 to 1.6).

Examining the standardized survival probabilities by age revealed further differences between the two survival outcomes. For OS, the baseline hazard for BCS with radiotherapy increased with age. Consequently, the difference in the survival curves becomes larger for older women (Fig. 3), being 1.9% for women aged 50 years and 6.5% for women aged 80 years. In contrast, for BCSS, the baseline hazard for BCS with radiotherapy remained small for women across the age range, and this translated into age-specific cumulative incidence functions that were very similar for BCS with radiotherapy and mastectomy (Fig. 4). The difference in standardized cumulative incidence functions for breast cancer death ranged from 0.9% for women aged 50 years to 1.2% for women aged 80 years.

## Discussion

This population-based cohort study of just over 100 000 women with EIBC in England investigated the association of age and patient fitness with survival outcomes after breast cancer surgery. Investigating the associations between age, co-morbidity and frailty with survival outcomes within contemporary cohorts is important for understanding survival outcomes for older patients with breast cancer<sup>33</sup> and in real-world settings. It is important to include both co-morbidity and frailty as confounders, as they are distinct health entities. The results from this paper can be shared with patients to inform discussions about their diagnosis and aid in the decision-making on treatment.

This study found higher levels of co-morbidity and frailty were associated with lower adjusted rates of 5-year OS. Furthermore,



the results suggest both co-morbidity and frailty are independently associated with poorer OS, after adjusting for each other and other important factors, among women who receive surgery for EIBC. While increasing age and greater number of co-morbidities were associated with lower BCSS, there was no evidence of an association with frailty. These findings are consistent with those from a previous study that found no association between degree of frailty and BCSS among women aged 65+ years with EIBC<sup>34</sup> and other studies that have reported an association between higher levels of co-morbidity and

inferior BCSS<sup>35–38</sup>. For more co-morbid patients, this reduction in survival was often associated with less extensive or omission of treatment. Ring et al. have demonstrated in a retrospective analysis of patients from the ATAC (Arimidex, Tamoxifen Alone or in Combination) study, that in patients with no co-morbidities, the risk of breast cancer recurrence was dominant over death from other causes, but as co-morbidity level increased, death from non-breast cancer causes had a greater influence<sup>39</sup>. This disparity became more prominent as age increased<sup>39</sup>. Among the current patient cohort, age, co-morbidity and frailty did not have a differential effect on survival outcomes after BCS with radiotherapy or a mastectomy.

At 5 years after surgery, the adjusted HRs were favourable for BCS with radiotherapy compared with mastectomy for both OS and BCSS. However, when translated into a standardized survival probability, the differences were small (3.3% for OS; 1.2% for BCSS). For OS, when examined by age, the difference between the type of locoregional treatment increased among older women compared with younger women, but this was because the baseline risk of death increased with age. The difference in standardized survival between BCS with radiotherapy and mastectomy remained small across the age groups for BCSS.

Several observational studies have compared survival outcomes between BCS with radiotherapy versus mastectomy and explored the impact of age<sup>17,18,20,22,23</sup>. Using data from the United States, one study found higher unadjusted OS estimates in women aged 50+ years who received BCS with radiotherapy compared with mastectomy, but no difference was seen for women aged <50 years<sup>17</sup>. Varying results on whether survival outcomes differed by age were reported by two other studies<sup>17,22</sup>. Although both studies analysed a large cohort of patients with population coverage, length of follow-up differed by 7.5 years, making it challenging to directly compare results (median follow-up 4.0 years versus 11.5 years). Two other studies reported improved OS across all age groups with BCS and radiotherapy<sup>18,23</sup>, whereas another found improved OS only in women aged 40+ years<sup>20</sup>. The results for BCSS

**Table 2 Type of axillary surgery and adjuvant treatments, stratified by type of surgery (BCS versus mastectomy)**

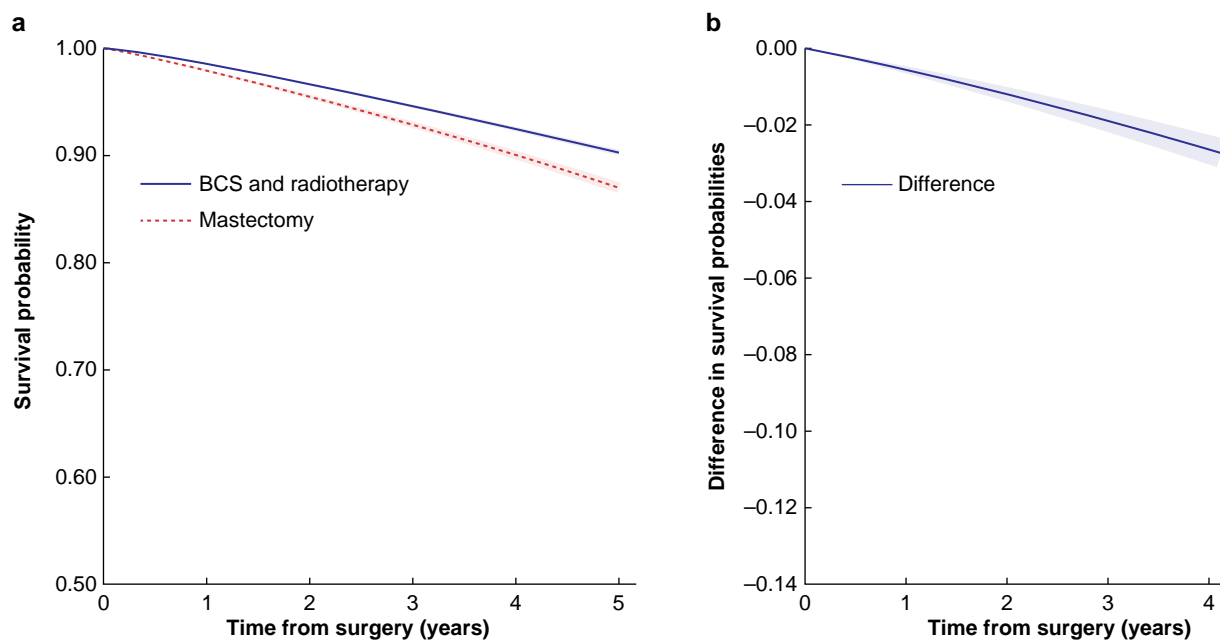
	Total	Type of surgery	
		BCS	Mastectomy
<b>Axillary surgery</b>			
SNB	80 207 (78.9)	62 527 (85.2)	17 680 (62.5)
AND	11 199 (11.0)	4844 (6.6)	6355 (22.5)
SNBAND	8029 (7.9)	4376 (6.0)	3653 (12.9)
None	2219 (2.2)	1613 (2.2)	606 (2.1)
<b>Chemotherapy</b>			
None	73 561 (72.4)	55 271 (75.3)	18 290 (64.6)
Adjuvant	21 462 (21.1)	14 354 (19.6)	7108 (25.1)
Neoadjuvant	6631 (6.5)	3735 (5.1)	2896 (10.2)
<b>Radiotherapy</b>			
No	16 589 (16.3)	0 (0.0)	16 589 (58.6)
Yes	85 065 (83.7)	73 360 (100.0)	11 705 (41.4)
<b>Endocrine therapy prescription</b>			
No	16 978 (16.7)	11 341 (15.5)	5637 (19.9)
Yes	84 676 (83.3)	62 019 (84.5)	22 657 (80.1)

Values are n (%). AND, axillary node dissection; BCS, breast-conserving surgery; SNB, sentinel node biopsy; SNBAND, sentinel node biopsy and axillary node dissection.

**Table 3 Five-year overall survival rates alongside unadjusted and adjusted hazard ratios (with 95% confidence intervals) according to age, co-morbidity, frailty and type of locoregional treatment**

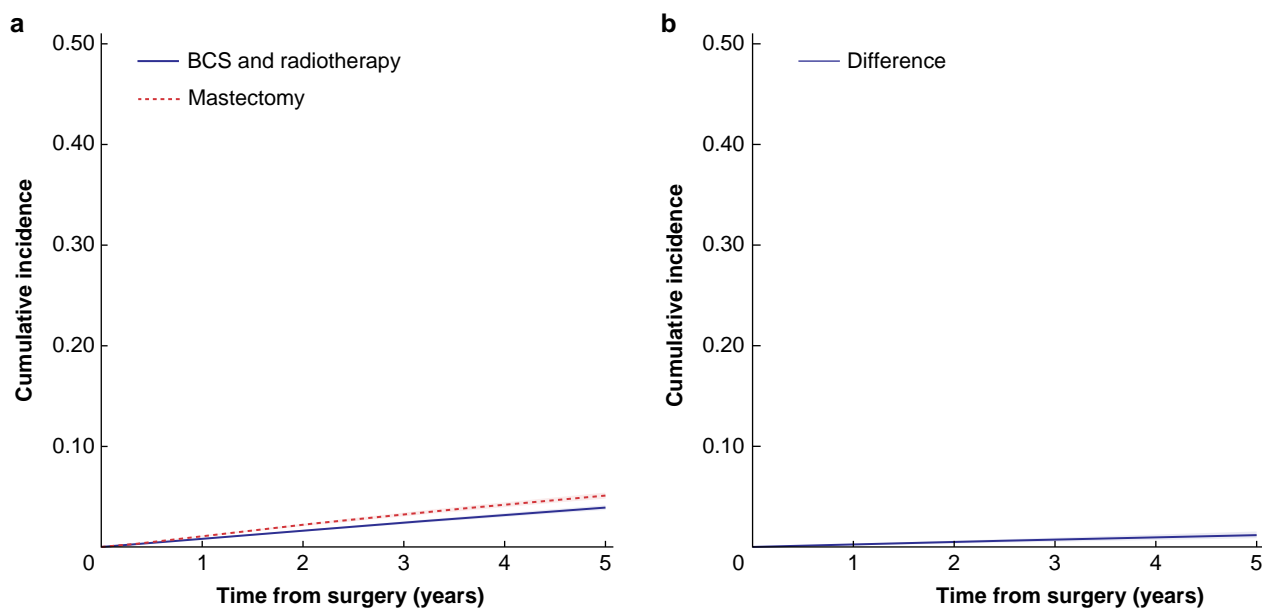
	5-year overall survival (95% c.i.)	Unadjusted hazard ratio (95% c.i.)	Adjusted hazard ratio (95% c.i.)	Grouped P
All women	89.2 (88.9, 89.4)	–	–	–
<b>Age (grouped), (years)</b>				
50–59	94.7 (94.4, 94.9)	1.00	1.00	–
60–69	92.5 (92.1, 92.8)	1.37 (1.28, 1.47)	1.54 (1.44, 1.65)	
70–79	84.5 (83.9, 85.1)	2.99 (2.80, 3.20)	2.39 (2.22, 2.57)	
80+	63.2 (61.8, 64.5)	7.98 (7.46, 8.55)	4.18 (3.85, 4.54)	
<b>Age (continuous)</b>				<0.001
Spline × 1	–	–	1.56 (1.52, 1.60)	
Spline × 2	–	–	0.95 (0.93, 0.97)	
<b>Charlson Index</b>				<0.001
0	90.5 (90.3, 90.7)	1.00	1.00	
1	82.4 (81.3, 83.4)	1.98 (1.86, 2.12)	1.27 (1.17, 1.39)	
2	71.4 (68.9, 73.8)	3.37 (3.07, 3.70)	1.55 (1.37, 1.75)	
3+	55.5 (50.5, 60.2)	6.10 (5.38, 6.91)	2.05 (1.74, 2.41)	
<b>SCARF Index</b>				<0.001
fit	90.9 (90.7, 91.1)	1.00	1.00	
mild	86.3 (85.5, 97.1)	1.54 (1.45, 1.65)	1.06 (0.98, 1.15)	
moderate	76.8 (75.3, 78.2)	2.76 (2.57, 2.98)	1.30 (1.18, 1.43)	
severe	56.7 (53.3, 60.0)	5.91 (5.39, 6.48)	1.58 (1.38, 1.81)	
<b>Type of surgery</b>				<0.001
BCS + RT	92.4 (92.2, 92.7)	1.00	1.00	
Mastectomy +/- RT	80.9 (80.3, 81.4)	2.99 (2.86, 3.13)	1.41 (1.33, 1.49)	

Age is included as categories for the unadjusted hazard ratios for ease of interpretation. Key: the other explanatory variables in the model used to produce adjusted results were: IMD quintile, tumour stage, nodal stage, referral source, ER status, HER2 status, grade, axillary surgery, chemotherapy, post-mastectomy radiotherapy, and endocrine therapy prescription. The adjusted HRs for co-morbidity, frailty and LRT type were estimated from the model with age as a continuous (spline) variable. BCS, breast-conserving surgery; RT, radiotherapy; SCARF Index, Secondary Care Administrative Records Frailty index.



**Fig. 1** Standardized survival probabilities among all women, with 95% confidence intervals

**a** Standardized survival probabilities for the event of overall survival by type of locoregional treatment. **b** The difference in standardized survival probabilities for the event of overall survival under breast-conserving surgery (BCS) with radiotherapy and under mastectomy.



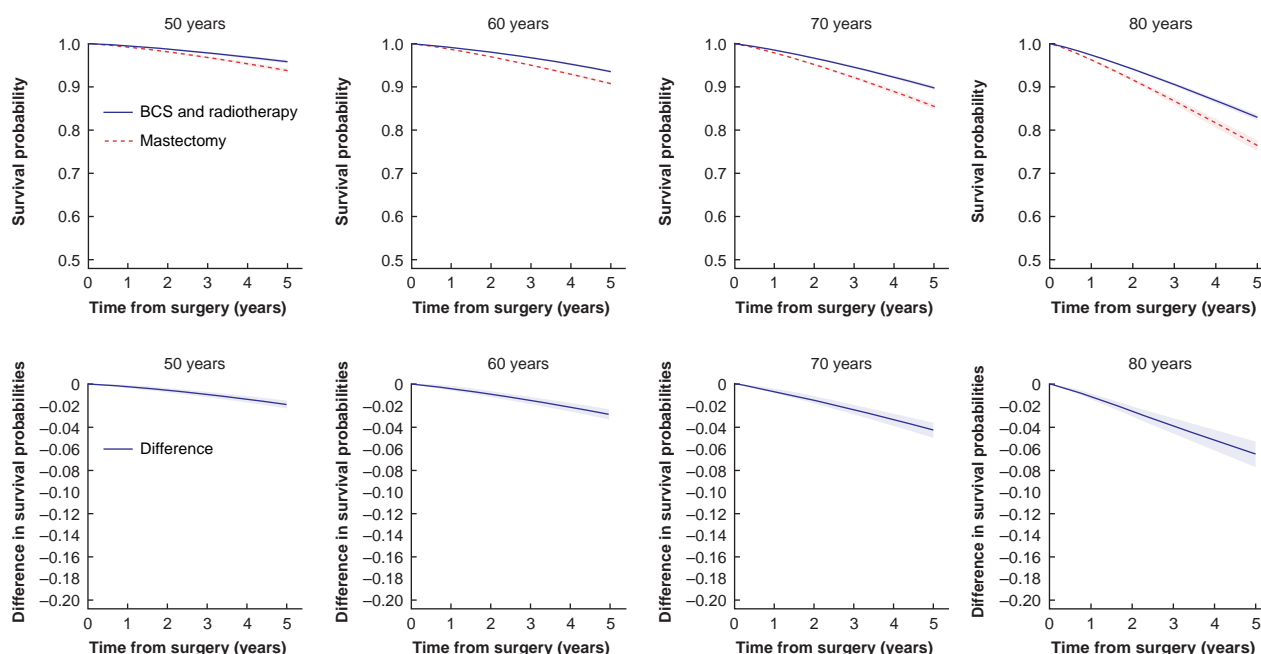
**Fig. 2** Standardized cumulative incidence of breast cancer death according to a type of locoregional treatment and b their difference

were variable across studies, with improved survival associated with BCS and radiotherapy either across all age groups<sup>18</sup>, only among patients aged 50+ years<sup>20</sup>, or minimal to no difference in BCSS between type of locoregional treatment regardless of age<sup>23</sup>.

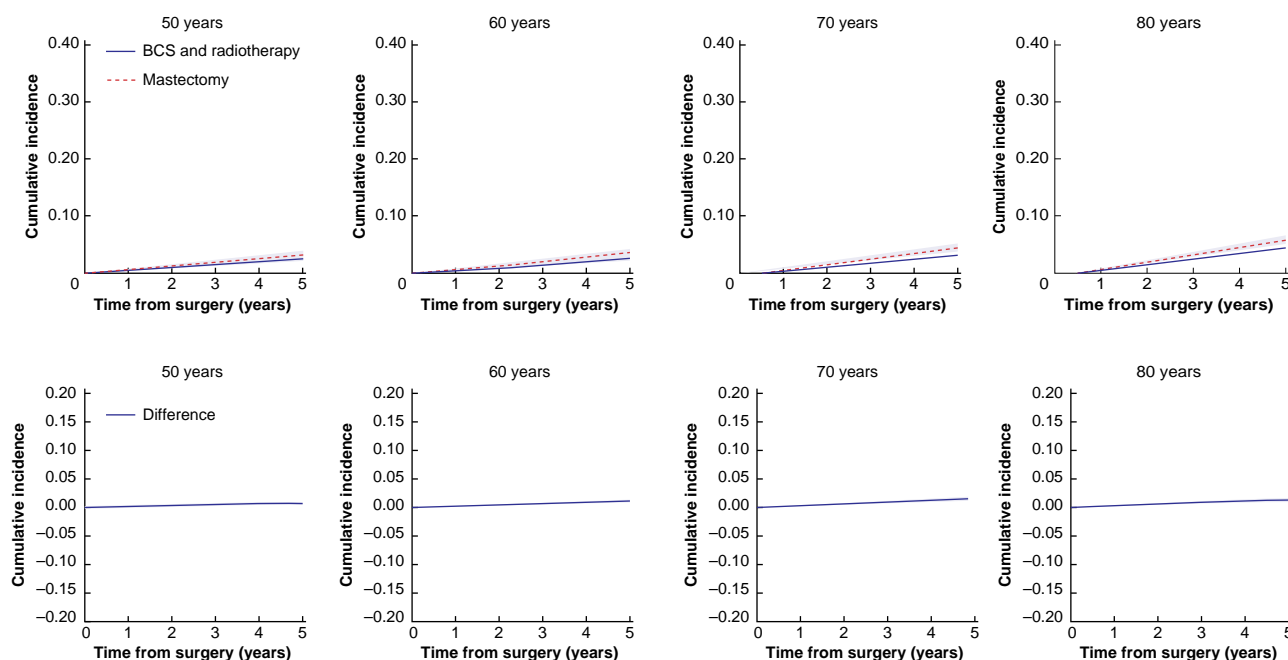
Each of the above studies used a variety of statistical methods and included women across different age ranges, making it challenging to synthesize the evidence and draw meaningful conclusions. Unlike the present analysis, none included information on both co-morbidity and frailty, and only one used a landmark approach to minimize immortal time bias. With these methodological limitations, it is not reasonable to conclude survival superiority of BCS with radiotherapy over mastectomy based on observational

data alone<sup>40</sup>. The current analysis highlights the value of presenting standardized survival estimates, alongside traditional HRs, as a more informative method to explore outcomes and aid clinical interpretation<sup>32</sup>.

There are several strengths to this study. It included a large cohort of women, diagnosed in a contemporary clinical setting using national cancer registration data, reflecting modern-day practice. Information on screening status was available, but was not for other population-based studies. The impact of immortal time bias was mitigated against, but was not considered in almost all other observational analyses. As older patients are more likely to have co-morbidities, this will influence rates of OS when reviewed by



**Fig. 3** Standardized survival probabilities, as well as their difference, for the event of overall survival after BCS with radiotherapy and after mastectomy, by age at diagnosis (with 95% confidence intervals)



**Fig. 4** Standardized cumulative incidence of breast cancer death for type of locoregional treatment and their difference, according to age at diagnosis (with 95% confidence intervals)

age, as there is a greater chance of competing risks of dying from causes other than breast cancer. By assessing BCS alongside OS, a more comprehensive picture of the effects of age and patient fitness on outcomes after breast cancer surgery is provided.

This study has limitations. The median follow-up time of 4.5 years is relatively short, although this allowed analysis of outcomes for contemporaneous treatment practices in England. Whereas national data that cover a diverse patient cohort were used, the analysis excluded women with missing data in key variables, which might reduce generalizability. Second, the

analysis controlled for several important patient, tumour and treatment factors, but there might be residual bias from unmeasured confounding factors. In addition, the selection of patient BCS and mastectomy cohorts will inherently be based on clinician and patient preferences. For example, clinicians may offer BCS in patients with greater co-morbidity or who are deemed less fit for surgery, or on the contrary may decide for mastectomy for the less fit in order to avoid reoperation after BCS for incomplete excision margins and the need for radiotherapy. Finally, co-morbidity and frailty indices rely on information within

administrative data sets and are potentially affected by errors in coding, although evidence suggests overall accuracy of routinely collected data is high and has improved over time<sup>41</sup>. The indices only identify medical conditions or frailty deficits for women who had an in-patient admission within the 2 years prior to diagnosis. Some patients who have frailty or co-morbidities with no hospital admissions prior to diagnosis may therefore be misclassified. However, the indices are likely to capture the most severe co-morbidities or frailty deficits, which are therefore likely to have a greater impact on outcomes.

This study examined the impact of patient age and fitness on outcomes after breast cancer surgery for women with EIBC in England from 2014 to 2019. It found that increasing age and a greater number of co-morbidities were associated with lower 5-year BCSS, but there was no evidence of an association with frailty. There was no evidence that patient age and fitness had a differential effect on 5-year survival outcomes after BCS with radiotherapy or mastectomy. These findings may facilitate discussions on selection of initial breast surgery type with older women, given recent reports of higher mastectomy rates among women aged 70+ years in England and Wales<sup>5</sup>. Although the differences in the standardized 5-year OS between BCS with radiotherapy and mastectomy increased among older women, this was not seen for 5-year standardized BCSS. The difference remained approximately 1% for all patient ages. The use of standardized survival probabilities alongside HRs is recommended for future research when evaluating evidence from observational studies that assess survival by type of surgery for breast cancer.

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This work uses data that have been provided by patients and collected by the NHS as part of their care and support. The data are collated, maintained and quality assured by the National Disease Registration Service, which is part of NHS Digital.

## Disclosure

The authors declare no conflict of interest.

## Supplementary material

[Supplementary material](#) is available at *BJS Open* online.

## Data availability

This work uses data that have been provided by patients and collected by the NHS as part of their care and support. The data are collated, maintained and quality assured by the National Disease

and Registration Service (NDRS), which is part of NHS England. The Data Access and Release Service (DARS) manage applications and enquiries for access to NDRS cancer registration data.

## Authors' contributions

KM: Conceptualization; Methodology; Formal analysis; Visualization; Writing—original draft; Writing—review & editing. MRG: Conceptualization; Data curation; Methodology; Writing—review & editing. JM: Conceptualization; Data curation; Writing—review & editing. KC: Conceptualization; Data curation; Writing—review & editing. DD: Conceptualization; Methodology; Writing—review & editing. KH: Conceptualization; Methodology; Writing—review & editing. MP: Conceptualization; Methodology; Writing—review & editing; Supervision. DAC: Conceptualization; Methodology; Formal analysis; Writing—review & editing; Supervision

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