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Original Article

The Association Between Survival and Receipt of Post-mastectomy Radiotherapy According to Age at Diagnosis Among Women With Early Invasive Breast Cancer: A Population-Based Cohort Study

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Abstract

Aims: Clinical trials of post-mastectomy radiotherapy (PMRT) for early invasive breast cancer (EIBC) have included few older women. This study examined whether the association between overall survival or breast cancer-specific survival (BCSS) and receipt of PMRT for EIBC altered with age.
Materials and methods: The study used patient-level linked cancer registration, routine hospital and radiotherapy data for England and Wales. It included 31 243 women aged ≥50 years diagnosed between 2014 and 2018 with low- (T1-2N0), intermediate- (T3N0/T1-2N1) or high-risk (T1-2N2/T3N1-2) EIBC who received a mastectomy within 12 months from diagnosis. Patterns of survival were analysed using a landmark approach. Associations between overall survival/BCSS and PMRT in each risk group were analysed with flexible parametric survival models, which included patient and tumour factors; whether the association between PMRT and overall survival/BCSS varied by age was assessed using interaction terms.
Results: Among 4711 women with high-risk EIBC, 86% had PMRT. Five-year overall survival was 70.5% and BCSS was 79.3%. Receipt of PMRT was associated with improved overall survival [adjusted hazard ratio (aHR) 0.75, 95% confidence interval 0.64–0.87] and BCSS (aHR 0.78, 95% confidence interval 0.65–0.95) compared with women who did not have PMRT; associations did not vary by age (overall survival, *P*-value for interaction term = 0.141; BCSS, $P = 0.077$). Among 10 814 women with intermediate-risk EIBC, 59% had PMRT; 5-year overall survival was 78.4% and BCSS was 88.0%. No association was found between overall survival (aHR 1.01, 95% confidence interval 0.92–1.11) or BCSS (aHR 1.16, 95% confidence interval 1.01–1.32) and PMRT. There was statistical evidence of a small change in the association with age for overall survival ($P = 0.007$), although differences in relative survival were minimal, but not for BCSS ($P = 0.362$).
Conclusions: The association between PMRT and overall survival/BCSS does not appear to be modified by age among women with high- or intermediate-risk EIBC and, thus, treatment recommendations should not be modified on the basis of age alone.

Key words: Breast cancer; older patient; post-mastectomy radiotherapy; survival

Introduction

Breast cancer is the most common cancer among females in the UK, with around 55 000 new cases diagnosed per annum [1]. For early invasive breast cancer (EIBC), the mainstay of treatment is surgery to remove the primary tumour, alongside multimodal adjuvant therapy to reduce the risk of local or distant recurrence. Adjuvant treatment may include radiotherapy, which is effective in reducing the risk of recurrence and improving survival [2].

Current UK guidelines from the National Institute for Health and Care Excellence state that post-mastectomy radiotherapy (PMRT) should be offered to all patients with node-positive invasive breast cancer, and considered for those with large (T3/T4) node-negative tumours [3]. However, the benefit of PMRT is uncertain in patients with intermediate-risk (e.g. one to three positive lymph nodes or T3 node negative) breast cancer [4–7]. An individual patient data meta-analysis of 22 clinical trials beginning prior to

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2000 assessing PMRT versus no PMRT [2] reported that for women with one to three positive axillary lymph nodes, PMRT reduced recurrence rates and breast cancer mortality [2]. However, these trials were conducted several decades ago and improvements to systemic therapy together with development of targeted treatments (such as trastuzumab) may have reduced the risk of recurrence for patients in contemporary clinical practice [8].

Alongside judging the risk of recurrence based on tumour factors, clinicians must consider how to adjust treatment decision-making when older patients have comorbidities or are frail [9–12]. Survival outcomes after radiotherapy may differ between younger and older patients, as the risk of death from non-cancer-related conditions increases with age. The original randomised trials commonly excluded patients aged 70 years and over [13,14], which means clinicians must extrapolate results from the younger cohort in order to guide treatment selection [15].

High-quality population-based observational studies have the potential to provide valuable insights into treatment patterns and outcomes among populations underrepresented in clinical trials [16,17]. This study aimed to describe the associations between adjuvant radiotherapy and survival among women with low-, intermediate- and high-risk EIBC, and to investigate whether these associations change with age at diagnosis among women who had mastectomy, in a population-based patient cohort.

Materials and Methods

Study Design and Data Sources

This study was carried out as part of the National Audit for Breast Cancer in Older Patients (NABCOP). The NABCOP is a national clinical audit, which reviews the management of breast cancer among older patients (aged ≥70 years) and compares this with management in younger women (aged 50–69 years) in England and Wales. The NABCOP receives pseudonymised patient-level data for all women with breast cancer aged 50 years and over, from the National Cancer Registration and Analysis Service for patients diagnosed in England and the Wales Cancer Network for patients in Wales. The national cancer registration data provide information on patient and tumour characteristics. For patients in England, this is augmented with information from the Cancer Outcomes and Services Dataset. Information from Hospital Episode Statistics (HES) and the Patient Episode Database for Wales (PEDW) provides details on in-patient hospital admissions, such as breast and axillary surgery. Details of chemotherapy use are provided in the Systemic Anti-Cancer Therapy dataset and the Cancer Network Information System Cymru (CANISC) for patients in England and Wales, respectively. Radiotherapy information is recorded within the National Radiotherapy Dataset (RTDS) for patients in England and within CANISC for patients in Wales. The RTDS contains information on radiotherapy episodes, which includes the prescribed dose and fraction, as well as information on treatment region (this information was not available in CANISC for patients in Wales). Details of endocrine therapy prescriptions dispensed in the community from April 2015 to March 2021 were available from the Primary Care Prescriptions Database for patients in England. Mortality data, including vital status and (underlying) cause of death, were provided by the Office for National Statistics death register. Further details of the NABCOP cohort can be found within the 2020 Annual Report [18].

Cohort Population and Variable Definitions

This study included women aged 50 years and over who were diagnosed between January 2014 and December 2018 with unilateral EIBC (overall stage 1–3a) in England and Wales. Women were included if they received a mastectomy within 12 months from diagnosis, either as primary surgery or subsequent to breast-conserving surgery (BCS), where the date of mastectomy was within 3 months from the date of BCS. Type of breast surgery (BCS, mastectomy, mastectomy and immediate reconstruction) and axillary surgery were defined using the OPCS Classification of Interventions and Procedures codes recorded within the HES/PEDW data. Exclusion criteria were the following: (i) death within 30 days from the date of surgery, (ii) BCS recorded after mastectomy, (iii) patients diagnosed in a single National Health Service Trust in England where radiotherapy attendances are not recorded in the RTDS dataset, (iv) missing or incongruous information on tumour stage or nodal stage, (v) the cancer registration record was unlinkable to HES or PEDW, as this prevented calculation of comorbidity or frailty level, and (vi) date of death or censoring that occurred before the landmark time.

Patients were considered to have received PMRT if a date for radiotherapy treatment existed within 6 months from the date of mastectomy. If women received adjuvant chemotherapy, which may delay the initiation of PMRT, they were counted as having PMRT when the first radiotherapy date was within 12 months from the date of mastectomy. Intended sites irradiated (obtained from predetermined categories) and radiotherapy regimen were available from the English RTDS data only.

The dataset was used to define the following patient characteristics: age at diagnosis (years), Index of Multiple Deprivation (IMD; grouped into quintiles), Charlson Comorbidity Index (0, 1, 2+ comorbidities) and Secondary Care Administrative Records Frailty (SCARF) index (fit, mild, moderate, severe frailty). Disease attributes included: tumour stage (T1, T2, T3), nodal stage (N0, N1, N2), tumour grade (G1, G2, G3, unknown), oestrogen receptor status (positive, negative, unknown) and human epidermal growth factor receptor 2 (HER2) status (positive, negative, unknown). Variables about treatment were: receipt of immediate reconstruction, receipt of axillary surgery (sentinel node biopsy, axillary node dissection, sentinel node biopsy and axillary node dissection, none), use of chemotherapy [neoadjuvant (yes/no), adjuvant (yes/no)] and having an endocrine therapy prescription.

Neighbourhood socioeconomic deprivation was provided as the 2019 IMD rank score for small areas in England [19] and Wales [20], with each patient being allocated to

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quintiles [from most (1) to least (5) deprived] based on their area of residence. Comorbidities were categorised according to the Royal College of Surgeons of England Charlson Comorbidity Index [21], using ICD-10 codes from in-patient admissions captured within the 2 years before diagnosis in HES or PEDW. Each patient was assigned a level of frailty according to the SCARF index [22], where frailty deficits are mapped from ICD-10 codes of hospital admissions data, with a 2-year lookback from diagnosis.

Patients were divided into risk groups based on recurrence risk as described in UK national guidelines [3,23]: low (T1-2N0), intermediate (T1-2N1, T3N0) or high risk (T1-2N2, T3N1-2). Women with low-risk breast cancer who would not routinely receive PMRT were included within the analysis for completeness.

Statistical Analysis

All analyses were carried out using Stata 17.0 (StataCorp LP, College Station, Texas, USA). Unadjusted rates of PMRT among women were produced according to recurrence risk. The primary outcome measures were 5-year overall survival and breast cancer-specific survival (BCSS). The reverse Kaplan–Meier method was used to estimate the median follow-up time of all patients.

The associations between survival and the explanatory variables were analysed using a flexible parametric survival model. Four variables (grade, oestrogen receptor status, HER2 status and route to diagnosis) contained some missing values. These were assumed to be 'missing at random' and values were imputed using the multiple imputation by chained equations method. Variables used within the imputation model included the Nelson-Aalen estimate of cumulative hazard, death status (yes/no), as well as the other explanatory variables. Ten imputed datasets with complete information were created using the 'mi' suite of commands in Stata.

A landmark approach was used for the survival analysis [24] to reduce the risk of immortal time bias. A landmark time of 6 months after the date of mastectomy was selected (or 12 months if a patient had adjuvant chemotherapy), which excluded those patients who had died or were censored prior to this time point and therefore did not have the opportunity to receive PMRT.

For each risk group and outcome measure, hazard ratios and survival probabilities for PMRT, age and other patient covariates were estimated by fitting flexible parametric models to each of the 10 datasets. These results were then combined using Rubin's rules [25] to produce an overall estimate. In addition to age and PMRT, the models included: IMD, referral source, Charlson Comorbidity Index, SCARF index, grade, tumour stage, nodal stage (omitted in low- and intermediate-risk groups), oestrogen receptor status, HER2 status, endocrine prescription, axillary surgery, neoadjuvant chemotherapy, adjuvant chemotherapy and immediate reconstruction.

Two flexible parametric models were developed for each risk group. The first incorporated PMRT, age and the other covariates to obtain the adjusted hazard ratio (aHR) for the association of PMRT with survival. The estimated coefficients for the variables in the full model are available in Supplementary Material Tables S1 and S2. The second model expanded the first model by including an interaction term between PMRT and age. The interaction term was tested for significance using a Wald test (*mi test* command). In each model, the baseline hazard was modelled using a restricted cubic spline with 2 degrees of freedom, and age was modelled using a restricted cubic spline with 2 degrees of freedom. These had the minimum Bayesian Information Criterion among splines with 1–3 degrees of freedom. The variable 'endocrine prescription' was included as a time-varying variable (with 2 degrees of freedom) after this was found to violate the proportional hazards assumption (examined using Schoenfield residuals and by visual inspection). All statistical tests were two-sided and *P*-values <0.05 were considered to demonstrate evidence of an association.

Results

Patient Characteristics and Care

The study cohort consisted of 31 243 women diagnosed between 1 January 2014 and 31 December 2018 with unilateral EIBC in England ($n = 29\,360$) and Wales ($n = 1883$). A flow diagram of cohort selection is presented in Supplementary Material Figure S1. The distribution of patient and tumour characteristics according to risk group is presented in Table 1. Most patients were classified as having low- ($n = 15\,718$) or intermediate-risk ($n = 10\,814$) breast cancer, with 4711 categorised as high risk.

Overall, 41% of women received PMRT. Women were more likely to receive PMRT if they had high-risk EIBC (86%), compared with women with low (15%) or intermediate risk (59%). The percentage of patients who received PMRT reduced as age at diagnosis increased, in all risk groups. Among women in England receiving PMRT, 59% ($n = 7271$) of patients received PMRT to the 'primary area only', 38% ($n = 4625$) to the 'primary and regional nodes', 1% ($n = 95$) to 'other site', with 2% ($n = 283$) of women having no recorded site of radiotherapy. Most patients in England receiving PMRT were recorded to have been prescribed 40 Gy in 15 fractions (88%), with 12% of patients receiving an alternative regimen (0.5% had missing information).

Survival Analysis

Among all patients, the median follow-up was 4.6 years (interquartile range 3.3–5.8). The 5-year overall survival rate was 80.8% among all women, 85.4% (95% confidence interval 84.7–86.0) in the low-risk group, 78.4% (95% confidence interval 77.5–79.3) in the intermediate-risk group and 70.5% (95% confidence interval 68.9–72.0) for the high-risk group. The 5-year BCSS rate was 90.2% (95% confidence interval 89.9–90.6) for the overall cohort and showed a similar pattern when analysed according to risk group (low risk:

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Table 1
Patient and tumour characteristics of women diagnosed with early invasive breast cancer in England and Wales between 2014 and 2018 who received a mastectomy, by risk group

Total	Total no. patients	Low risk		Intermediate risk		High risk	
		Total no.	% receiving PMRT	Total no.	% receiving PMRT	Total no.	% receiving PMRT
	$n = 31\,243$	($n = 15\,718$)	15%	($n = 10\,814$)	59%	($n = 4711$)	86%
Age groups (years)							
50–54	5459	2536	18%	2004	65%	919	90%
55–59	3967	1818	19%	1438	64%	711	87%
60–64	4086	2065	17%	1369	65%	652	86%
65–69	4614	2473	15%	1555	61%	586	85%
70–74	4009	2101	14%	1332	58%	576	89%
75–79	4143	2102	13%	1438	56%	603	84%
80–84	3197	1680	11%	1084	51%	433	79%
85+	1768	943	8%	594	35%	231	69%
Year of diagnosis							
2014	6535	3428	15%	2182	56%	925	86%
2015	6485	3263	16%	2287	60%	935	85%
2016	6166	3075	15%	2174	59%	917	86%
2017	5978	2990	14%	2065	60%	923	86%
2018	6079	2962	14%	2106	63%	1011	85%
Method of diagnosis							
Screened	8868	5452	12%	2524	57%	892	89%
Non-screened	21 733	9911	16%	8074	60%	3748	85%
Unknown	642	355	13%	216	51%	71	82%
Tumour stage							
T1	10 334	7486	9%	2506	47%	342	84%
T2	16 653	8232	21%	6762	61%	1659	84%
T3	4256	.	.	1546	75%	2710	87%
Nodal stage							
N0	17 264	15 718	15%	1546	75%	.	.
N1	11 198	.	.	9268	57%	1930	87%
N2	2781	.	.	.	.	2781	85%
Tumour grade							
1	2592	1767	7%	674	44%	151	87%
2	17 643	8899	13%	6098	58%	2646	86%
3	10 628	4793	21%	3944	64%	1891	85%
Unknown	380	259	12%	98	53%	23	87%
Oestrogen receptor status							
Positive	23 427	11 786	13%	8132	58%	3509	86%
Negative	5093	2529	20%	1750	63%	814	84%
Unknown	2723	1403	17%	932	62%	388	87%
HER2 status							
Positive	6657	3133	19%	2446	60%	1078	86%
Negative	20 952	10 651	14%	7154	60%	3147	86%
Unknown	3634	1934	14%	1214	57%	486	82%
Charlson Comorbidity Score							
0	26 984	13 469	16%	9392	61%	4123	87%
1	2943	1546	11%	990	54%	407	81%
2+	1316	703	11%	432	45%	181	75%
SCARF index							
Fit	24 709	12 292	16%	8593	61%	3824	87%
Mild	3566	1843	13%	1247	56%	476	86%
Moderate	2176	1147	12%	720	52%	309	79%
Severe	792	436	7%	254	40%	102	69%
IMD quintiles							
1 – Most deprived	5025	2387	15%	1851	58%	787	86%
2	5680	2846	14%	1938	61%	896	84%
3	6365	3188	16%	2241	60%	936	87%
4	6977	3594	15%	2348	59%	1035	86%
5 – Least deprived	7196	3703	15%	2436	59%	1057	84%

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Table 1 (*continued*)

Total	Total no. patients	Low risk		Intermediate risk		High risk	
		Total no.	% receiving PMRT	Total no.	% receiving PMRT	Total no.	% receiving PMRT
	$n = 31\ 243$	($n = 15\ 718$)	15%	($n = 10\ 814$)	59%	($n = 4711$)	86%
Axillary surgery							
None	847	579	11%	210	50%	58	71%
SLNB	19 208	14 080	14%	4381	56%	747	84%
ALND	7108	651	26%	3723	66%	2734	86%
SLNB and ALND	4080	408	28%	2500	55%	1172	85%
Type of surgery							
Mastectomy only	25 886	12 514	16%	9169	60%	4203	86%
Mastectomy and immediate reconstruction	5357	3204	12%	1645	56%	508	86%
Chemotherapy							
Neoadjuvant	3058	739	53%	1529	84%	790	91%
Adjuvant	7763	2453	24%	3250	71%	2060	95%
No	20 422	12 526	11%	6035	47%	1861	72%
Endocrine therapy prescription							
No	7866	4313	16%	2445	59%	1108	81%
Yes	23 377	11 405	15%	8369	59%	3603	87%

ALND, axillary lymph node dissection; IMD, Index of Multiple Deprivation; SCARF, Secondary Care Administrative Records Frailty; SLNB, sentinel lymph node biopsy; HER, human epidermal growth factor receptor 2.

94.9%, 95% confidence interval 94.5–95.2; intermediate risk: 88.0%, 95% confidence interval 87.3–88.7; high risk: 79.3%, 95% confidence interval 77.9–80.7).

Among women with low-risk EIBC, PMRT was not associated with improved overall survival (aHR 1.08, 95% confidence interval 0.95–1.23) or BCSS (aHR 1.50, 95% confidence interval 1.24–1.80). The predicted hazard ratio for overall survival varied with age (Supplementary Material Figure S2A, *P*-value for interaction term <0.001) but this translated into only minor absolute differences in predicted survival by receipt of PMRT (Supplementary Material Figure S2B) due to the high baseline survival rate. For BCSS, there was no statistical evidence to suggest the association with PMRT varied by age (Supplementary Material Figure S3, *P*-value for interaction term = 0.188).

For women in the intermediate-risk group, PMRT was not associated with improved overall survival (aHR 1.01, 95% confidence interval 0.92–1.11) or BCSS (aHR 1.16, 95% confidence interval 1.01–1.32). The predicted hazard ratio for overall survival showed a shallow parabolic relationship with age (Figure 1A, *P*-value for interaction term = 0.007). However, as with low-risk EIBC, this translated into little difference in the predicted survival curves for women according to age (Figure 1B). The association between PMRT and BCSS for women of different age groups exhibited a similar shape but there was no evidence of a varying association by age (Figure 2, *P*-value for interaction term = 0.362).

Among women with high-risk breast cancer, PMRT was associated with improved overall survival (aHR 0.75, 95% confidence interval 0.64–0.87) and BCSS (aHR 0.78, 95% confidence interval 0.65–0.95). The predicted hazard ratio for overall survival after PMRT again showed a shallow parabolic relationship with age at diagnosis, but there was no statistical evidence to suggest the association between overall survival and PMRT varied by age (Figure 3A, *P*-value for interaction term = 0.141). The predicted survival curves for women of different ages showed minimal separation between women who did and did not receive PMRT (Figure 3B). The same pattern was observed for BCSS (Figure 4A, *P*-value for interaction term = 0.077). The predicted survival curves for selected ages (Figure 4B) showed minimal separation between women who receive PMRT versus those who do not.

Discussion

This population-based study explored whether the association between survival and radiotherapy varied with age at diagnosis, among women aged 50 years and over diagnosed with EIBC in England and Wales who received a mastectomy. Extending the regression models to allow the association between overall survival/BCSS and radiotherapy to vary by age at diagnosis suggested that the association between PMRT use and survival did not change with age at diagnosis, in any of the three risk groups. For overall survival, there was stronger evidence of an interaction between age and PMRT for women with low- and intermediate-risk EIBC. However, the differences between the predicted survival curves when assessed by age were minimal. For the BCSS outcome, there was no evidence of an interaction between PMRT and age.

The results of this study are consistent with trial evidence, with the regression models showing that, on average, PMRT was associated with improved overall survival or BCSS among women with high-risk EIBC. However, this study found that PMRT was not associated with improved survival among women in low- or intermediate-

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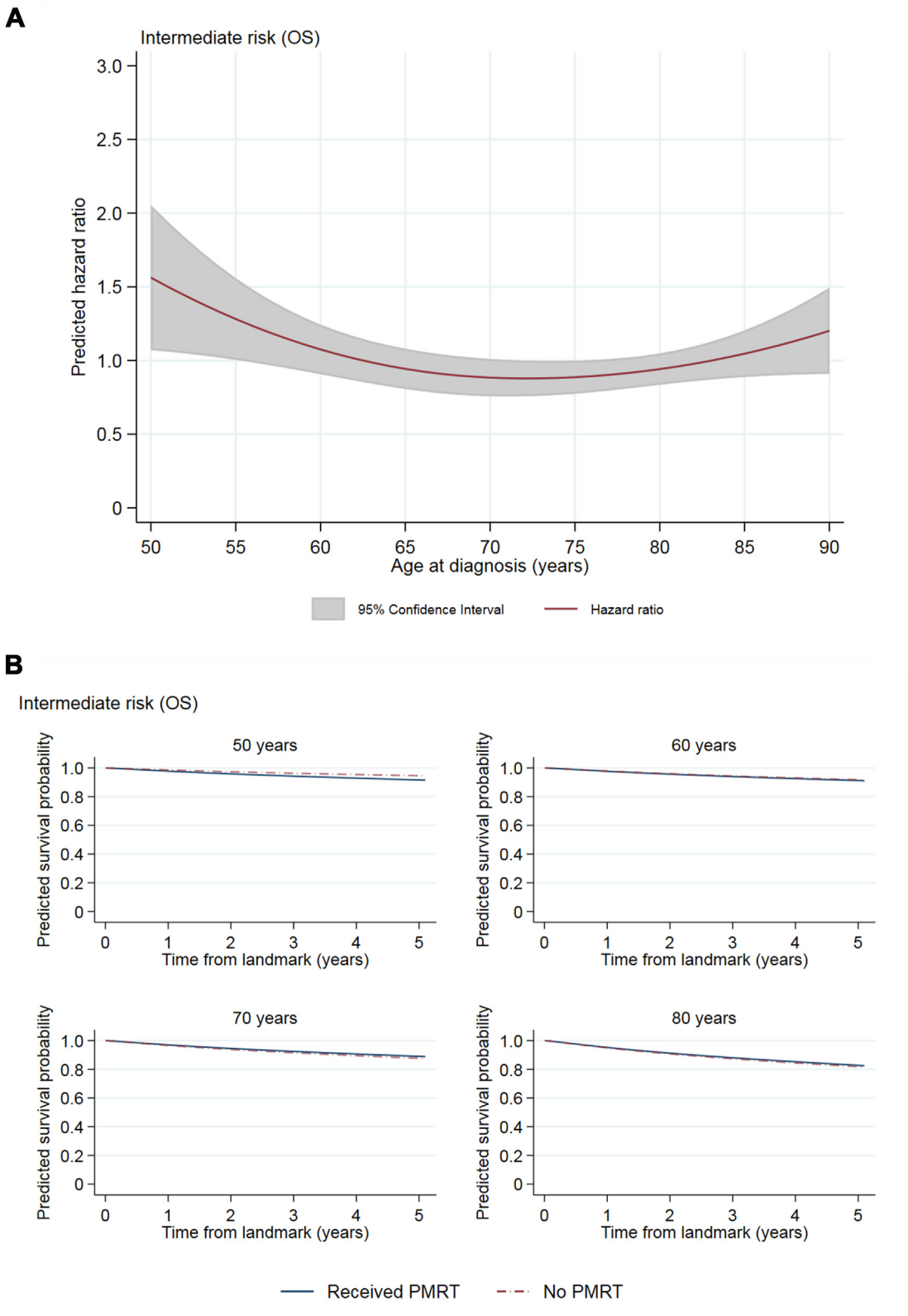

Fig 1. Predicted estimates for overall survival from a flexible parametric model including the interaction between post-mastectomy radiotherapy (PMRT) and age at diagnosis (modelled as a restricted cubic spline), among women with intermediate-risk breast cancer. (A) The predicted hazard ratio for overall survival for the interaction between PMRT and age. (B) Predicted overall survival among women of different age groups, according to receipt of PMRT. Covariates in the prediction were held at their baseline values. Exceptions to this were tumour stage, which was held at T2, and the interaction term between age and PMRT. Note: Each graph in (A) presents the hazard ratios associated with receiving PMRT compared with not receiving PMRT.

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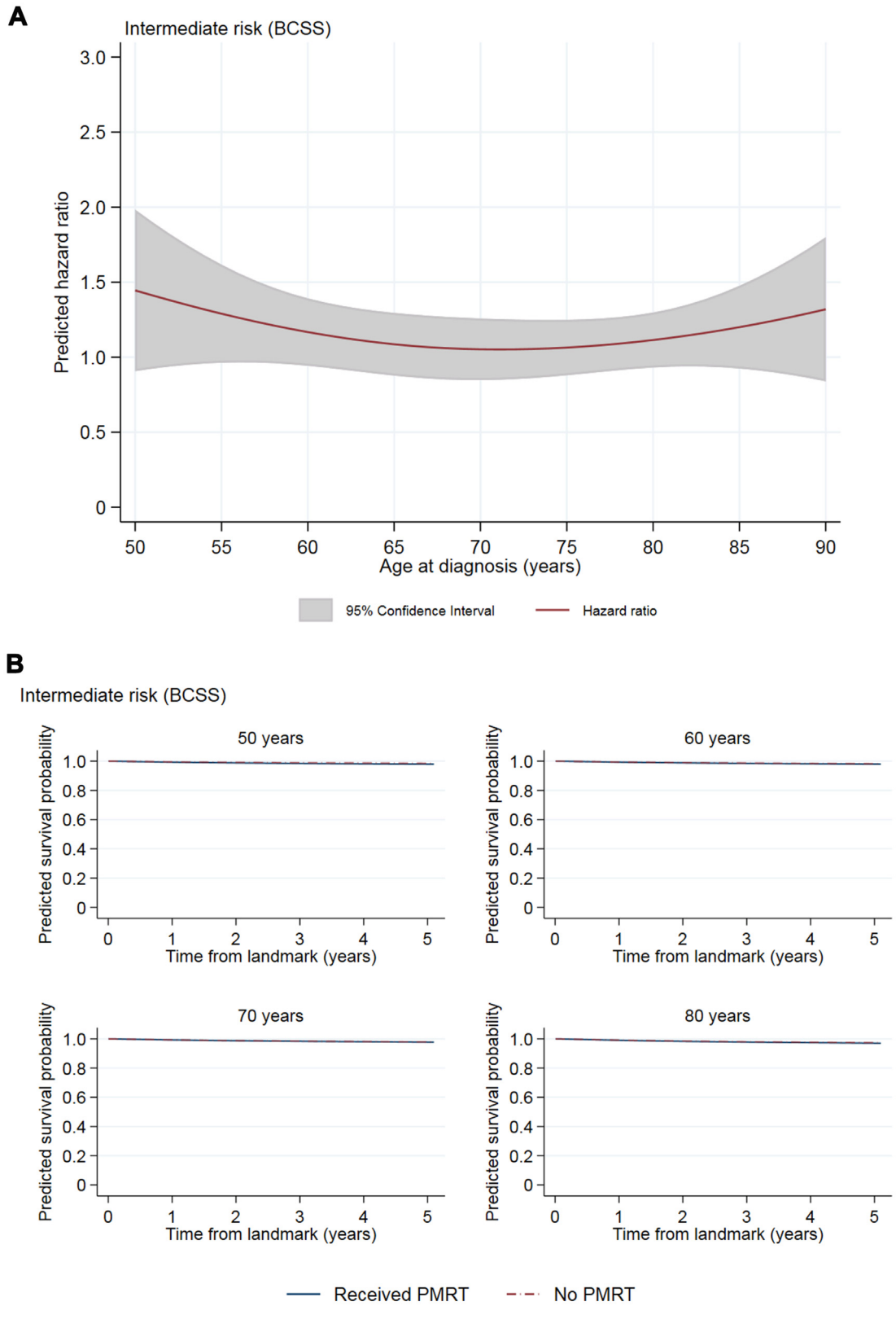

Fig 2. Predicted estimates for breast cancer-specific survival (BCSS) from a flexible parametric model including the interaction between post-mastectomy radiotherapy (PMRT) and age at diagnosis (modelled as a restricted cubic spline), among women with intermediate-risk breast cancer. (A) The predicted hazard ratio for BCSS for the interaction between PMRT and age. (B) Predicted BCSS among women of different age groups, according to receipt of PMRT. Covariates in the prediction were held at their baseline values. Exceptions to this were tumour stage, which was held at T2, and the interaction term between age and PMRT. Note: Each graph in (A) presents the hazard ratios associated with receiving PMRT compared with not receiving PMRT.

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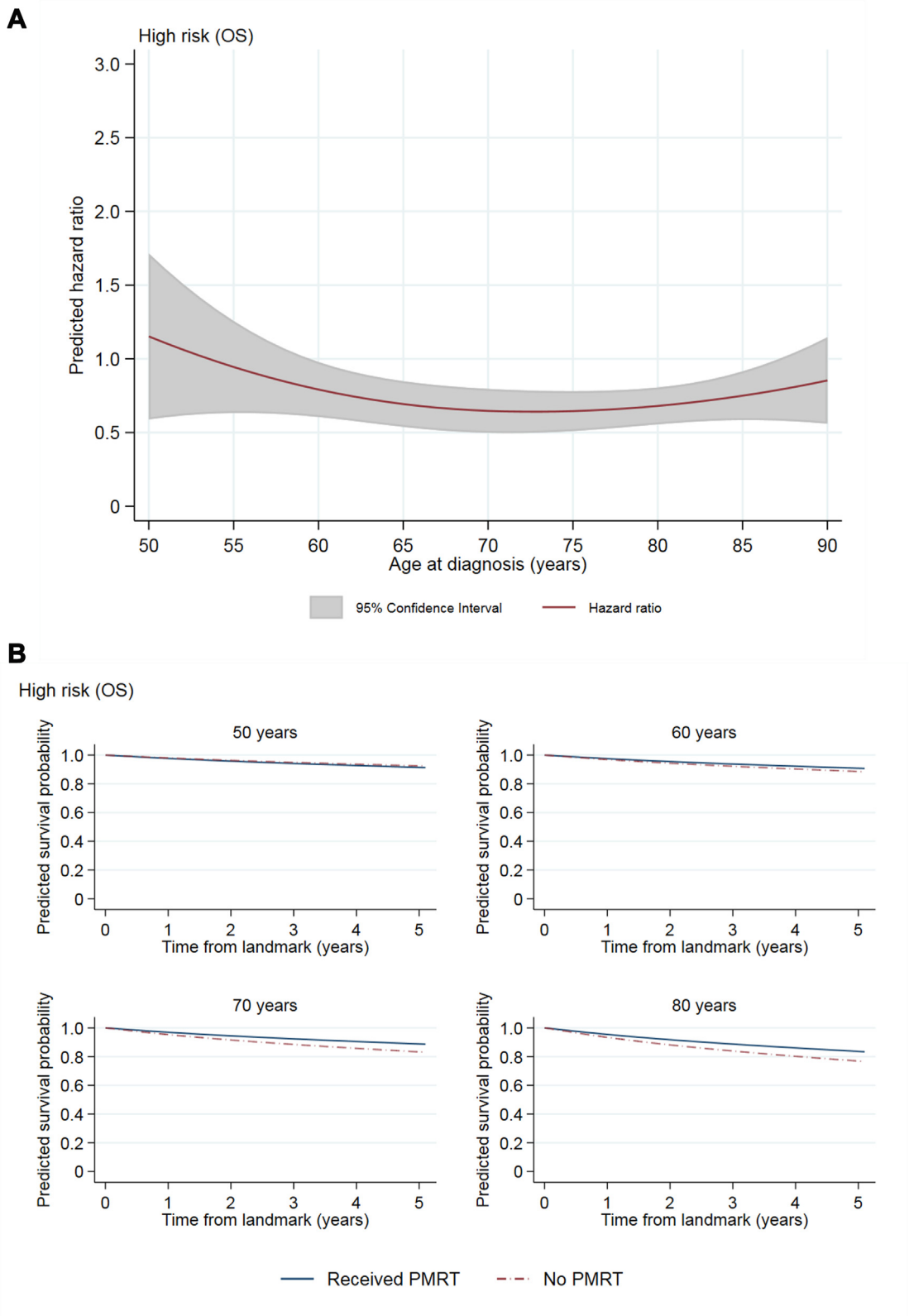

Fig 3. Predicted estimates for overall survival from a flexible parametric model including the interaction between post-mastectomy radiotherapy (PMRT) and age at diagnosis (modelled as a restricted cubic spline), among women with high-risk breast cancer. (A) The predicted hazard ratio for overall survival for the interaction between PMRT and age. (B) Predicted overall survival among women of different age groups, according to receipt of PMRT. Covariates in the prediction were held at their baseline values. Exceptions to this were tumour stage, which was held at T2, and the interaction term between age and PMRT. Note: Each graph in (A) presents the hazard ratios associated with receiving PMRT compared with not receiving PMRT.

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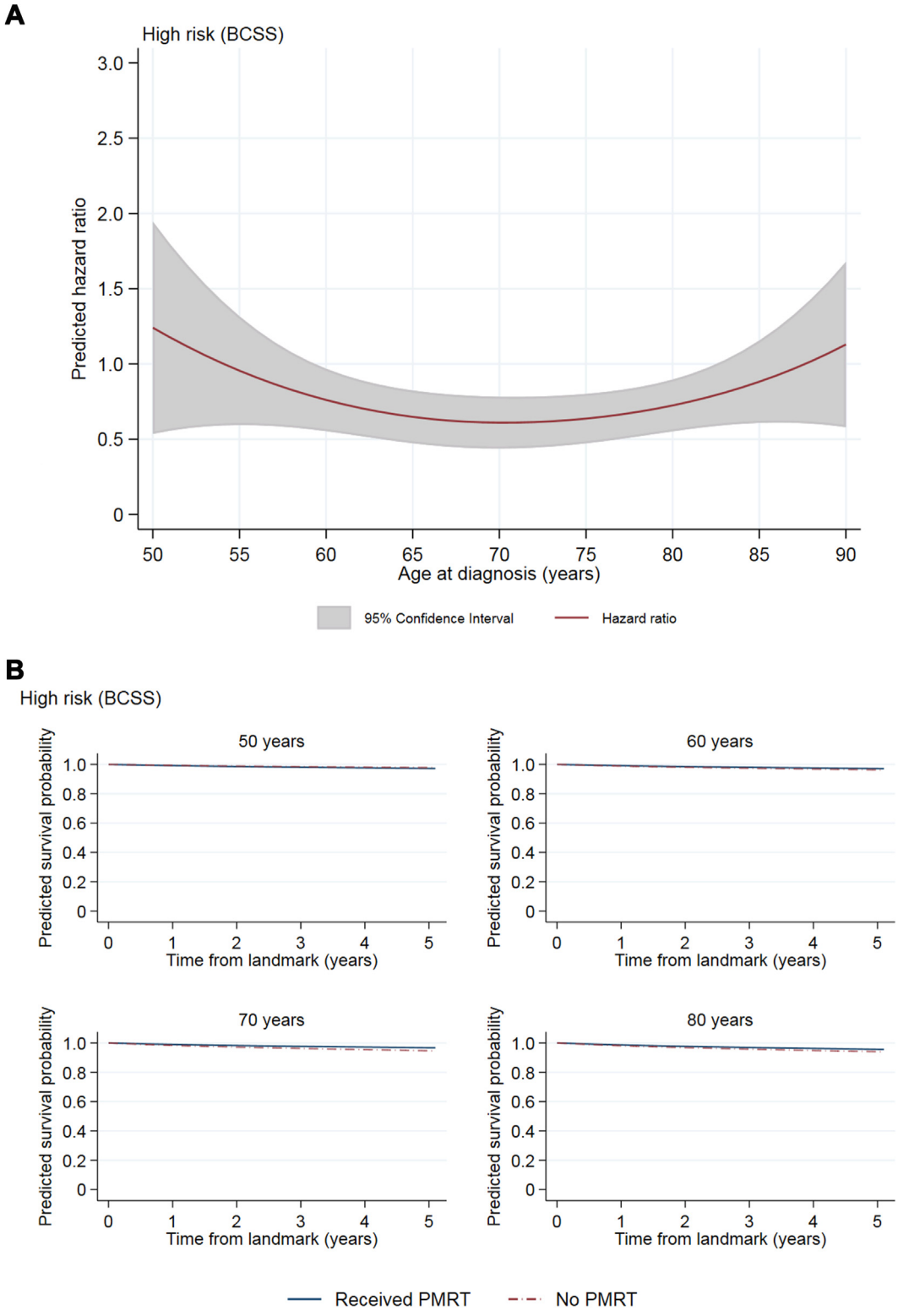

Fig 4. Predicted estimates for breast cancer-specific survival (BCSS) from a flexible parametric model including the interaction between post-mastectomy radiotherapy (PMRT) and age at diagnosis (modelled as a restricted cubic spline), among women with high-risk breast cancer. (A) The predicted hazard ratio for BCSS for the interaction between PMRT and age. (B) Predicted BCSS among women of different age groups, according to receipt of PMRT. Covariates in the prediction were held at their baseline values. Exceptions to this were tumour stage, which was held at T2, and the interaction term between age and PMRT. Note: Each graph in (A) presents the hazard ratios associated with receiving PMRT compared with not receiving PMRT.

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risk groups. This is in contrast to the results of the Early Breast Cancer Trialists' Collaborative Group meta-analysis, which reported that among 1314 women who had one to three positive lymph nodes and received axillary dissection, radiotherapy reduced 20-year breast cancer mortality (risk ratio 0.80, 95% confidence interval 0.67–0.95) [2]. It should be noted, however, that these results are not directly comparable with those of this study, owing to differences in follow-up time and our inclusion of patients with T3N0 tumours within the intermediate-risk group.

The strengths of this study include the large cohort size, using routinely collected patient-level data, which means the cohort is probably representative of 'real-world' practice, and the ability to adjust for relevant disease factors as well as comorbidity and frailty, which are important confounders among the older population.

This study also has various limitations. First, the relatively short follow-up time meant we were limited to assessing 5-year survival, and did not consider locoregional or distant recurrence-free survival due to a lack of complete recurrence data [26]. Second, although the stratification of women to risk groups using tumour and nodal stage for this study was based on national guidelines [3,23], risk of recurrence is based on multiple other factors [8,27,28], and recommendations for PMRT will probably vary between clinicians based on these factors. Third, there are recognised weaknesses in routine hospital admissions data, including coding inaccuracies and the omission of diagnostic codes. However, the accuracy of ICD-10 coding has improved over time, and we do not anticipate this to have a large impact on our results [29]. Finally, the study used an observational dataset. The treatments received by women were not randomly allocated and this may result in biased estimates, due to confounding from unmeasured variables or systematic differences in the characteristics of women who received PMRT versus those who did not (selection bias). However, our findings that PMRT was only associated with improved survival in the high-risk group (women whose tumours had the worst prognostic factors) is consistent with evidence from randomised trials. The survival models included several important patient, tumour and treatment factors, but we recognise there are variables that we were unable to account for (such as patient preference). We note that PMRT seemed to be associated with worse BCSS in the low-/intermediate-risk groups for younger women and this may be a result of confounding or selection bias. For example, there may be unmeasured factors that prompted use of PMRT among women in the low-risk group (for whom PMRT is not recommended), which were not captured within our dataset. Consequently, we do not recommend interpreting the association between survival and use of PMRT as an estimate of treatment benefit as reported by randomised controlled trials. The results of this study should be interpreted as hypothesis generating about the potential for the effect of PMRT to be modified by age.

Several other studies have used large observational datasets to assess the association of PMRT with survival outcomes among women of various disease stages [30–36] but only a handful have specifically assessed or reported the association between PMRT and outcomes according to age. In a systematic review and meta-analysis of two retrospective cohort studies [37,38], Tseng *et al.* [39] found no association between PMRT and overall survival or BCSS in women aged 65 years and over with intermediate-risk breast cancer, although both studies were reported to be of low quality. Chen *et al.* [40] conducted a retrospective analysis of SEER data to investigate BCSS after PMRT among women diagnosed with T1-2N1M0 breast cancer between 2000 and 2014. With a median follow-up of 62 months, PMRT was not associated with improved BCSS (aHR 0.99, 95% confidence interval 0.92–1.06), and in subgroup analysis, PMRT was not associated with improved BCSS in women of different age groups, including women aged ≥70 years. Another study using SEER data of 3437 women with T3N0 breast cancer (age range 20–90 years) found no interaction between PMRT and age or comorbidity level [41]. In an analysis of women aged 70 years and over with low-, intermediate- and high-risk breast cancer from the SEER database, Smith *et al.* [36] found that PMRT was associated with improved overall survival among the high-risk group (hazard ratio 0.85, 95% confidence interval 0.75–0.97) but not for women in the intermediate- (hazard ratio 1.23, 95% confidence interval 0.75–0.97) or low-risk (hazard ratio 1.06, 95% confidence interval 0.90–1.24) groups. This study cohort was comprised of women diagnosed three decades ago (1992–1999) and reported use of PMRT was significantly lower than in this present study. Although three of the five studies adjusted for a measure of comorbidity [36,37,41], none used a measure of frailty, which is an important and distinct predictor of overall health in the older population. The NABCOP Annual Reports have shown that relative survival is comparable across age groups for women with EIBC who receive surgery, but when separated by level of frailty, the substantial negative impact of poor patient fitness on subsequent survival is clear [26].

In addition to survival outcomes, radiotherapy-related toxicity and quality of life effects [42] are important endpoints to assess among older patients receiving radiotherapy. In a prospective multicentre cohort study of women aged 70 years and over with early breast cancer, with comprehensive measures of fitness and frailty, radiotherapy after BCS or mastectomy had an initial but temporary impact on quality of life [43]. This finding was reflected in a single institution analysis of women aged 70 years and over who received surgery (BCS or mastectomy) and postoperative radiotherapy, which suggested that age did not have an impact on radiotherapy-related toxicity [44]. Two-year quality of life results from the SUPREMO trial (Selective Use of Postoperative Radiotherapy AftEr MastectOmy) investigating the role of PMRT among patients with operable intermediate-risk breast cancer, with no upper age limit, reported that PMRT was associated with worse self-reported chest wall symptoms (than no PMRT), but the authors suggested that the effect was unlikely to be of clinical significance [45]. Methods to identify treatment-related toxicity within English national cancer datasets have been developed for systemic anti-cancer treatments [26,46] but are currently lacking for radiotherapy.

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Developing equivalent methods to identify radiotherapy-related toxicity among patients with breast cancer using national cancer datasets would be a valuable area of further study.

Conclusions

The results from this population-based cohort study suggest the association between survival and use of PMRT demonstrates minimal variation by age at diagnosis, in women with low-, intermediate- or high-risk breast cancer. PMRT was associated with improved overall survival and BCSS among women with high-risk EIBC, but not for low- or intermediate-risk EIBC. The study found no evidence that the association between overall survival/BCSS and PMRT varied by age at diagnosis among women in any of the three risk groups. We provide no evidence to support the possibility that radiotherapy may be less effective in older women. Given the absence of randomised evidence in older patients, overall fitness for treatment rather than chronological age alone should dominate decision-making for PMRT and provide equity of care among older women with EIBC.

Ethical Considerations

This study is exempt from UK National Research Ethics Committee approval as it includes secondary analysis of an existing pseudonymised dataset. The NABCOP has approval for processing healthcare information under Section 251 (reference number: 16/CAG/0079).

Conflicts of Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: K. Clements reports funding received for a Breast Cancer Research Manager role within NHS England as part of the Cancer Grand Challenges PRECISION team that includes: employment. D. Cromwell reports a relationship with Healthcare Quality Improvement Partnership that includes: funding grants. D. Cromwell reports a relationship with Pregnancy Outcome Prediction Study (POPS2) Trial that includes: member of steering committee. K. Horgan reports a relationship with Endonet that includes: chair of trial steering committee.

Author Contributions

KM was responsible for conceptualisation, methodology, formal analysis, visualisation and writing (original draft, review and editing). MRG was responsible for acquisition of data, methodology and writing (review and editing). JM was responsible for acquisition of data and writing (review and editing). KC was responsible for acquisition of data and writing (review and editing). DD was responsible for conceptualisation and writing (review and editing). KH was responsible for conceptualisation and writing (review and editing). MP was responsible for conceptualisation, methodology, writing (review and editing) and supervision. DAC was responsible for conceptualisation, methodology, formal analysis, writing (review and editing) and supervision.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2023.01.008.

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