Patient and tumour factors affecting the receipt of breast surgery in older women with ER-positive or ER-negative early invasive breast cancer in England and Wales

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Abstract

Introduction

Studies reporting lower rates of surgery for older women with early invasive breast cancer (EIBC) have focused on women with oestrogen receptor (ER-) positive tumours. This study examined the factors that influence receipt of breast surgery in older women with ER-positive and ER-negative EIBC.

Methods

Women aged ≥50yrs with unilateral EIBC (stage 1-3A) diagnosed between 2014-2017 were identified from linked English and Welsh cancer registration and routine hospital datasets. Logistic regression was used to evaluate influence of tumour and patient factors on receipt of surgery.

Results

Among 83,188 women, 87% had ER-positive and 13% had ER-negative EIBC. This percentage was unaffected by age at diagnosis. In comparison to women with ER-negative EIBC, a higher percentage of women with ER-positive EIBC presented with low risk tumour characteristics: G1 (20% vs. 2%), T1 (61% vs. 44%) and N0 (74% vs. 69%). The percentages of women with any recorded comorbidity (14% vs. 14%) or degree of frailty (25% vs. 26%) were similar among women with ER-positive and ER-negative disease, respectively. In women with ER-positive EIBC aged 70-74yrs, 75-79yrs and ≥80yrs, rates of no surgery were 6%, 11% and 42%, respectively. The rates were 4%, 4% and 12% among women with ER-negative EIBC. The relative lower rate of surgery for ER-positive EIBC persisted in women with good fitness.

Conclusion

Fewer fit older women in England and Wales receive surgery if diagnosed with ER-positive compared to ER-negative EIBC. Reasons for this variation should be explored, to ensure consistency of treatment decisions among older women.

Introduction

Oestrogen is the main hormonal regulator for modulating growth, differentiation and function of breast tissue. Invasive breast cancer is often described by its oestrogen receptor (ER) status, which is either positive based on the presence, or negative based on the very low presence or complete absence, of receptors to oestrogen. Up to 80% of women with early invasive breast cancer (EIBC) have ER-positive tumours, and these women have a better prognosis than women with ER-negative EIBC[1].

Surgery is recommended as standard of care for women with EIBC and this is irrespective of ER status[2]. UK population-level studies consistently report a lower rate of surgery in older women in comparison to their younger counterparts[3-6]. This pattern has been particularly apparent in older women with ER-positive EIBC. Recent findings by the National Audit of Breast Cancer in Older Patients (NABCOP) are of a higher rate of surgery in women aged ≥ 70 years with ER-negative EIBC compared to women of similar age with ER-positive disease[7]. There was also less variation in the rate of surgery for older women with ER-negative EIBC across NHS organisations in England and Wales[7, 8].

A key difference in the treatment of women with ER-positive and ER-negative EIBC is the option of primary endocrine therapy (PET) for women with ER-positive EIBC and poor fitness/life expectancy[2, 9]. Outcomes from PET are inferior to those receiving surgery[10, 11], and therefore PET is not a true equally effective alternative primary treatment for EIBC. For women with ER-negative disease, there is no alternative systemic treatment equivalent to PET and clinical guidelines offer no recommendations on how primary treatment should be modified in the presence of poor fitness[9].

This study aimed to investigate the relationship between tumour and patient factors on the likelihood of not receiving surgery for women aged ≥ 50 years with ER-positive and ER-negative EIBC.

Methods

Data source

The population-level cohort study was undertaken as part of the NABCOP[13]. The NABCOP uses pseudonymised patient-level datasets provided by the National Cancer Registration and Analysis Service (NCRAS) in England and Wales Cancer Network for Wales. The datasets included national cancer registrations and extracts from the routine hospital admission databases for NHS hospitals (the English Hospital Episode Statistics (HES) and the Patient Episode Database for Wales (PEDW)). Survival information is recorded in the Civil Registration/Mortality data. Full details of the NABCOP cohort are described in the 2019 annual report[7].

Study population and definitions

The study included women aged ≥ 50 years, newly diagnosed with unilateral early stage (UICC TNM staging classification, 7th edition[12]: stage 1 – 3A) invasive breast cancer (ICD-10 code: C50) from 1 January 2014 to 31 December 2017 in England and Wales. Among the 109 018 eligible women in the NABCOP datasets, women with a missing record of ER status (n = 10 951 (10%)) or other key study variables (n = 14 837 (14%)), or who were borderline ER status (n = 42), were excluded from the study.

Information on patient demographics (age, social deprivation), date of diagnosis, method of presentation and tumour characteristics was obtained from the national cancer registration dataset. Social deprivation was measured using the Index for multiple deprivation (IMD), with the IMD values for geographical area in England[13] and Wales[14] converted to quintiles. Patient fitness was assessed using comorbidity and frailty measures. Comorbidity burden was measured using the Royal College of Surgeons of England modified Charlson Comorbidity Index (CCI)[15] excluding malignancy[16]. This index is calculated based on the presence of specific medical problems, identified using the ICD-10 diagnostic information in HES and PEDW up to two years prior to the date of cancer diagnosis. The study also used a measure of frailty, a distinct concept from comorbidity that describes age-related decline in physiological reserve and increased vulnerability to stressors[17]. Frailty was measured using the secondary care administrative records frailty (SCARF) index[18], which shares a similar construct of frailty deficits to the electronic Frailty Index (eFI)[19], for use within routine hospital databases. The SCARF index is calculated from 32 frailty deficits, identified using the ICD-10 diagnosis codes within the hospital admission records in HES / PEDW, up to two years prior to the date of diagnosis[18].

Outcomes

Surgery was defined by the first type of breast surgical resection recorded in HES and PEDW during the twelve months following the date of diagnosis, to allow for the use of any neoadjuvant therapy. Both HES and PEDW capture surgical procedures using Office of Population Censuses and Surveys (OPCS) codes with the code B28 (excluding B28.4 and B28.6) defining breast conserving surgery (BCS) and the code B27 defining mastectomy.

The study also examined a number of short-term outcomes associated with surgical safety, namely, the duration of inpatient hospital stay (defined as the number of days from date of surgery to discharge) 30-day postoperative mortality, and 30-day emergency readmission rates after discharge.

Statistical analysis

The percentage of patients not receiving surgery was calculated for women with ER-positive and ER-negative EIBC, and among groups with different patient and tumour characteristics. The statistical significance of differences between the groups was assessed using statistical tests appropriate for continuous or categorical variables. Patient and tumour factors of interest included age, deprivation quintile, CCI, SCARF index, tumour grade, tumour size (T stage), the presence of malignant lymph nodes (N stage), human epidermal growth factor receptor 2 (HER2) status and mode of presentation (screen-detected or symptomatic). Short-term surgical outcomes were also calculated for women aged 50-69 or ≥70 years with ER-positive and ER-negative disease.

Multi-variable logistic regression was used to investigate how all the patient and tumour factors were associated with the likelihood of no surgery. Age was included in the model as a continuous variable, and a cubic spline was used to accommodate its non-linear effect[20]. The spline knots were defined at ages 51, 73, 85 and 90 years, which were selected based on the Akaike information criterion (AIC). The model also included Interaction terms to capture differences in the patterns of surgery between women with ER-positive and ER-negative EIBC. The interaction terms were ER-status and age, ER-status and N-stage, and ER-status and frailty. The performance of the model was evaluated in terms of its calibration and discrimination[21] in the overall cohort and within the two ER subgroups.

As the spline coefficients and the interaction terms are difficult to interpret, predictions from the model were produced to illustrate the relationship between age and the likelihood of no surgery for women with ER-positive and ER-negative EIBC[22]. The predictions were produced for four patient subgroups: women with low risk (grade 1, stage T1 N0) or high risk (grade 3, stage T2 N1) breast cancer, with each stratified by two levels of fitness: good (no comorbidities, not frail) and poor (comorbidity score ≥ 2 and severe frailty). Analysis for this study was conducted as a complete case analysis using Stata 15.1 *(StataCorp LP, College Station, Texas USA).* All statistical tests were two sided.

Results

The study analysed data on 83 188 women aged ≥50 years, who were newly diagnosed with unilateral EIBC in NHS organisations in England and Wales between January 2014 and December 2017. Overall, 87% of women had ER-positive and 13% had ER-negative EIBC, with similar percentages in each age group (Figure 1).

Baseline patient and tumour characteristics for women with each ER status subtype are summarised by age group at diagnosis in Table 1. There were several differences in tumour characteristics across all age groups between women with ER-positive and ER-negative EIBC. For example, women with ER-positive EIBC were more likely to present with grade 2 tumours, while a greater percentage of women with ER-negative EIBC had grade 3 tumours. The percentages of women with a HER2-negative subtype or nodal metastases (≥N1) were lower among those with ER-positive tumours compared to ER-negative. In contrast, there were few differences in patient demographics between women with ER-positive and ER-negative tumours. The prevalence of comorbidity or frailty was as expected, and greater among older women, regardless of ER status.

Overall, 76 312 (92%) of women received surgery and the rate of surgery was observed to be lower in older women in both ER subgroups (Figure 2). In women aged 70–74 years, 75–79 years and ≥80 years, the percentages that did not have surgery in the ER-positive subgroup were 6%, 11% and 42%, respectively. The corresponding values in the ER-negative subgroup were 4%, 4% and 12%. Among women who had surgery, the rate of mastectomy in contrast to BCS increased with age, irrespective of ER status. Table 2 describes the unadjusted percentages of women not receiving surgery in relation to individual patient and tumour factors.

The multivariable regression model used to examine the likelihood of no surgery contained all the patient and tumour factors except deprivation quintile. This model had good calibration and discrimination (overall c-statistic = 0.84). Table 2 describes the model coefficients for each of the explanatory variables. In addition to age, the model revealed that lower grade, the absence of malignant lymph nodes and poor patient fitness, were strongly associated with an increased likelihood of not receiving surgery for EIBC.

Figure 3 shows the predicted likelihood of not having surgery by age at diagnosis for the four patient subgroups. In each subgroup, the estimated rates for women with ER-positive and ER-negative EIBC diverge as age at diagnosis increases. However, each subgroup shows a different degree of separation, with the changes in rates of surgery occurring predominantly in women with ER-positive EIBC. In women with a high burden of comorbidity (CCI ≥2) or severe frailty, the percentage of women with ER-positive EIBC not having surgery increases as age of diagnosis extends above 70 years. Fewer than 50% of women aged ≥85 years had surgery in both the low-risk (Figure 3C) and high-risk (Figure 3D) subgroups. In women with no comorbidity or frailty, the increase in the percentage of women with ER-positive disease not having surgery is less marked, particularly among women with high-risk disease.

In contrast, among women with ER-negative disease, the relationship between age and the likelihood of not receiving surgery is largely unchanged by either the level of tumour risk or the level of physical fitness. Lastly, except for women with low-risk EIBC and poor physical fitness, the estimated rates of surgery among women aged 50-65 years are very similar (and the uncertainty associated with the curves (illustrated in Appendix 1)).

Table 3 describes the percentage of women with a post-operative inpatient stay exceeding 48 hours and other selected short-term outcomes. The differences between ER-positive and ER-negative groups, while statistically significant, are small. The risk of 30-day postoperative mortality is less than 1 in 500 women for both ER-positive and ER-negative groups and rates of 30-day emergency re-admission are also low (<3%). Across all ER subgroups, more women aged ≥70 years had a longer hospital stay following breast surgery compared to women aged 50-69 years. The difference in the percentage of women with a prolonged hospital stay was greater between the age groups, than between women with ER-positive and ER-negative EIBC.

Discussion

In this study of women aged ≥50 years diagnosed with unilateral EIBC in England and Wales, 87% of women had ER-positive and 13% had ER negative EIBC. This percentage was unaffected by age at diagnosis. In the analysis of treatment patterns for this cohort, older age at diagnosis was associated with a reduced likelihood of receiving surgery, and this relationship differed according to ER status. Overall, only 8% of women did not have surgery but in women aged ≥80 years, the percentages for the ER-positive and ER-negative subgroups were 42% and 12%, respectively. For women with ER-positive EIBC, the relationship between the likelihood of surgery and age was strongly influenced by the level of tumour risk and physical fitness. In contrast, among women with ER-negative EIBC, the influence of these factors was less marked. Although the comorbidity burden level and frailty among older women was similar across the ER-status subgroups, the short-term outcomes after breast surgery were broadly similar despite a higher percentage of women with ER-negative EIBC receiving surgery.

Currently, few studies of treatment patterns provide results for both ER-positive and ER-negative subgroups of older women with EIBC. When considered as separate cohorts, the observed rate of surgery among women aged ≥ 70 years with ER-positive EIBC in this study was higher than rates of 54 – 72% reported in earlier UK based studies[3, 4, 11]. Yet, this rate of surgery for women with ER-positive EIBC remains lower than those reported in countries such as the Netherlands and the USA[23-25]. In comparison, a population-level study of treatment patterns in older women with ER-negative EIBC in the USA reported rates of surgery that were similar to those reported in this study[26].

There is no evidence to support a different approach to primary treatment for EIBC in older women based solely on ER status. PET is available as a systemic treatment option for older women with ER-positive EIBC and poor fitness, but there is no equivalent alternative for women with ER-negative breast cancer. It would not be appropriate for all older women with EIBC to be offered surgery regardless of their functional or fitness level[27]. However, it may be that health professionals are more inclined to offer surgery in older women with ER-negative EIBC and comorbidities or frailty than their ER-positive counterparts. A noteworthy result from this study is the greater percentage of older women with ER-positive EIBC not undergoing surgery despite no record of comorbidity or frailty. This is inconsistent with the SIOG/EUSOMA recommendations that "*PET should only be offered to elderly individuals with ER-positive tumours who have a short estimated life-expectancy (<2-3 years), who are considered unfit for surgery after optimization of medical conditions…"*[9]. Although patient preferences may account for some of the differences in the rate of surgery between women with ER-positive and ER-negative EIBC, these are likely to be strongly influenced by the advice given by their health professionals[28, 29].

The estimation of life expectancy among older patients with breast cancer is complex, and has been shown to be inconsistent among healthcare professionals[30]. For those patients whose life expectancy is under-estimated, it is possible that the current recommendations for older women with ER-positive EIBC[2, 9] are leading to less advocacy for surgical resection when treatment options are discussed. This is despite little evidence to suggest that older age is associated with a higher risk of adverse surgical outcomes after breast surgery[31]. Inconsistencies in assessing the prognosis from EIBC and competing risks of death from underlying comorbidities and frailty are also likely to contribute to this. In addition, few UK breast cancer units have designated specialists or operational dedicated service pathways to objectively assess and optimise patient fitness for surgery[30].

There were several strengths to this study. First, the study used information from national cancer registration data that was linked to routinely collected administrative datasets, using pseudonymised patient identifiers. This approach produced a patient cohort that is likely to be an accurate representation of current clinical practice in England and Wales. Second, the regression model developed during the analysis demonstrated good calibration and discrimination, suggesting that the predictions describing the influence of age on the rate of surgery for ER-positive and ER-negative EIBC are reliable.

The study also has several limitations. Firstly, routinely collected cancer registration and hospital data may contain errors in the coding of surgical procedures, which could influence the estimated treatment rates. However, validation work has shown HES to accurately capture major procedures, with 90-93% agreement with data provided by surgeons[32]. Secondly, these datasets have few data items on measures of patient fitness[7]. This study therefore adopted a similar methodology to other UK based studies[3, 11] and used the diagnostic information in the administrative datasets to derive measures of fitness (CCI and SCARF index). Given that administrative datasets such as HES and PEDW do not capture all comorbid conditions, this approach may under-estimate the burden of poor fitness within this cohort. Nonetheless, the study observed the expected increase in prevalence of comorbidities and frailty with older age. Lastly, the results were based on a complete case analysis, with 10% of records dropped because they did not have a known ER status and another 14% of records dropped because of missing values (mostly related to HER-2 status (9%)). This might introduce bias in the observed relationship between ER status and the outcomes, but the effect is likely to be small. Furthermore, the distributions of missing data were similar among women with ER-positive and ER-negative, so it is unlikely that any issues in data capture would affect the two ER status subgroups differently.

In conclusion, the percentage of women receiving surgery for ER-positive EIBC in England and Wales decreased at a faster rate with older age, compared to women with ER-negative EIBC. Moreover, the relationship between the likelihood of surgery and age was strongly influenced by the level of tumour risk and degree of patient fitness among women with ER-positive EIBC. The reasons for these observed differences in treatment patterns, especially in the absence of poor fitness, are unclear. Assessment for suitability and advice for surgery should be consistent for all older women with EIBC, and clinical guidelines should aim to be clear and objective in their recommendations.

Additional information

Ethics approval

The study is exempt from UK National Research Ethics Committee approval as it involved secondary analysis of an existing dataset of anonymised data. The NABCOP has approval for processing health care information under Section 251 (reference number: 16/CAG/0079) for all NHS patients aged 50 years and over diagnosed with breast cancer in England and Wales.

This work uses data that has 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 Cancer Registration and Analysis Service, which is part of Public Health England (PHE). Access to the data was facilitated by the PHE Office for Data Release.

Data sharing

No additional data available. Data on English cancer registrations can be accessed via the Office for Data Release at Public Health England. https://www.gov.uk/government/publications/accessingpublic-health-england-data/about-the-phe-odr-and-accessingdata.

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