**Abstract**

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

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

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

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

## Introduction

Women 65 years and older in the UK are less likely to have primary surgery for early operable breast cancer compared to younger postmenopausal women[1;2]. Previous studies demonstrate reduced odds of surgery from the age of 70 years and older[3;4]. The King's Fund reports that improved management of older cancer patients could reduce overall cancer mortality in England[5]. The impact of lack of surgery on older patients' survival needs to be investigated. There is good evidence that poor survival is a particular problem for older breast cancer patients in the UK. Moller *et al* (2010) found that the 5 year relative survival for women aged ≥80 years is 61% in UK compared to 74% in Norway & Sweden. Moreover the excess death rate for British breast cancer patients increases dramatically with age group compared to those in Norway and Sweden, particularly in the first year after diagnosis,[6] which 'leads to important questions about the adequacy of care provided for the oldest patients.' However, Moller *et al* did not investigate the effect of access to treatment on survival. Moreover, the proportion of patients with co-morbidities or frailty, and later stage breast cancer increase with age and both of these factors may also effect survival.

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

## Method

This paper analyses of short term (3.8 years) breast cancer specific survival, undertaken as a subsidiary study of a wider research programme involving a cohort of 944 women aged ≥65 years diagnosed with early stage (1-3a) breast cancer (from 01/07/10- 31/03/13) at 22 UK breast units. The main study, investigating the impact of health and choice on older patients' access to surgical treatments, is reported elsewhere[1]. This paper focuses on 910 members of the cohort with a diagnosis date up to 31/12/12 in order that all participants had > 3 years survival at the time of analysis. As breast cancer mortality in the UK rises sharply from the age of 70 years, 65-69 year olds are included here as a reference group[4;7]. Data on surgical treatment, pre-operative health measures and tumour characteristics were collected by patient interview (at diagnosis/ before surgery if undertaken) and/or case note review (at 3 months post diagnosis)[1]. Surgery rates did not differ significantly between breast units[1]. The core variables used in this survival analysis were collected for the entire sample, including 136 eligible participants aged 65-69 years. All participants were followed up to a census date of 5/2/16 i.e. 37 months from the last participant entering the study. The primary end point is breast cancer specific mortality, which was defined as time from diagnosis to death due to breast cancer. Cause of death was based on underlying cause of death provided by the Health and Social Care Information Centre. Participants dying from other causes were censored at their date of death.

Independent variables include undergoing primary surgery (mastectomy or wide local excision) within 90 days of diagnosis, age group, socio-economic status[8], co-morbidity (Charlson Index 0, 1, 2+)[9] and functional status group (ELPHS ADL 1-2 vs. 3-4)[10]. Pre-treatment assessment of steroid receptor status, grade and tumour stage (1 vs. 2-3a) based on clinical, imaging and fine needle/core biopsy assessments were recorded[11]. Expected and observed deaths were compared using the log rank test ($\alpha < 0.05$). A disease free survival curve comparing patients who received vs those who did not receive surgery was plotted using the Kaplan–Meier method and compared by means of the log rank test. Cox's proportional hazards regression was used to examine the effect of surgery on survival adjusting for age, tumour stage, grade, steroid receptor status, co-morbidity and functional status. Data were analysed using Stata version 12.1[12]. Ethical approval was granted by the UK NHS National Research Ethics Service (10/H1014/32 & 33).

## Results

Of the 910 women in the study (mean age 77.01 95% CI: 76.55 – 77.46), 178 died before the end point of the study (5/2/16): 71 of breast cancer and 107 of other causes. The mean follow up time was 3.76 years (95% CI: 3.69-3.83). Baseline characteristics of the sample are detailed in Table 1. The number of observed breast cancer deaths significantly exceeded those expected, for participants whom did not have primary surgery, were aged ≥85 years, were steroid receptor negative and had a higher grade or stage tumour (Table 1); the difference in death rate between patients who received primary surgery vs those who did not is illustrated in the Kaplan Meier plot (figure 1) ($P < 0.001$). The same variables predicted increased hazard of breast cancer death in univariate Cox's regression analyses (Table 2).

Adjusting for tumour stage, comorbidity and functional status, women undergoing primary surgery had a third the hazard of dying of breast cancer compared to those not undergoing surgery (Table 2). Those who were steroid receptor test negative (vs. positive) had over twice the hazard of breast cancer death (Table 2).

## Discussion

These results are in broad agreement with previous studies both in the UK and elsewhere. Surgery has become such a mainstay of treatment for early stage breast cancer that trials testing its efficacy for older patients are scarce and subject to poor recruitment[13;14]. Morgan *et al*'s (2014) Cochrane review of primary surgery vs. medical treatment with endocrine therapy for breast cancer patients aged ≥70 years included two trials (based in UK and Italy) which had breast cancer specific survival as an outcome. Combined analyses indicate reduced hazard of breast cancer death for patients undergoing primary surgery (HR 0.70 95% CI: 0.51 – 0.95)[15]. Amongst observational studies, Bourchardy *et al* (2007) found that both mastectomy and breast conserving surgery followed by adjuvant treatment significantly reduced the hazard of dying of breast cancer (HR 0.2 (95% CI: 0.1-0.7) & HR 0.1 (95% CI: 0.03-0.4) respectively) amongst 407 patients aged ≥80 years in the United States[16]. More recently Cortadellas *et al* (2013) also found that surgery increased breast cancer survival in a prospective cohort study of 259 Spanish breast cancer patients aged ≥80 years[17]. The finding that surgery increases survival are by no means universal: Traa *et al* (2011) for example found that surgery did not significantly reduce the hazard of dying of breast cancer amongst a cohort of 346 breast cancer patients aged ≥75 years in the Netherlands (HR 0.78 95% CI: 0.44-1.39)[18]. However, Traa *et al* did not adjust for co-morbidities, which they comment is a limitation of their results.

Previous cohort studies have adjusted for a range of explanatory variables that may ameliorate the effects of surgery on survival for older breast cancer patients. Adjustment for tumour characteristics was based on improved prognosis for receptor positive and earlier stage breast cancer. However, although we have found and effect of steroid receptor status we did not find an effect of stage; probably due to the inclusion of only early stage breast cancer patients. Being aged 65 years or older was not found to predict breast cancer specific survival once tumour characteristics and surgical treatment were adjusted for. This finding supports breast cancer guidelines which state that age should not be the sole determinant in deciding treatment for patients[19]. However, it should be noted that the hazard of death for the oldest age group, women aged ≥85 years, was of borderline significance even adjusting for co-morbidities and functional status. Hence this result should be treated with caution.

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

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

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**TABLE 63: Baseline characteristics by observed and expected breast cancer-specific deaths (n = 910)**

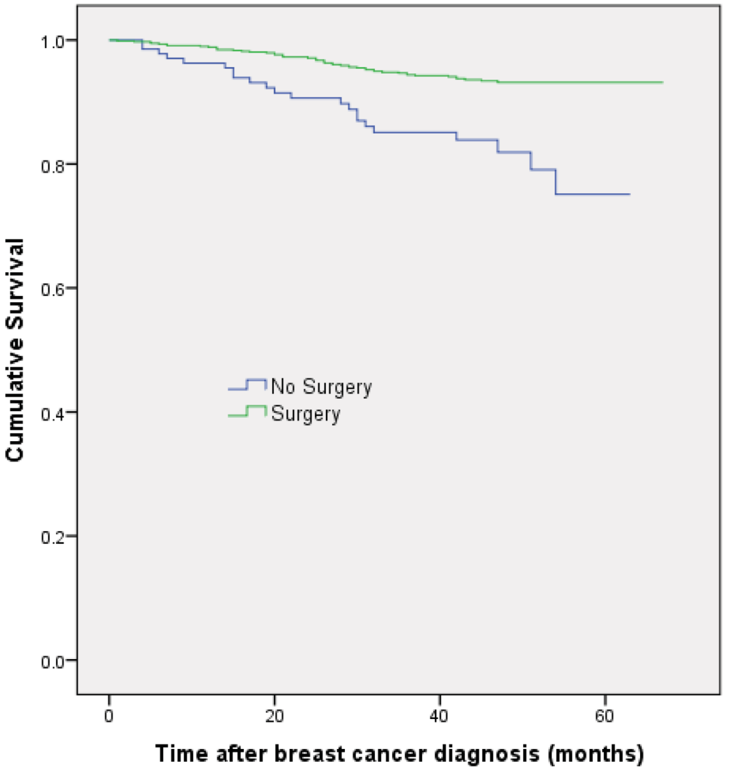
| Variable | Category | n | Percent | No. Deaths Observed | No. Deaths Expected | Log ranks test# P* |
|---|---|---|---|---|---|---|
| Primary surgery | Yes | 772 | 84.8 | 49 | 61.99 | |
| | No | 138 | 15.2 | 22 | 9.01 | **<0.001** |
| Age group (years) | 65-69 | 136 | 15.0 | 6 | 11.14 | |
| | 70-74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

* P values for each variable for complete data reported first followed by data including missings if relevant.
# The Log Rank test tests the equality of survivor function across groups

**TABLE 64: Cox's proportional hazards regression of breast cancer-specific survival (unadjusted n = 910, adjusted n = 906)**

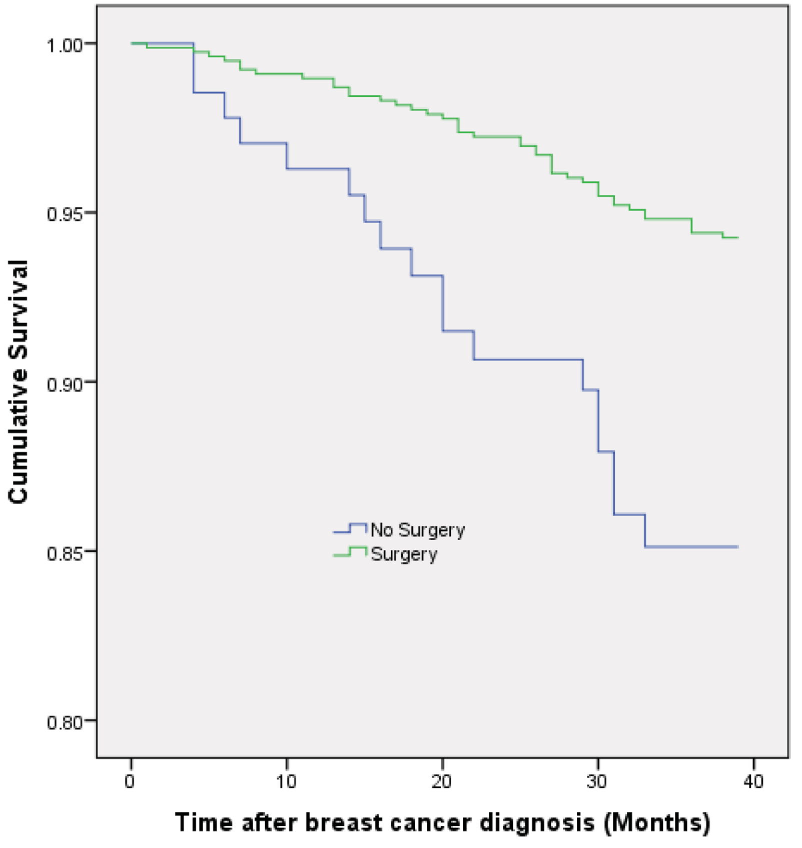
| Variable | Category | Unadjusted HR | Univariable 95% CI | P Value | Adjusted HR# | Multivariable 95% CI | P Value |
|---|---|---|---|---|---|---|---|
| Primary surgery | No | (ref) | | | (ref) | | |
| | Yes | 0.32 | 0.19-0.53 | **<0.001** | 0.36 | 0.20-0.66 | **0.001** |
| Age group (years) | 65-69 | (ref) | | | (ref) | | |
| | 70-74 | 1.53 | 0.61-3.86 | 0.364 | 1.31 | 0.52-3.34 | 0.565 |
| | 75-79 | 1.35 | 0.51-3.54 | 0.548 | 1.04 | 0.39-2.77 | 0.933 |
| | 80-84 | 2.39 | 0.92-6.22 | 0.074 | 1.72 | 0.65-4.56 | 0.272 |
| | 85+ | 4.02 | 1.61-10.01 | **0.003** | 2.61 | 0.99-6.91 | **0.053** |
| Grade | 1 | (ref) | | | (ref) | | |
| | 2 | 1.37 | 0.60-3.14 | 0.453 | 1.18 | 0.51-2.71 | 0.704 |
| | 3 | 4.55 | 2.01-10.31 | **<0.001** | 3.23 | 1.36-7.65 | **0.008** |
| | Missing | 1.34 | 0.39-4.57 | 0.642 | 1.10 | 0.30-4.00 | 0.890 |
| ER or PR positive | Yes | (ref) | | | (ref) | | |
| | No | 3.50 | 2.02-6.08 | **<0.001** | 2.75 | 1.49-5.09 | **0.001** |
| | Missing | 1.12 | 0.41-3.11 | 0.825 | 1.60 | 0.54-4.79 | 0.396 |
| Tumour Stage | I | (ref) | | | (ref) | | |
| | II and IIIa | 2.25 | 1.33-3.81 | **0.002** | 1.48 | 0.85-2.57 | 0.164 |
| Co-morbidity (Charlson) | 0 | (ref) | | | (ref) | | |
| | 1 | 1.02 | 0.60-1.74 | 0.935 | 0.97 | 0.56-1.67 | 0.917 |
| | 2+ | 0.96 | 0.50-1.84 | 0.902 | 0.80 | 0.41-1.57 | 0.518 |
| Functional status* | Independent (1-2) | (ref) | | | (ref) | | |
| | Dependent (3-4) | 1.69 | 0.97-2.95 | 0.064 | 1.00 | 0.53-1.88 | 0.995 |

# Adjusted for all other variables in table
* Missing data omitted as only 4 cases. See Table 1




| No. at risk | | | |
|---|---|---|---|
| No Surgery | 138 | 114 | 80 |
| Surgery | 772 | 734 | 654 |

FIGURE 22. Kaplan Meier breast cancer-specific survival curve for patients not treated with surgery vs. treated with surgery for breast cancer




| No. at risk | | | | | |
|---|---|---|---|---|---|
| No Surgery | 138 | 129 | 114 | 98 | 84 |
| Surgery | 772 | 761 | 734 | 710 | 689 |

FIGURE 23. Kaplan Meier breast cancer-specific survival curve for patients not treated with surgery vs. treated with surgery for breast cancer (patients censored at 37 months).