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

Older women 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]. They conclude that this '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.

Guidelines state that adjuvant therapy should be considered for all patients with early invasive breast cancer (NICE, 2009: 1.65). Radiotherapy is strongly recommended following breast conserving surgery and should be offered to patients after mastectomy who are at high risk of recurrence (NICE, 2009: 1.11.1 & 1.11.3). Although recommendations for chemotherapy are less clear cut, it is advised that the decision should be based on prognostic and predictive factors and the potential benefits and side effects of treatment (NICE, 2009: 1.6.6). Guidelines converge in stating that treatment of breast cancer patients should be based on tumour characteristics, patient health and choice. The role of age in considering treatment options is more contested; NICE guidelines (2009) state that breast cancer treatments should be offered to patients with early stage cancer irrespective of age whereas European Society for Medical Oncology guidelines (2015) recommend taking age into account along with other factors in breast cancer treatment planning. EMSO states breast cancer treatment "should be based on the tumour burden/location (size and location of primary tumour, number of lesions, extent of lymph node involvement) and biology (pathology, including biomarkers and gene expression), as well as the age and general health status of the patient.

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

Study Design. This study followed an established cohort of patients aged ≥65 years to three years after diagnosis. At diagnosis all patients had early stage (stage 1 to IIIa) invasive breast cancer and were recruited from 22 Trusts in England between 01/07/2010 to 31/03/2013; more details of methods, inclusion and exclusion criteria can be found elsewhere (Lavelle *et al*, 2014). The primary outcomes were curative adjuvant treatment, either radiotherapy or chemotherapy within 12 months of diagnosis, adjusting for health measures, type of primary surgery, tumour characteristics demographics and patient choice.

For more details on explanatory variables see Lavelle *et al* (2014), but in brief measures of health were Charleson Index of Co-morbidity (Charlson *et al,* 1987), Elderly Population Health Status Survey's (ELPHS), ADL (Sharpes *et al,* 2002) functional status measure and Eastern Co-operative Oncology Group-Performance Status (Oken *et al*, 1982). Primary surgery was classed either

mastectomy or wide local excision within 3 months of diagnosis. Tumour characteristics, based on biopsy, imaging and clinical assessment, were pre-surgical assessment of stage, grade, nodal and steroid receptor status (oestrogen and progesterone). ((cTNM (UICC, 2009)). Socioeconomic classification was measured using the Office of National Statistics Socio-Economic Classification (ONS, Office of National Statistics, 2013).

Patient choice: Patient choice was measured using Degner *et al* (2007) control preferences scale (CPS). This is a five point scale where the patient identifies if they were active, collaborative or passive in the treatment decision. The patient has 2 options if they considered themselves active in the decision; I made the final decision about which treatment I would receive or I made the final decision about my treatment after seriously considering my doctor's opinion. They have 1 choice for collaborative; my doctor and I shared responsibility for deciding which treatment was best for me. If the patient thinks the doctor made the treatment decision and they were passive they have 2 choices; my doctor made the final decision about which treatment would be used but seriously considered my opinion or my doctor made the final decision about which treatment I would receive.. Choice was measured for both the chemotherapy and radiotherapy treatment decision. The CPS can only be used if a treatment decision was discussed and therefore patients were given the option of indicating they were given no choice as chemotherapy or radiotherapy treatment was not discussed with them.

Data collection: A case note review was carried out 3 years post-diagnosis using a proforma developed for the project. Data was extracted on radiotherapy and chemotherapy, which treatments were received. Patients were classed as receiving curative adjuvant treatment if they initially underwent primary surgery (within 3 months of diagnosis) and were treated with radiotherapy and/or chemotherapy (within 12 months of diagnosis) and they did not have metastatic disease or a recurrence of breast cancer. Inter-rater agreement was checked for 10% of the pro-formas and satisfied Kappa > 0.6 showing substantial to perfect agreement (Landis and Koch, 1977).

Surviving patients who were not precluded from further contact (e.g. due to cognitive impairment) were surveyed for role in the adjuvant treatment decision using the CPS (Degner *et al,* 1997). Surveys

and a freepost envelope for survey return were posted where possible at 3 years post diagnosis (-/+ 2 weeks). However, due to timing of the receipt of project funding 39% patients were surveyed at 3-4 years post diagnosis. If a patient did not reply within 2 weeks a further survey was posted out. If again no reply was received in 2 weeks the patient was contacted by telephone and offered the option of completing the survey by telephone at a convenient time. If patients did not want to complete the questionnaire and did not want any further contact, they were offered the option of returning the blank survey in the freepost envelope. Postal surveys were sent out to 628 of the sample (91.3%) and returned by 513 (81.7% return rate). Ten per cent of case note review proformas and 10% of patient surveys were checked for data input errors. Data input errors were less than 0.3% and therefore no further checking was necessary.

Sample size. As this study was following up an existing cohort, the sample size was circumscribed to the patients that were originally recruited. Initially 944 patients were recruited from 01/07/2010 to 31/03/2013. For this project patients recruited after 31/12/12 were excluded in order that all patients would have at least 3 years follow up at case note review. Other reasons for exclusion were that the case notes were not available (34 patients), patients died (16) or moved away (55 patients) within 12 months. This study was concerned with adjuvant treatment in addition to primary surgery so all patients who were not treated with surgery were removed from the sample. Following these exclusions, the final sample was 688 patients (figure 1).

Analyses: Explanatory variables were investigated in univariable analysis using Pearson's χ^2 test, Fisher's exact test, and χ^2 test for trend. Logistic regression analyses of receipt of adjuvant chemotherapy and radiotherapy, adjusted for health measures, patient preference, tumour characteristics and demographic variables. Tumour characteristics include those used to determine chemotherapy status in clinical guidelines (tumour stage, grade, nodal and steroid receptor status). As clinical guidelines indicate that radiotherapy is necessary after lumpectomy but not always following mastectomy (NICE, 2009), multivariate logistic regression predicting receipt of radiotherapy was also

limited to the number of patients in the cohort receiving lumpectomy. Logistic regression models should have around ten patients for each explanatory variable for both categories of the dependent variable (Bland, 2005; Peduzzi, 1996), although in other scenarios it has been shown that five patients for each explanatory variable is sufficient (Vittinghoff, 2007). To help meet this guidance, variables in the multivariate models were limited to those essential to the core research question and with significant coefficients (at the 5 per cent level) in the univariate analyses. Both the main and nested models were tested for goodness of fit (Hosmer & Lemeshow, 2000), variance inflation factors and discrimination (area under receiver operating characteristic curve). Data were analysed using STATA version 12.

Survival analysis is based 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 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 ($\alpha < 0.05$). 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

Adjuvant Therapy. To analyses adjuvant therapy 688 patients were included all of whom had primary surgery (45.1% mastectomy and 54.9% wide local excision). Of those who had primary surgery, 90 (13.1% 95% CI: 10.7-15.8) also had chemotherapy and 453 (65.8% 95% CI: 62.2-69.4) radiotherapy. The mean age of the patients in the sample was 75.7 years (95% CI: 75.2-76.1) (table 1). Just over half the patients had a Charlson Co-morbidity score of 0, 90% had independent functional status and 74.3% had a performance status of 0-1. The stage of disease in 48.8% of patients was 1 and 51.2% patients had stage 2-3a disease. The majority of patients (83.7%) had an oestrogen or progesterone positive tumour and most had grade 2 disease (53.2%).

Chemotherapy : The univariable analysis showed unsurprisingly that significantly more patients in the 65-69 year age group had chemotherapy compared patients aged 85 years and older, 25.4% compared to 1.6% (P<0.001) (Table1). Chemotherapy rates were also significantly higher for patients with stage 2 or 3a disease (18.5%) compared to stage 1 (7.4%) (P <0.001) and oestrogen or progesterone negative tumours (36.9%) compared to oestrogen and progesterone positive tumours (10.9%) (P<0.001). The proportion of patients receiving chemotherapy was 18% more in patients with a grade 3 tumour compared to patients with a grade 2 tumour, and over 27% compared to patients with a grade 1 tumour (P<0.001). Patients were significantly less likely to receive chemotherapy if they perceived that the choice of having or not having chemotherapy was not discussed with them (2.8%) compared to patients who stated they were given a choice but did not indicate the role they took (37.5%) or those active (43.8%) or passive (50.0%) in the treatment decision (P<0.001). In the univariate analysis, measures of health and functional status were not significantly associated with receiving chemotherapy.

TABLE 57 Baseline characteristics and adjuvant treatment (n = 688)

Baseline Characteristics				Adjuvant Treatment					
				Chemotherapy			Radiotherapy		
Variable	**Category**	**n**	**%**	**n**	**%**	**P***	**n**	**%**	**P***
Age group (Years)	65-69	118	17.2	30	25.4		88	74.6	
	70-74	233	33.9	45	19.3		176	75.5	
	75-79	175	25.4	12	6.9		107	61.1	
	80-84	99	14.4	2	2.0		55	55.6	
	85+	63	9.2	1	1.6	**<0.001**[c]	27	42.9	**<0.001**[c]
Co-morbidity (Charlson)	0	383	55.7	54	14.1		258	67.4	
	1+	305	44.3	36	11.8	0.375[d]	195	63.9	0.346[d]
Functional status	Independent (1-2)	619	90.0	86	13.9		422	68.2	
	Dependent (3-4)	67	9.7	4	6.0	0.068[d]	29	43.3	**<0.001**[d]
	Missing	2	0.3	0	0	0.137[e]	2	100	**<0.001**[e]
Performance status	0-1	511	74.3	72	14.1		357	69.9	
	2+	163	23.7	14	8.6	0.067[d]	86	52.8	**<0.001**[d]
	Missing	14	2.0	4	28.6	**0.033**[e]	10	71.4	**<0.001**[d]
Surgery[a]	Mastectomy	310	45.1	50	16.1		100	32.3	
	Wide Local Excision	378	54.9	40	10.6	**0.032**[d]	353	93.4	**<0.001**[d]
Stage	1	336	48.8	25	7.4		245	72.9	
	2 & 3a	352	51.2	65	18.5	**<0.001**[d]	208	59.1	**<0.001**[d]
Nodal involvement	No/not recorded	501	72.8	32	9.5		226	67.3	
	Yes	187	27.2	39	31.2	**<0.001**[d]	87	69.6	0.633
ER or PR positive	Yes	576	83.7	63	10.9		380	66.0	
	No	65	9.5	24	36.9	**<0.001**[d]	44	67.7	0.781[d]
	Missing	47	6.8	3	6.4	**<0.001**[e]	29	61.7	0.794[d]
Grade	1	131	19.0	3	2.3		94	71.8	
	2	366	53.2	42	11.5		245	66.9	
	3	133	19.3	40	30.1	**<0.001**[e]	87	65.4	0.497[d]
	Missing	58	8.4	5	8.6	**<0.001**[e]	27	46.6	**0.008**[d]
Socioeconomic classification	Professional	379	55.1	56	14.8		251	66.2	
	Intermediate	180	26.2	23	12.8		113	62.8	
	Manual	125	18.2	11	8.8	0.227[d]	85	68.0	0.600[d]
	Missing	4	0.6	0.0	0.0	0.349[e]	4	100	0.453[e]
Chemotherapy choice	Active/collaborative	80	11.6	35	43.8				
	Passive	48	7.0	24	50.0				
	No choice	325	47.2	9	2.8				
	Choice[b]	8	1.2	3	37.5	**<0.001**[e]			
	Missing/Died	227	33.0	19	8.37	**<0.001**[e]			
Radiotherapy choice	Active/collaborative	200	29.1				162	81.0	
	Passive	108	15.7				98	90.7	
	No choice	156	22.7				61	39.1	
	Choice[b]	28	4.1				22	78.6	**<0.001**[d]
	Missing/Died	196	28.5				110	56.1	**<0.001**[d]
Total		688	100	90			453		

Abbreviations: NR = Not recorded

[a]Most extensive surgery [b]Patient indicated they had a choice but did not select a role [c]χ^2 test for trend for age [d] χ^2 Pearson [e]Fisher's exact test *P values <0.05 are shown in bold

TABLE 58. Multivariable logistic regression of receiving chemotherapy (vs. not receiving chemotherapy) (unadjusted odds n = 688, adjusted odds n = 686)[a]

Variable	Category	Unadjusted odds ratio	95% CI	P value*	Adjusted odds ratio[c]	95% CI	P value*
Age	65-69	(ref)	-	-	(ref)	-	-
	70-74	0.70	0.41-1.19	0.188	0.43	0.21-0.89	**0.021**
	75-79	0.22	0.11-0.44	**<0.001**	0.06	0.02-0.16	**<0.001**
	80-84	0.06	0.01-0.26	**<0.001**	0.03	0.00-0.14	**<0.001**
	85+	0.05	0.01-0.36	**0.003**	0.02	0.00-0.15	**<0.001**
Co-morbidity	0	(ref)	-	-			
	1+	0.82	0.52-1.28	0.376			
Functional Status	Independent (1-2)	(ref)	-	-	(ref)	-	-
	Dependent (3-4)	0.39	0.14-1.11	0.078	0.28	0.08-1.07	0.058
Performance Status	0-1	(ref)		-			
	2+	0.57	0.31-1.05	0.070			
	Missing	2.44	0.74-7.98	0.141			
Surgery	Mastectomy	(ref)	-	-	(ref)	-	-
	WLE	0.62	0.39-0.96	**0.033**	0.81	0.43-1.55	0.530
Stage	1	(ref)	-	-	(ref)		
	2 & 3a	2.82	1.73-4.59	**<0.001**	2.89	1.49-5.62	**0.002**
Nodal involvement	No/NR	(ref)	-	-			
	Yes	3.2	2.04-5.06	**<0.001**			
ER & PR Positive	Yes	(ref)	-	-	(ref)		
	No	4.77	2.70-8.41	**<0.001**	1.4	0.62-3.06	0.432
	Missing	0.56	0.17-1.84	0.336	0.49	0.10-2.43	0.380
Grade	1	(ref)	-	-	(ref)		
	2	5.53	1.68-18.16	**0.005**	2.57	0.69-9.55	0.160
	3	18.35	5.51-61.13	**<0.001**	14.82	3.80-57.79	**<0.001**
	Missing	4.03	0.93-17.45	0.063	6.09	1.09-33.93	**0.039**
SEC[a]	Professional	(ref)	-	-			
	Intermediate	0.84	0.50-1.42	0.527			
	Manual	0.56	0.28-1.10	0.092			
Choice	Active/collaborative	(ref)	-	-	(ref)		
	Passive	1.29	0.63-2.64	0.493	1.44	0.61-3.41	0.408
	No choice	0.04	0.02-0.81	**<0.001**	0.05	0.02-0.14	**<0.001**
	Choice[b]	0.77	0.17-3.45	0.734	1.72	0.22-13.20	0.603
	Missing/Died	0.12	0.06-0.22	**<0.001**	0.15	0.07-0.32	**<0.001**

Abbreviations: SEC = Socioeconomic classification, ER = Oestrogen receptor positive PR = Progesterone receptor positive, WLE = Wide local excision, CI = Confidence interval, NR = Not reported

[a] SEC Missings are omitted from the model

[b]Patients indicated they were given a choice, but did not select a role

[c]Adjusted for all other variables in the column. Variables significant at 5% in univariable analyses entered into the multivariable model (axillary nodes represented within tumour stage and functional status included as representative/ most complete health measure -essential to research question). All variance inflation factors < 10. Goodness of fit test χ^2 Hosmer-Lemeshow = 5.11 d.f. = 8 P=0.746. Area under receiver operator characteristics curve= 0.922 *P values <0.05 are shown in bold

TABLE 59. Multivariable logistic regression of receiving radiotherapy (vs. not receiving radiotherapy) (unadjusted odds n = 688, adjusted odds n = 686)[a]

Variable	Category	Unadjusted odds ratio	95% CI	P value*	Adjusted odds ratio[c]	95% CI	P value*
Age	65-69	(ref)	-	-	(ref)	-	-
	70-74	1.05	0.63-1.75	0.844	1.37	0.67-2.83	0.389
	75-79	0.54	0.32-0.90	**0.018**	0.88	0.43-1.82	0.733
	80-84	0.43	0.24-0.76	**0.004**	0.98	0.43-2.23	0.962
	85+	0.26	0.13-0.49	**<0.001**	0.65	0.26-1.60	0.352
Co-morbidity	0	(ref)	-	-			
	1+	0.86	0.63-1.18	0.346			
Functional Status[a]	Independent (1-2)	(ref)	-	-	(ref)	-	-
	Dependent (3-4)	0.36	0.21-0.59	**<0.001**	0.39	0.16-0.92	**0.031**
Performance Status	0-1	(ref)	-	-	(ref)	-	-
	2+	0.48	0.34-0.69	**<0.001**	0.82	0.46-1.45	0.492
	Missing	1.08	0.33-3.49	0.900	1.27	0.24-6.68	0.777
Surgery	Mastectomy	(ref)	-	-	(ref)	-	-
	WLE	29.7	18.53-47.46	**<0.001**	38.03	20.92-69.13	**<0.001**
Stage	1	(ref)	-	-	(ref)	-	-
	2 & 3a	0.54	0.39-0.74	**<0.001**	2.24	1.30-3.83	**0.003**
Nodal Involvement	No/NR	(ref)					
	Yes	0.96	0.68-1.4	0.839			
ER & PR Positive	Yes	(ref)	-	-			
	No	1.08	0.62-1.87	0.781			
	Missing	0.83	0.45-1.53	0.554			
Grade	1	(ref)	-	-	(ref)	-	-
	2	0.80	0.51-1.24	0.310	1.00	0.52-1.92	0.999
	3	0.74	0.44-1.25	0.268	1.46	0.69-3.08	0.321
	Missing	0.34	0.18-0.65	**0.001**	0.50	0.19-1.33	0.164
SEC[a]	Professional	(ref)	-	-			
	Intermediate	0.86	0.59-1.24	0.424			
	Manual	1.08	0.70-1.67	0.715			
Choice	Active/collaborative	(ref)	-	-	(ref)	-	-
	Passive	2.30	1.10-4.82	**0.028**	2.22	0.92-5.34	0.076
	No choice	0.15	0.09-0.24	**<0.001**	0.23	0.12-0.43	**<0.001**
	Choice[b]	0.86	0.33-2.27	0.761	2.37	0.73-7.63	0.149
	Missing/Died	0.30	0.19-0.47	**<0.001**	0.51	0.28-0.92	**0.026**

Abbreviations: SEC = Socioeconomic classification, ER = Oestrogen receptor positive PR = Progesterone receptor positive, CI = Confidence interval, NR = Not Recorded

[a] Missings are omitted from the model. See table 1.

[b]Patients indicated they were given a choice, but did not select a role

[c]Adjusted for all other variables in the column. Variables entered into the multivariable model if significant at the 5% level in the univarible analyses. All variance inflation factors < 10. Goodness of fit test χ^2 Hosmer-Lemeshow = 4.18 d.f. = 8 P = 0.840. Area under receiver operator characteristics curve= 0.907

*P values <0.05 are shown in bold

TABLE 60 Multivariable logistic regression of receiving radiotherapy (vs. not receiving radiotherapy) for patients who were treated with wide local excision. (unadjusted odds n = 378, adjusted odds n = 376)

Variable[a]	Category	Unadjusted odds ratio	95% CI	P value*	Adjusted odds ratio[c]	95% CI	P value*
Age	65-69	(ref)			(ref)	-	-
	70-74	2.32	0.69-7.85	0.176	2.35	0.69-8.09	0.174
	75-79	0.90	0.29-2.81	0.860	0.92	0.29-2.91	0.884
	80-84	0.99	0.23-4.17	0.985	1.12	0.25-4.94	0.883
	85+	0.34	0.09-1.34	0.123	0.60	0.13-2.69	0.504
Functional Status[d]	Independent (1-2)	(ref)			(ref)	-	-
	Dependent (3-4)	0.27	0.09-0.78	**0.016**	0.30	0.09-0.98	**0.046**
Choice	Active/collaborative	(ref)					
	Passive	2.15	0.44-10.59	0.348			
	No choice	0.28	0.10-0.79	**0.016**			
	Choice	0.69	0.08-6.05	0.737			
	Missing/Died	0.71	0.23-2.18	0.546			
Choice	Choice[b]	(ref)			(ref)	-	-
	No choice	0.23	0.9-0.60	0.003	0.26	0.09-0.70	**0.008**
	Missing/Died	0.59	0.21-1.68	0.322	0.63	0.22-1.84	0.403

[a]Tumour characteristics omitted from model as not significant

[b]Patients perceived they had been given a choice

[c]Adjusted for all other variables in the column. All variance inflation factors < 10. Goodness of fit test χ^2 Hosmer-Lemeshow = 1.33 d.f. = 5 P=0.932. Area under receiver operator characteristics curve= 0.737

[d] Missings not included in model (n = 2)

*P values <0.05 are shown in bold

In the multivariable analysis the odds of having chemotherapy were significantly greater for those having stage 2 & 3a compared to stage 1 tumours (OR 2.89, 95% CI: 1.49-5.62) and grade 3 compared to grade 1 tumours (OR14.83, 95% CI: 3.80-57.79) (Table 2). All participants aged 70 years and older had decreased odds of chemotherapy compared to 65-69 year olds and these odds decrease with age with those aged over 85 having 0.02 times the odds of chemotherapy compared to 65-69 year olds (95% CI: 0.00-0.15). Chance of chemotherapy was not significantly different if the patients were passive in the decision compared if they were actively involved in deciding to have the treatment (P = 0.408). However, if the patient perceived that the choice of having versus not having chemotherapy was not discussed with them, the odds of having chemotherapy significantly reduced to 0.05 (95% CI: 0.02-0.14). The reduction in odds of chemotherapy for those with dependent functional status failed to reach significance at the 5% level (P = 0.063)

The model was robust; all variance inflation factors were under 10, the goodness of fit test χ^2 showed no significant difference between observed and expected values (Hosmer-Lemeshow = 5.11 d.f. = 8 P=0.746) and the area under the receiver operator characteristics was 0.92 showing excellent discrimination (Hosmer and Lemeshow, 2000).

Radiotherapy

The analysis of whether or not patients received radiotherapy was first carried out on the whole sample of 688; this included patients treated with mastectomy as well as wide local excision. In the univariate analysis, older age, dependent functional status, a performance status of 2+, and not been offered a choice significantly reduced the chance that patients would be given radiotherapy (table1). Seventy four percent of patients aged 65 to 69 years had radiotherapy compared to 42.9% of patients aged 85 years and older (P<0.001). Patients with poorer measures of health had significantly reduced chance of having radiotherapy compared to those who were healthier; dependent functional status 43.3% of patients with dependent functional status had radiotherapy compared to 68.2% independent functional status patients (P<0.001) and 52.8% of patients with performance status 2+ had

radiotherapy compared to 69.9% with a performance status of 0-1 (P<0.001). Having primary surgery of wide local excision significantly increased the chance of having radiotherapy (93.4%) compared to 32.3% for patients whose primary surgery was a mastectomy (P<0.001).

In the multivariate analysis, adjusting for health, tumour characteristics, sociodemographics and choice, age was no longer a significant factor in receiving radiotherapy (table 3). However, patients with poorer health – a dependent functional status - had less chance of receiving radiotherapy (OR 0.36 95% CI: 0.16-0.92). Also patients who perceived that they were not offered a choice had 0.23 the odds of receiving radiotherapy compared to patients who were active in the decision (95% CI: 0.12-0.43). Patients who identified as being passive in the decision had 2.21 the odds of receiving the treatment compared to those who were active (95% CI: 0.92-5.34). Additionally, patients treated with wide local excision had over 38 times the odds of having radiotherapy compared to patients having mastectomy (OR 38.03 95% CI: 20.92-69.13).

The model was robust; all variance inflation factors were under 10, in the goodness of fit χ^2 showed no significant difference between observed and expected values (Hosmer-Lemeshow = 4.18 d.f. = 8 P=0.840) and the area under the receiver operator characteristics curve was 0.907 showing excellent discrimination (Hosmer-Lemeshow, 2000).

A sub group analysis was conducted on patients treated with wide local excision, as breast cancer guidelines strongly recommend radiotherapy after wide local excision whereas it is only advisable after mastectomy if the patient is a high risk of recurrence (table 4). However, the number of patients not receiving radiotherapy following breast conserving surgery was low at 25 of 378 patients (6.61%). This meant that the number of variables the model would support was reduced. Functional status was retained in the model as the most complete measure of health, which predicted receipt of radiotherapy in the univariate analyses. As passitivity was not significant in the univariable analysis, choice was reduced to whether the patient identified that they took a role in the treatment decision compared to if they perceived that a choice was not offered to them. In the final model older age did not predict having radiotherapy after wide local excision. However those with a dependent functional status had

just a third of the odds of radiotherapy (OR 0.3 95% CI: 0.09-0.98) and patients perceiving that the option of radiotherapy was not discussed with them had around a quarter of the chance of receiving this adjuvant treatment (OR 0.26 95% CI: 0.09-0.70).

The model was robust; all variance inflation factors were under 10, in the goodness of fit χ^2 showed no significant difference between observed and expected values (Hosmer-Lemeshow = 1.33 d.f. = 5 P=0.931) and the area under the receiver operator characteristics curve was 0.737 showing satisfactory discrimination (Hosmer-Lemeshow, 2000).

Survival analyses included all of the 910 women in the study (mean age 77.01 95% CI: 76.55 – 77.46),of whom 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 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 (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. Older age 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 to 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 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 61: 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 62: 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