Treatment choices for older women with primary operable breast cancer and cognitive impairment: Results from a prospective, multicentre cohort study.

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ABSTRACT

Objectives: The presence of dementia co-existing with a diagnosis of breast cancer may render management more challenging and have a substantial impact on oncological outcomes. The aim of this study was to examine the treatment and outcomes of older women with co-existing cognitive impairment and primary breast cancer.
Materials and methods: A prospective, multicentre UK cohort study of women aged 70 years or over with primary operable breast cancer. Patients with and without cognitive impairment were compared to assess differences in treatment and survival outcomes.
Results: In total, 3416 women were recruited between 2013 and 2018. Of these, 478 (14%) had a diagnosis of dementia or cognitive impairment, subcategorised as mild, moderate and severely impaired. Up to 85% of women with normal cognition underwent surgery compared to 74%, 61% and 40% with mild, moderate, and severe impairment ($p = 0.001$). Among women at higher risk of recurrence, the uptake of chemotherapy was 25% for cognitively normal women compared to 20%, 22% and 12% for mild, moderate and severe impairment groups ($p = 0.222$). Radiotherapy use was similar in the subgroups. Although patients with cognitive impairment had shorter overall survival (HR: 2.10, 95% CI: 1.77–2.50, $p < 0.001$), there were no statistically significant differences in breast cancer specific or progression-free survival.
Conclusion: Cognitive impairment appears to play a significant part in deciding how to treat older women with breast cancer. Standard treatment may be over-treatment for some women with severe dementia and careful consideration must be given to a more tailored approach in these women.

1. Introduction

Many diseases and co-morbidities are linked to ageing; the majority of cancers are more prevalent in older age groups and often present in patients with age-related co-morbidities, including dementia. With increasing age, the possibility of having a co-existing cancer and a diagnosis of dementia increases [1] and is associated with decreased cancer specific and overall survival [2,3].

It is estimated that 7–10% of breast cancer patients have a co-existent diagnosis of cognitive impairment (CI) or dementia [4]. Compared to non-cognitively impaired patients, this group has a six-fold higher risk of all-cause mortality within two years of diagnosis, which emphasises the importance of minimising treatment morbidity in this

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group [5]. Patients with dementia often present with later stage disease [6], which contributes to inferior breast cancer specific survival for these women [4,7]. Overall survival is also reduced in patients with dementia and cancer, as dementia increases the risk of all-cause mortality [8], in particular pneumonia [9]. Our previous analysis of UK registry data showed that patients with breast cancer and dementia have inferior overall and breast cancer specific survival if surgery is omitted [10]. Dementia was also an independent risk factor for non-guideline concordant care [4,11].

People living with dementia may present complex challenges from legal, ethical, and practical perspectives, particularly in cases where the patient does not have capacity to give informed consent to treatment and has not put in place an advance care plan. Dementia itself is a complex disease with multiple aetiologies and symptoms including memory loss, lack of cognitive capacity, confusion, and anxiety. The impact of cancer treatments will vary according to the severity of dementia and ability to monitor side effects. Surgery under general anaesthetic in the over 70s may cause prolonged post-operative cognitive dysfunction [12], acute post-operative delirium [13], and long-term cognitive decline, especially following major surgical resections, further compromising cognitive function [14]. The precise aetiology of this is not clear [15]. Cognitive impairment may also complicate the delivery of adjuvant treatments, including chemotherapy. For example, it is vital that patients receiving chemotherapy proactively report side-effects, including fever, which may signal life-threatening sepsis. Furthermore, patients undergoing chemotherapy may experience a degree of cognitive dysfunction, such as chemo-brain, which might exacerbate existing cognition problems in a person living with dementia [16,17].

In some cases, reduced life expectancy may reduce the risk of breast cancer mortality, especially with indolent cancers, and some low grade, oestrogen receptor positive (ER+) breast cancers. Primary endocrine therapy (PET), where surgery is omitted in women with ER+ breast cancer, may be selected in these situations, trading reduced therapeutic benefit (reduced breast cancer specific survival and a higher rate of local disease progression) against reduced surgical morbidity [18]. Primary endocrine therapy is not without adverse effects. These may include hot flushes, bone density loss and joint pain due to use of aromatase inhibitors, although the majority of women who have surgery will also be advised to take adjuvant aromatase inhibitors therapy for 5 years, so these side effects will affect both groups equally [19]. Some women with very low risk ER+ breast cancer may safely omit adjuvant endocrine therapy after surgery, especially in countries like the Netherlands where guidelines do not advise endocrine therapy for low risk ER+ breast cancers. The main disadvantage of PET is the risk of development of endocrine resistance after a median of ~3 years which may necessitate a change of management and an increased risk of failure of local and systemic disease control.

The decision-making process to select treatments for older patients is complex and wide variation exists in their use [20,21]. The treatment decision-making process for patients with dementia is therefore challenging and should include consideration of the cancer prognosis, the physical health of the patient, the degree of dementia or impairment, and the wishes of the patient and their caregivers. The aims of this study were to examine a large prospective UK cohort of older women with primary breast cancer, with or without co-existing CI or dementia, and evaluate their treatment patterns and survival outcomes.

2. Materials and Methods

2.1. Study Design

Ethics approval was granted by London South East Research Ethics Committee in November 2012 (12/LO/1808, IRAS ID: 115550). All patients (or their caregivers) gave written informed consent. The recruitment of participants with a formal diagnosis of dementia was compliant with Section 33 of the Mental Capacity Act (UK legislation to protect the rights of people with cognitive impairment) [22,23].

Bridging the Age Gap in Breast Cancer was a prospective UK multicentre cohort study, which collected data on patient and cancer characteristics, treatment allocation, and survival outcomes in older women (>70) with primary operable breast cancer [24–26].

To identify individuals with CI, participants who were assented to the study by a consultee were categorised as having severe impairment, as proxy consent was an indicator for the patient being unable to give informed consent to participate in the study. Where patients gave informed consent to participate, cognition status was ascertained through completion of the Charlson Index [27] form or the MMSE. The MMSE scored participants as having mild, moderate, or severe impairment according to standard scoring protocols (normal [27–30], mild CI [21–26], moderate CI [11–20], and severe CI (0—10)) [28]. The MMSE score always took precedence over Charlson Index categorisation if available, with participants re-categorised according to MMSE score. Where available, a review of current medications was also performed. Participants who were able to give informed consent to join the study and had no other indication of impairment were assumed to have normal cognition.

2.2. Study Data Collection

2.2.1. Baseline

Patient demographics and co-morbidity data were collected using a Modified Charlson Index score; for the purposes of this analyses, age and presence of dementia were omitted from the standard calculation. Functional status was determined by the validated Activities of Daily Living (ADL) score [29], Instrumental Activities of Daily Living (IADL) [30] and the Eastern Cooperative Oncology Group performance status (ECOG-PS) [31] scores. Nutritional status was assessed using the Abridged Patient Generated Subjective Global Assessment (aPG-SGA) [32–34]. Scoring of each tool followed standard published criteria. Primary breast tumour characteristics collected included grade, biological subtype and tumour stage (clinical, imaging and pathological stage used the TNM system, Version 8 [35]). Pathological axillary stage was not collected for patients who did not have surgery, but clinical assessment and preoperative ultrasound and biopsy of nodal disease were recorded.

2.2.2. Follow-up

All patients were directly followed up at 6 weeks, and at 6, 12, 18, and 24 months to collect data on the treatment they received, adverse events, recurrence, and survival. Cause of death was assessed by certification and classed as either breast cancer-specific or other cause. Recurrence and mortality were obtained directly from participating breast cancer units for up to 24 months and from the UK cancer registry (following specific patient or caregiver consent) for up to a median follow-up of 52 months.

2.2.3. Recruitment and Eligibility

Recruitment took place at 56 breast cancer units in England and Wales between February 2013 and June 2018. Participants were recruited after a new diagnosis of primary operable breast cancer. Eligibility criteria: women aged 70 or over, primary operable breast cancer (TNM: T1-3 and some T4b, N0-1, M0). Exclusion criteria: metastatic disease, previous invasive breast cancer within five years. There were no limits for language or cognitive function.

2.2.4. Data Analysis

Statistical analyses were performed in IBM SPSS (Version 26.0) and Stata (Version 16.1). Each patient or tumour characteristic was summarised in relation to cognitive category. Discrete characteristics were summarised by numbers and percentages, with statistical significance assessed by Chi-squared test. Continuous characteristics were summarised as the median and range, and statistical significance assessed by a non-parametric Kruskal Wallis test.

Overall survival and breast cancer specific survival were both compared between patients with CI (of any severity) and without impairment by propensity score matching. Two matching approaches were used. In the first analysis, patients with CI were matched with up to three non-impaired patients that had the same category of Nottingham Prognostic Index (NPI; risk categories ≤3.4, >3.4 to ≤5.4, >5.4), oestrogen receptivity (ER) and treatment (surgery and ER+, surgery and ER-, PET and ER+), and age to within a calliper width of one year (approximately 1/6th of a standard deviation) [36]. The second approach matched on NPI category, ER category, and treatment and also a more detailed propensity score including functionality (ADL, IADL, and ECOG), nutrition (aPG-SGA) and co-morbidity (CCI score excluding dementia and age) to a calliper of 0.015 propensity score units (approximately 0.2 standard deviations) with up to two matches allowed. The comparisons were quantified by Kaplan-Meier curves and Cox regression, presented for unadjusted and the matched analyses; matching was accounted for by use of shared frailty terms [37].

3. Results

3.1. Patient Characteristics

A total of 3416 women were included in the analysis. Of these, 2938 (86%) were considered to have normal cognition and 478 (14%) had

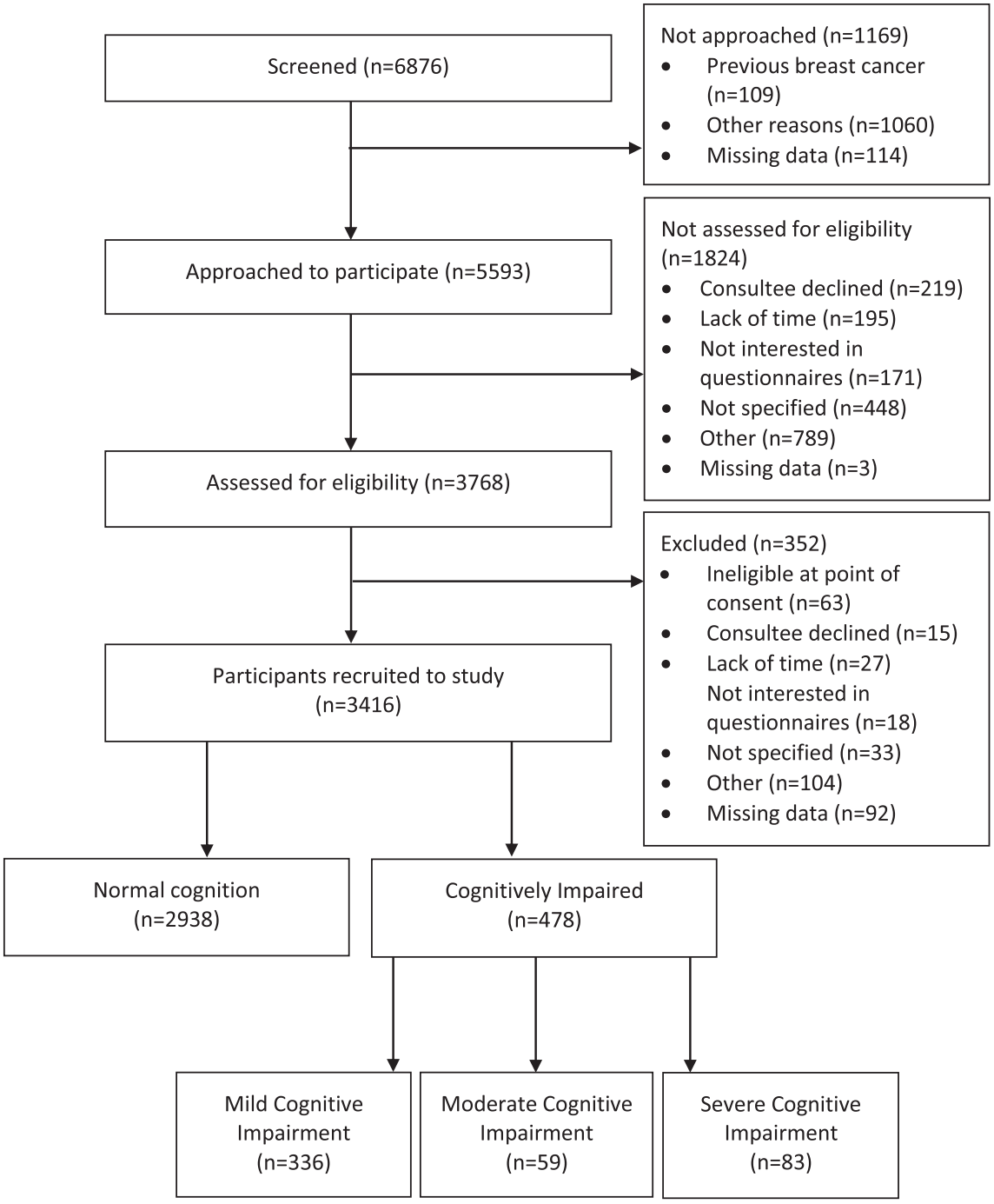

Fig. 1. Study recruitment summary (patient flow diagram).

Table 1
Baseline demographics and characteristics of study participants by cognitive impairment level.

	Cognition category				
	Normal function ($N = 2938$)	Mild impairment ($N = 336$)	Moderate impairment ($N = 59$)	Severe impairment ($N = 83$)	*P* value
Age					
Median (range)	76 (69–102)	79 (70–96)	80 (70–99)	83 (70–97)	<0.001
ADL Score*					
Completed	2607 (88.7%)	321 (95.5%)	57 (96.6%)	33 (39.8%)	
Median Score (range)	100 (5–100)	100 (30−100)	100 (30–100)	70 (20−100)	<0.001
Percentage (%) of women scoring[a]					
100	1982 (76.0%)	194 (60.4%)	29 (50.9%)	4 (12.1%)	
95	314 (12.0%)	40 (12.5%)	7 (12.3%)	2 (6.1%)	
≤90	311 (11.9%	87 (27.1%)	21 (36.8%)	27 (81.8%)	
IADL Score[b]					
Median (range)	8 (0–8)	8 (0–8)	7 (0–8)	2 (0–8)	<0.001
CCI Score[c]					
Median (range)	1 (0−13)	1 (0–7)	1 (0–8)	2 (0–7)	<0.001

[a] ADL scored according to Lawton and Brody (1969).
[b] IADL scored according to Lawton and Brody (1969).
[c] Age and presence of dementia was omitted from the CCI calculation.

some level of cognitive impairment, identified by MMSE score completion or a previous diagnosis of dementia (summarised in Fig. 1). The median age of women with normal cognition was 76 years (range 69–102; five women attended shortly before their 70th birthday and were retained in the study), while women with mild, moderate and severe CI had a median age of 79, 80 and 83, respectively. ADL, IADL and CCI scores are summarised in Table 1.

3.2. Tumour Characteristics

Tumour characteristics were similar between groups, with no statistically significant difference found in terms of nodal status, grade, ER and HER2 status. There was difference in the size of tumour at presentation; women with moderate or severe CI were more likely to have larger tumours than women with normal cognition (Chi-squared, $p < 0.001$) Table 2.

3.3. Treatment Selection

Primary treatment data were available for 3315 patients, of whom 2811 (82.3%) underwent surgery (+/− adjuvant treatment) and 504 (14.8%) were treated with PET. Only 365/2938 (12.4%) of women with normal cognition were treated with PET compared to 75/336 (22.3%) of women with mild, 21/59 (35.6%) moderate and 43/83 (51.8%) with

Table 2
Tumour characteristics of study participants by cognitive impairment level.

	Cognition category					
Tumour characteristics	Normal function	Mild impairment	Moderate impairment	Severe impairment	Total	P value *
Unilateral	2871 (97.7%)	326 (97.0%)	59 (100%)	79 (95.2%)	3335 (97.6%)	0.24
Bilateral	67 (2.3%)	10 (3.0%)	0 (0%)	4 (4.8%)	81 (2.4%)	
Size						
T1	1745 (59.4%)	205 (61.0%)	29 (49.2%)	34 (41.0%)	2013 (58.9%)	<0.001
T2	1110 (37.8%)	122 (36.3%)	24 (40.7%)	48 (57.8%)	1304 (38.2%)	
T3	71 (2.4%)	8 (2.4%)	6 (10.2%)	0 (0%)	85(2.5%)	
Unknown	12 (0.4%)	1 (0.3%)	0 (0%)	1 (1.2%)	14 (0.4%)	
Number of positive nodes						
None	2468 (84.0%)	284 (84.5%)	46 (78.0%)	68 (81.9%)	2866 (83.9%)	0.54
1–3	380 (12.9%)	44 (13.1%)	6 (10.2%)	9 (10.8%)	439 (12.9%)	
4 +	23 (0.8%)	1 (0.3%)	1 (1.7%)	2 (2.4%)	27 (0.8%)	
Unknown	67 (2.3%)	7 (2.1%)	6 (10.2%)	4 (4.8%)	84 (2.5%)	
Provisional grade						
1	455 (15.5%)	48 (14.3%)	5 (8.5%)	15 (18.1%)	523 (15.3%)	0.26
2	1760 (59.9%)	212 (63.1%)	33 (55.9%)	52 (62.7%)	2057 (60.2%)	
3	587 (20.0%)	62 (18.5%)	18 (30.5%)	13 (15.7%)	680 (19.9%)	
Unknown	136 (4.6%)	14 (4.2%)	3 (5.1%)	3 (3.6%)	156 (4.6%)	
Nottingham Prognostic Index (NPI)						
≤3.4	1290 (43.9%)	139 (41.4%)	17 (28.8%)	32 (38.6%)	1478 (43.3%)	0.19
>3.4 to ≤5.4	1297 (44.1%)	159 (47.3%)	28 (47.5%)	38 (45.8%)	1522 (44.6%)	
>5.4	121 (4.1%)	11 (3.3%)	5 (8.5%)	5 (6.0%)	142 (4.2%)	
Unknown	230 (7.8%)	27 (8.0%)	9 (15.3%)	8 (9.6%)	274 (8.0%)	
ER						
Negative	343 (11.7%)	40 (11.9%)	7 (11.7%)	8 (9.6%)	398 (11.7%)	0.95
Positive	2561 (87.2%)	292 (86.9%)	52 (88.1%)	74 (89.2%)	2979 (87.2%)	
Unknown	34 (1.2%)	4 (1.2%)	0 (0%)	1 (1.2%)	39 (1.1%)	
HER2						
Negative	1992 (67.8%)	207 (61.6%)	45 (76.3%)	60 (72.3%)	2304 (67.5%)	0.39
Inconclusive	83 (2.8%)	12 (3.6%)	1 (1.7%)	1 (1.2%)	97 (2.8%)	
Positive	283 (9.6%)	37 (11.0%)	5 (8.5%)	4 (4.8%)	329 (9.6%)	
Unknown	580 (19.7%)	80 (23.8%)	8 (13.6%)	18 (21.7%)	686 (20.1%)	

* *p*-value excludes patients with missing or unknown data.

Table 3
Treatment choice by cognitive impairment level.

	Cognition category				
Primary treatment: all tumour types/patients	Normal function (N = 2938)	Mild impairment (N = 336)	Moderate impairment (N = 59)	Severe impairment (N = 83)	P value
Surgery (+/− adjuvant therapy	2494 (84.9%)	248 (73.8%)	36 (61.0%)	33 (39.8%)	<0.001
PET	365 (12.4%)	75 (22.3%)	21 (35.6%)	43 (51.8%)	
No treatment/unknown	79 (2.7%)	13 (3.9%)	2 (3.4%)	7 (8.4%)	

ER positive patients	Normal function (N = 2561)	Mild impairment (N = 292)	Moderate impairment (N = 52)	Severe impairment (N = 74)	P value
Surgery (+/− adjuvant	2139 (83.5%)	208 (71.2%)	30 (57.7%)	25 (33.8%)	<0.001
PET	362 (14.1%)	75 (25.7%)	20 (38.5%)	43 (58.1%)	
No treatment/ unknown	60 (2.3%)	9 (3.1%)	2 (3.8%)	6 (8.1%)	

Adjuvant therapy	Normal function	Mild impairment	Moderate impairment	Severe impairment	P value
Chemotherapy in women with high recurrence risk cancer[a]	342/1346 (25.4%)	28/139 (20.0%)	4/18 (22.2%)	2/17 (11.8%)	0.32
Radiotherapy in women following BCS or high risk histology post mastectomy[b]	727/1161 (62.6%)	66/110 (60.0%)	9/15 (60%)	4/13 (30.8%)	0.12
Trastuzumab in women with HER-2 positive disease[c]	126/289 (43.6%)	10/34 (29.4%)	1/4 (25.0%)	2/5 (40.0%)	0.39

[a] Among participants for whom chemotherapy should be considered on the basis of having any of the following: (i) HER2+; ii) ER-; iii) ER+ and histological grade 3; iv) presence of one or more positive lymph nodes or v) oncotype DX recurrence score of 30 or above.
[b] Among participants for whom radiotherapy should be considered on the basis of having any of the following after mastectomy: i) tumour of > 5 cm or T4, ii) presence of four or more positive lymph nodes, iii) tumour resection margins positive, iv) histological grade 3 AND any nodal disease, v) nodal disease (1–3 nodes) if other risk factors such as adverse tumour biology (triple negative phenotype or HER-2 positive), or all women following breast conserving surgery.
[c] Among participants for whom Trastuzumab should be considered on the basis of a HER-2+ tumour greater than 0.5 cm.

severe CI ($p < 0.001$, Table 3). Cognitive impairment was also associated with an increasing rate of PET in the 2979 women with ER+ cancers. Use of adjuvant chemotherapy following surgery was more similar between the groups. Among the 1520 women with high recurrence risk cancer, chemotherapy was given to 342/1346 (25.4%) women with normal cognition compared to 28/139 (20.0%) with mild impairment, 4/18 (22.2%) with moderate impairment, and 2/17 (11.8%) with severe impairment ($p = 0.321$). The use of radiotherapy and trastuzumab were slightly higher among patients with normal cognitive function, though not significantly so. Similarly, analysis of the use of trastuzumab was limited by small numbers of patients with cognitive impairment and HER2 positive disease. Use of radiotherapy (if indicated by breast conservation surgery or high risk histology after mastectomy) also appeared higher in the normal cognition group, although numbers did not reach statistical significance ($P < 0.12$, Table 3). There were 727/1161 (62.6%) with normal cognition having radiotherapy compared to 4/13 (30.8%) in those with severe CI.

3.4. Surgical Treatment

Breast cancer surgery was significantly higher in women with normal cognition compared to cognitively impaired patients; 84.9% of women with normal cognition underwent surgery compared to women with mild (73.8%), moderate (61.0%), and severe (39.8%) impairment ($p = 0.001$). A total of 2735 surgeries could be categorised according to cognition status with 56 cases missing data, which could not be analysed. Of these, rates of wide local excision and mastectomy were comparable across all groups. There was a trend for women with cognitive impairment to undergo mastectomy compared to breast conserving treatment, but this difference did not reach statistical significance ($P < 0.19$, Table 4). For women with normal function, the rate of wide local excision (57.4%) was higher than those undergoing mastectomy (36.5%), whereas for women with severe impairment, rates were nearly equal (16/33, 48.5%). This may be accounted for by the slightly larger primary tumour size seen in cognitively impaired participants.

3.5. Adverse Events and Systemic Complications

Data on adverse events relating to surgery and other treatments were recorded during study follow-up according to standard Common Terminology Criteria for Adverse Events (CTCAE) [38]. There were seven systemic complications in patients with CI compared to 50 in women with normal cognition (Supplemental Table 1). There was no clear association between cognitive impairment and systemic complications following surgery, as numbers were too small for meaningful analysis.

Table 4
Breakdown of surgical treatment type for all patients undergoing surgery.

	Cognition category			
Type of surgery	Normal function	Mild impairment	Moderate impairment	Severe impairment
Breast conserving treatment				
Wide local excision	1432 (57.4%)	132 (53.2%)	18 (50.0%)	16 (48.5%)
Therapeutic mammoplasty	46 (1.8%)	3 (1.2%)	1 (2.8%)	1 (3.0%)
Mastectomy				
Mastectomy	911 (36.5%)	110 (44.4%)	13 (36.1%)	15 (45.4%)
Mastectomy & reconstruction	34 (1.4%)	1 (0.4%)	2 (5.6%)	0 (0%)
Other	19 (0.8%)	0 (0%)	1 (2.8%)	0 (0%)
Missing	52 (2.1%)	2 (0.8%)	1 (2.8%)	1 (3.3%)
Totals	2494	248	36	33

3.6. Survival

Patients with cognitive impairment had reduced overall survival compared to those without impairment (hazard ratio: 2.10, 95% CI 1.77 to 2.5, $p < 0.001$), but the effect was greatly reduced (although not removed) when comparing patients matched for other characteristics (Fig. 2; Table 5). The effect sizes were similar for both models: matching for age, NPI, ER and treatment gave a hazard ratio (HR) of 1.39 (95% CI 1.09 to 1.78, $p = 0.01$) whilst adding functionality, nutrition and co-morbidity gave a HR of 1.23 (95% CI 0.94 to 1.62, $p = 0.13$). By contrast, both breast cancer specific survival and progression-free survival were similar with no significant difference in hazard both with and without propensity matching despite the differences in treatment allocation.

Table 5
Results of Cox proportional hazard analysis of overall, breast cancer specific and progression free survival.

Comparison*	Hazard ratio (95% CI)	p-value
Overall survival		
Unadjusted	2.10 (1.77, 2.50)	<0.001
Matched for age, treatment and NPI	1.39 (1.09, 1.78)	0.01
Matched for age, treatment, NPI and functionality	1.23 (0.94, 1.62)	0.13
Breast cancer specific survival		
Unadjusted	1.39 (1.00, 1.93)	0.05
Matched for age, treatment and NPI	0.96 (0.61, 1.50)	0.86
Matched for age, treatment, NPI and functionality	0.93 (0.58, 1.49)	0.76
Progression free survival		
Unadjusted	1.08 (0.74, 1.60)	0.68
Matched for age, treatment and NPI	1.43 (0.89, 2.28)	0.14
Matched for age, treatment, NPI and functionality	0.91 (0.52, 1.60)	0.74

4. Discussion

This analysis demonstrates the variation between the treatments that older women with CI receive compared to women with normal cognitive function. The use of PET is increased in women with cognitive impairment, particularly those with severe impairment. Similar figures were found by Hooper and colleagues [39], with PET offered to 62% of patients with co-morbidities (inclusive of dementia). This practice is in keeping with UK NICE guidelines which state that PET can be an

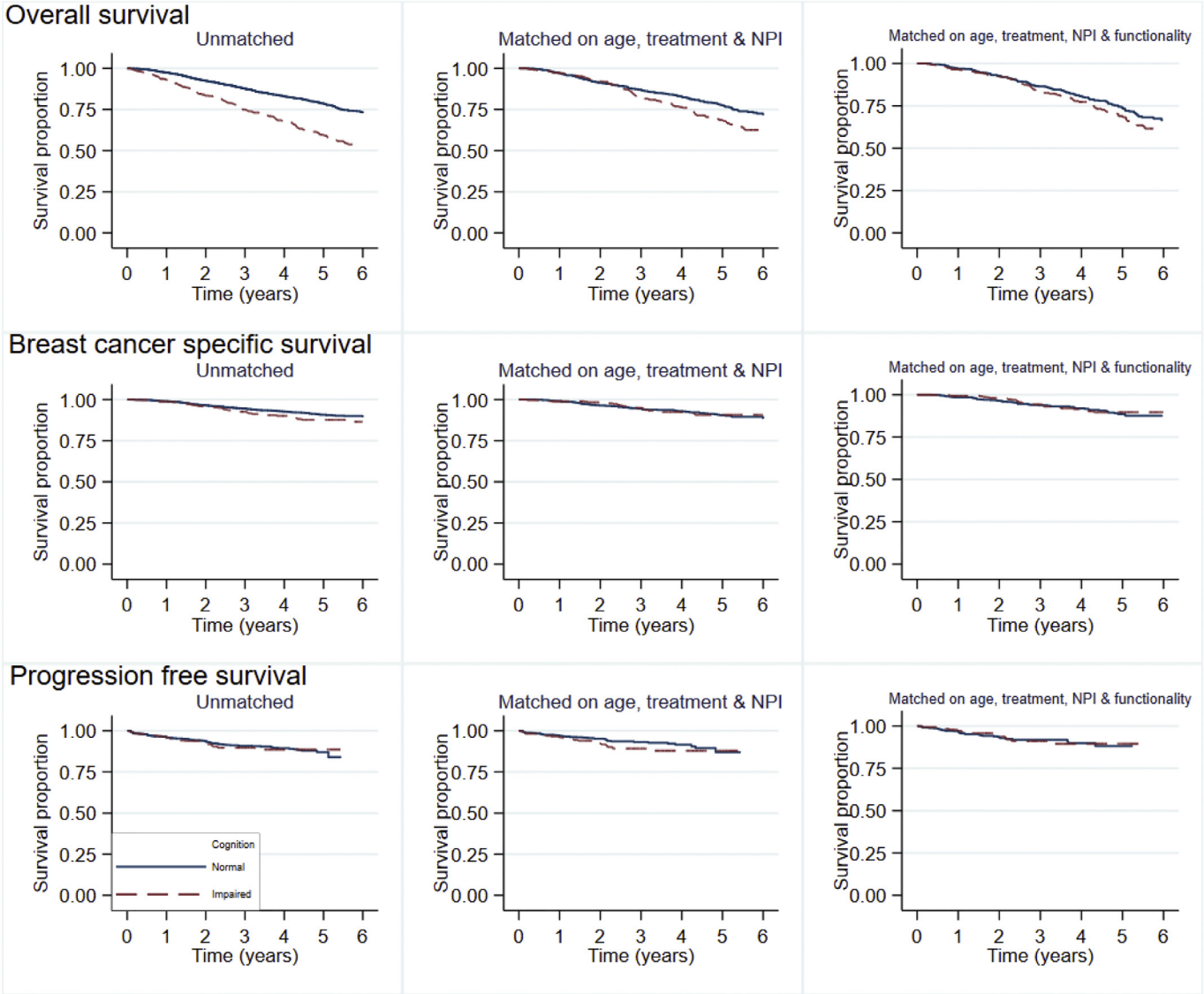

Fig. 2. Kaplan-Meier survival curves (overall, breast cancer specific and progression free survival) and comparisons between propensity matched patients with and without cognitive impairment.

appropriate option for women with ER+ tumours, short life expectancy or those considered too frail to withstand surgery [40].

In the sub-analysis of ER+ cases, the rate of PET use in patients with normal cognition was significantly lower than in women with cognitive impairment. These findings are reflected in other studies which present the view that in some cases, non-surgical management may be more appropriate for women with ER+ cancers [41,42]. In this study, rates of PET in patients with dementia were higher than reported in the recent UK national audit (NABCOP) rate of 24% [20]. However, the NABCOP audit reported all women over 70 and did not sub-analyse for a cohort with cognitive impairment.

The study observed a decrease in surgical management in women with cognitive impairment (Supplemental Material 2). Reasons for lower rates of breast conserving surgery in the cognitively impaired groups may include clinicians offering PET due to a perceived risk of co-morbidities and age, patient and caregiver preferences for what is perceived as a lower risk/lower morbidity option in women with lower life expectancy, and a wish on the part of patients' caregiver to optimise quality of life. Another factor may be clinician preference [26] where cognitive impairment has been shown to be a significant clinician driver for non-surgical treatment [11].

Women with cognitive impairment were slightly more likely to undergo mastectomy compared to women with normal cognition, although this difference did not reach statistical significance. This may reflect a desire to avoid post-operative radiotherapy [43] or may be a result of larger tumour sizes seen in women with cognitive impairment. Other drivers for mastectomy may include patient or caregiver preference, the desire to optimise patient outcomes; local disease control and a reduced risk of recurrence are often perceived as more likely with mastectomy, despite evidence to the contrary [44]. There may be a perception that a patient with CI may be less concerned about body image. In contrast it could also be argued that wide excision is less major surgery with a lower risk of morbidity for a group of patients who are generally in poorer health.

In this study, cognitive impairment was associated with a decreased rate of overall survival, which includes death from all causes, including breast cancer. This is to be expected as our study participants with cognitive impairment were older, had poorer functional status and higher rates of co-morbidities. When propensity matched analysis was performed, the difference in overall survival is reduced but remains significant. When breast cancer specific survival was examined, there was minimal difference in outcomes between patients with and without cognitive impairment and this disappeared completely when matching was performed. This suggests that non-breast cancer causes of death are relatively more important in patients with dementia, and the selective use of PET in the cohort of older women with ER+ breast cancer does not increase breast cancer specific mortality.

Systemic complications reported in this study were low, which suggests that treatment tolerance in patients with cognitive impairments is acceptable, although another explanation may be that some adverse events are underreported in cognitively impaired groups. There were no deaths attributed to surgery in the study [25] although there were five deaths within 90 days of surgery (which suggests these women were over-treated). In general those individuals at the greatest risk of surgical morbidity received PET, keeping surgical mortality to a minimum. Follow-up at 52 months showed no difference in rates of progression free survival, and rates of local control were similar between groups.

4.1. Study Limitations

Bridging the Age Gap is one of the largest prospective studies of treatment and outcomes in patients over 70, and has uniquely collected detailed data about cognitive status by permitting proxy consent of patients with cognitive impairment [26,45]. In addition, the study collected detailed baseline health and fitness status allowing us to tease out the contribution of impairment from other co-morbidities, frailty and older age, which often confound these analyses. There are some limitations to the categorisation of proxy consented patients, as this group were not expected to complete a MMSE form. Cognitive severity was not formally assessed for women who self-consented to the study and had a diagnosis of dementia indicated on the Charlson form, unless a MMSE score was available. A review of medications was performed where MMSE was unavailable for these women. Cognitive impairment was only recorded at baseline, which may also be viewed as a limitation of the study.

The first propensity matching technique was relatively simple and only matched for age, tumour stage and biology, and treatment type. In particular, the matching did not include other co-morbidities which may have been a source of bias when attempting to show association of cognitive impairment with survival. By contrast, the second match (which included co-morbidity score and measures of functionality) may have caused overmatching, wherein the impact of dementia on outcome is diluted by including patients in the matched group that were similar in terms of underlying cognition [46].

A second limitation is missing data. This was due to some patients choosing not to complete optional questionnaires (ADL, MMSE) and unavailable data on treatment, adverse events and HER2 status. The data do however have advantages over registry data where dementia severity is not categorised and may be less fully or accurately recorded than in this prospective observational cohort study. Finally, follow-up of this cohort is only 52 months and longer term follow-up will be needed to validate the survival outcomes, especially for women with ER+ cancers, where events occur over several decades.

4.2. Clinical Implications

The variation in treatment offered to older women is reflected in the lack of best practice evidence-based guidelines that take into account the heterogeneity of frailty and fitness levels in older age groups. Older women continue to be poorly represented in randomised trials [47], meaning that there is little guidance on whether surgery or PET is more beneficial for women with multi-morbidity. Where previous trials have attempted to investigate this, the recruitment of older participants has been challenging [48]. As a result, there are a lack of data on how older patients tolerate treatments, and there are no models or guidelines to guide clinicians on the benefit of systemic therapies in patients over 80 years of age. There are also differences in opinion from clinicians on how women within this age group should be treated [21].

5. Conclusion

This analysis confirms that the severity of cognitive impairment is a significant predictor of PET for older women with breast cancer, and cognition appears to play a significant part in deciding how to treat older women with breast cancer. The presence of cognitive impairment is linked to higher rates of overall mortality but has limited impact on breast cancer related death, suggesting that breast cancer is being adequately (not under-)treated in this group, despite the reduced treatments delivered. The high rate of non-breast cancer causes of death at one year after diagnosis may suggest that some of these women may have been over-treated. Careful consideration must be given to a more tailored approach in these women.

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Declaration of Competing Interest

The authors declare no conflict of interest. Professors Thompson Robinson and Stephen Walters are National Institute for Health Research (NIHR) Senior Investigators and Jenna Morgan is a NIHR Clinical Lecturer.

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Appendix A. Supplementary data

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