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Comprehensive geriatric assessment in 326 older women with early breast cancer

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Background: One-third of new early breast cancer diagnoses occur in women over 70 years old. However, older women are less likely to receive radical curative treatments. This study prospectively evaluated a cohort of older women using a Comprehensive Geriatric Assessment (CGA) to determine whether fitness explained the apparent under-treatment in this patient group.

Methods: In this multi-centre prospective study, patients aged ≥ 70 years with Stages I–III breast cancer underwent a pretreatment baseline CGA consisting of eight assessment tools. Patients were defined as 'fit' if they had normal score in seven out of eight of the assessment tools. 'High risk' patients were defined as those with grade 3, ER negative, HER2 positive, or node positive breast cancer.

Results: Data on 326 patients were available for full analysis. The median age was 77 years. In all, 182 (56%) of the total population were defined as high risk, with 49%, 61% and 53% of those in the 70–74, 75–84 and ≥ 85 years age groups respectively having high risk tumours. A total of 301 patients had sufficient CGA records of whom 131 (44%) were reported as fit, with 34%, 54% and 12% of them in the 70–74, 75–84 and ≥ 85 years age groups respectively. More fit than unfit patients underwent primary breast surgery (100% vs 91%, $P=0.0002$), axillary surgery (92% vs 84%, $P=0.0340$), and adjuvant chemotherapy for high-risk disease (51% vs 20%, $P=0.0001$). Rates of adjuvant radiotherapy after wide local excision were not significantly different (88% vs 90% respectively, $P=0.8195$).

Conclusions: In this study, all women ≥ 70 years deemed fit by CGA underwent primary surgery. Nearly 50% of fit women with high-risk disease did not receive adjuvant chemotherapy suggesting under treatment in this group.

Between 2012 and 2014, 17 954 women per year aged 70 years or older were diagnosed with breast cancer, representing approximately 34% of all new breast cancer diagnoses in the United Kingdom (Cancer Research UK, 2015). The number of women in this age group is increasing rapidly, such that many older people will be diagnosed with cancer over the forthcoming decades (Khaw, 1999). In 2010, the UK National Cancer Equality Initiative concluded that older patients experienced inequalities in access to cancer services and treatment; furthermore, they also had worse outcomes, which were improving at a slower rate than those for younger patients (National Cancer Equality Initiative, 2010).

It is well recognised that older women with breast cancer are less likely to be offered or receive a full diagnostic work-up, surgery or

radiotherapy and that such under-treatment is likely to have an impact on prognosis (Bouchardy *et al*, 2003; Lavelle *et al*, 2007; Schonberg *et al*, 2010). Several studies from the US and UK also report low rates of receipt of adjuvant chemotherapy in older women (Enger *et al*, 2006; Buist *et al*, 2009; Ring *et al*, 2013).

However older patients represent a highly heterogeneous population. While the median life expectancy of a 70-year-old woman in the UK is 16 years (Rowan, 2009), there is considerable variability in terms of life-expectancy, co-morbidities, fitness, social situation, cognitive function and desire for treatment. In order to more accurately interpret data describing treatment patterns in older patients, it is vital that the data be put in the context of these variables so as to ascertain whether there is a population of old but

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fit women who are being denied treatment on the basis of age alone.

A baseline assessment of the general health of older patients using a Comprehensive Geriatric Assessment (CGA) may help to inform this debate by enabling the identification of where under-treatment may be occurring. This would ultimately facilitate better informed discussions with patients about their fitness to undergo treatment as well as their likely long-term benefits from adjuvant therapy (Gosney, 2005).

The primary objective of The Functional Assessment in Early Breast Cancer in Older Patients (FABIO) study was to characterise a population of women aged 70 years or older with newly diagnosed stages I–III breast cancer by using a CGA to objectively assess their fitness to undergo primary surgery and subsequent adjuvant therapies. The secondary objective was to use these measures to ascertain what proportion of fit older patients are not undergoing radical curative treatments including, surgery, radiotherapy, chemotherapy and anti-human epidermal growth factor receptor 2 (HER2) therapy.

MATERIALS AND METHODS

This was a multi-centre prospective cohort study. Eligible patients were women aged 70 years or older with a new diagnosis of early (stages I–III) breast cancer, who were willing to provide written informed consent and comply with the study questionnaire and interview schedule. Patients were recruited within 6 weeks of their first diagnosis of early invasive breast cancer. Patients were excluded from the study if they commenced treatment prior to registration into study, lacked mental capacity to consent, and/or their expected prognosis was less than 3 months. Each participant underwent an interview by telephone or in person with a research nurse, to complete a panel of geriatric assessment tools. These were: the 6-Cognitive Impairment Test (6-CIT), American Society of Anesthesiologists (ASA) grade, Eastern Cooperative Oncology Group (ECOG) performance status, Vulnerable Elders Survey (VES-13), Activities of Daily Living (ADL), Instrumental Activities of Daily Living (IADL), G8 score and the Charlson's Co-morbidity index (CCI) (Dripps, 1963; Katz *et al*, 1963; Lawton and Brody, 1969; Charlson *et al*, 1987; Saliba *et al*, 2001; Hodigere and Ramesh, 2006; Upadhyaya *et al*, 2010; Stokoe *et al*, 2012 respectively). The interview data were supplemented by further clinical information regarding comorbidities from the patient's general practitioner. Diagnosis details (including tumour type, grade, stage), and treatment received were extracted from the medical records. In the event of recording reduced mental capacity while implementing the 6-CIT test, the patient was considered as a screen failure, and withdrawn from the study. In this situation, notification to the GP, and key-worker was made. Pre-defined thresholds for determination of fitness according to individual geriatric assessment tools were used based on the published literature (Katz *et al*, 1963; Lawton and Brody, 1969; Saliba *et al*, 2001; Owusu *et al*, 2011; Bellera *et al*, 2012). Scores categorising patients as 'fit' were as follows: ECOG performance status (PS) \leq 1, ASA grade \leq II, 6-CIT \leq 7, VES-13 \leq 2, ADL \geq 6, IADL \geq 8, G8 \geq 15 and CCL \leq 1.

Statistical considerations. The primary objective of this study was to characterise the population of women aged 70 or over with newly diagnosed stages I–III breast cancer in terms of objective health assessments. A minimum sample size of 300 was chosen as an achievable target to reach within the timeframes available for conducting the project. The distribution of the CGA scores in this patient population was not known. For the secondary objectives it was estimated that the proportions of fit patients eligible for the radical treatment but not receiving it were 10%, 20% and 70% for

surgery, radiotherapy and chemotherapy respectively. For the purposes of chemotherapy analysis: high-risk patients were defined as those with one or more of the following high-risk features: grade 3, node positive, oestrogen receptor (ER) negative or HER2 positive (Leonard *et al*, 2011; Ring *et al*, 2013).

Analysis was conducted using GraphPad Software 2017. Two-tailed *P*-values were calculated using Fisher's exact test, and a *P*-value of <0.05 was considered significant.

Follow-up. Patients will be followed up within this cohort for treatment-related toxicity, functional status (by repeat interval measurements of VES-13, ADL and IADL) and long-term (years 1, 2 and 5) survival data.

Patients' management was not influenced by involvement in this study, and the clinicians responsible for the patients as well as the patients themselves were not informed of the results of the assessments. The study was approved by Surrey Research Ethics Committee (11/LO/1672) and by Research and Development departments in participating centres. The study was adopted on to the UK National Cancer Research Network portfolio (study ID 89511).

RESULTS

Between January 2012 and October 2015, 24 UK specialist breast cancer teams recruited 356 patients into this study. Eight patients withdrew consent and therefore, did not undergo initial assessments; a further 22 patients did not have adequate data points recorded at baseline. Therefore, there were 326 patients available for this analysis. The median age of patients recruited was 77 years. Baseline tumour and treatment characteristics are shown in Table 1.

High-risk patients were defined as those with grade 3, ER negative, HER2 positive, or node-positive breast cancer. Based on this definition: 182 (56%) of the total population were defined as high risk of recurrence, with 49%, 61% and 53% of the 70–74, 75–84 and \geq 85 years respectively having high-risk tumours.

The eight constituent CGA parameter scores for the population according to pre-defined cut-offs are shown in Table 2.

Fit patients were defined as those did not fail more than one of the eight parameters constituting the CGA. This analysis was possible in 301 patients with sufficient CGA records. On this basis: 131 (44%) of the total study population were reported as 'fit', with 34%, 54% and 12% of them in the 70–74, 75–84 and \geq 85 years age groups respectively.

Treatment received according to 'fitness' is shown in Table 3.

DISCUSSION

In this study, 84% of participants had T1 and T2 early breast cancer and 63% had lymph node negative disease. These findings are similar to those in a large early breast cancer series from the San Antonio Breast Cancer Database and the US Surveillance, Epidemiology, and End Results (SEER) registry (Diab *et al*, 2000). However 56% patients had high-risk disease (as defined by the presence of HER2-positive and/or ER-negative disease or ER-positive grade 3 disease and/or positive axillary lymph nodes), suggesting that a significant proportion of patients in this study had a high risk of recurrence. This is in contrast to the widely held perception that breast cancer in older women is an indolent disease. These patients, assuming that they have a low risk of death from competing causes of mortality and are fit enough for treatment, may derive a benefit from adjuvant radiotherapy and adjuvant systemic therapy.

Table 1. Patient tumour and treatment characteristics (N = 326)

Tumour and treatment characteristics	Patient age group							
	70–74yrs		75–84yrs		≥85yrs		All patients	
	N	%	N	%	N	%	N	%
T stage								
T1	49	43%	78	44%	12	43%	139	43%
T2	51	44%	67	38%	16	41%	134	41%
T3	9	8%	17	10%	2	9%	28	9%
T4	0	0%	3	2%	0	1%	3	1%
Unknown	6	5%	12	7%	4	7%	22	7%
N stage								
Node +	33	29%	58	33%	10	31%	101	31%
Node –	76	66%	108	61%	22	63%	206	63%
Node status unknown	6	5%	11	6%	2	6%	19	6%
Grade								
I	12	10%	21	12%	6	12%	39	12%
II	71	62%	85	48%	18	53%	174	53%
III	30	26%	68	38%	10	33%	108	33%
Unknown	2	2%	3	2%	0	2%	5	2%
Histology								
IDC	81	70%	151	85%	27	79%	259	79%
ILC	23	20%	13	7%	3	12%	39	12%
Other	5	4%	5	3%	1	3%	11	3%
Unknown	6	5%	8	5%	3	5%	17	5%
Receptor status								
<i>ER status</i>								
ER +	104	90%	153	86%	28	87%	285	87%
ER –	11	10%	24	14%	6	13%	41	13%
<i>HER2 status</i>								
HER2 +	15	13%	27	15%	4	14%	46	14%
HER2 –	95	83%	144	81%	28	82%	267	82%
Unknown	5	4%	6	3%	2	4%	13	4%
Surgery								
Mastectomy	41	36%	56	32%	10	29%	107	33%
WLE	70	61%	113	64%	22	65%	205	63%
No surgery at all	4	3%	6	3%	2	6%	12	4%
Unknown	0	0%	2	1%	0	0%	2	1%
Axillary surgery	102	89%	159	90%	26	76%	287	88%
Adjuvant radiotherapy								
Yes	79	69%	125	71%	25	74%	229	70%
No	32	28%	50	28%	9	26%	91	28%
Unknown	4	3%	2	1%	0	0%	6	2%
WLE + adjuvant radiotherapy	63	90%	103	91%	19	86%	185	90% ^a
Adjuvant chemotherapy								
Yes	17	15%	40	23%	8	24%	65	20%
No	95	83%	136	77%	26	76%	257	79%
Unknown	3	3%	1	1%	0	0%	4	1%
HER2-positive patients receiving Trastuzumab + Chemotherapy ^b	7	47%	18	67%	4	100%	29	63%
Endocrine therapy								
ER-positive patients receiving adjuvant endocrine therapy	95	91%	137	90%	27	96%	259	91%

Abbreviations: ER = oestrogen receptor; HER2 = human epidermal growth factor receptor 2; IDC = Infiltrating ductal carcinoma; ILC = Infiltrating lobular carcinoma; WLE = wide local excision.

^a90% = 185 of the 205 patients who underwent WLE and subsequently received adjuvant radiotherapy.

^bFour patients received Trastuzumab without concomitant chemotherapy: 1 in the 70–74 years age group, 2 in the 75–84 years age group, and 1 in the ≥85yr group.

The International Society of Geriatric Oncology (SIOG) and the European Society of Breast cancer Specialists (EUSOMA) both recommend that a baseline geriatric assessment should be undertaken in all patients ≥70 years of age prior to consideration of chemotherapy (Pallis *et al*, 2010; Wildiers *et al*, 2014). However, there is no consensus on the optimum geriatric assessment (Puts *et al*, 2012) or on which specific assessment tools should be incorporated into a standardised CGA. Nonetheless, a CGA may help identify patients who may experience functional decline (Hoppe *et al*, 2013) and also those who are likely to experience

toxicity with adjuvant treatment (Freyer *et al*, 2005; Maione *et al*, 2005; Hurria *et al*, 2011; Puts *et al*, 2012). However there is only limited published evidence regarding the ability of a CGA to reliably predict survival in early breast cancer (Clough-Gorr *et al*, 2012; Soubeyran *et al*, 2014). A limitation of interpretation of all of these studies is lack of a uniformly agreed definition of what constitutes a CGA.

What is well-established in the geriatric literature is that any CGA or global assessment of health status needs to incorporate a number of different domains as for the most part these domains

Table 2. Complete Geriatric Assessment (CGA) parameter scores by age group

Complete Geriatric Assessment (CGA) parameters		Patient age group							
		70–74 years		75–84 years		≥85 years		All Patients	
		N	%	N	%	N	%	N	%
ECOG PS									
≤1	Fit	83	72%	136	77%	10	29%	229	70%
≥2	Unfit	29	25%	36	20%	23	68%	88	27%
	ECOG PS not recorded	3	3%	5	3%	1	3%	9	3%
ASA grade									
≤II	Fit	85	74%	137	77%	23	68%	245	75%
≥III	Unfit	14	12%	20	11%	4	12%	38	12%
	ASA not recorded	16	14%	20	11%	7	21%	43	13%
6-CIT									
≤7	Fit	90	78%	145	82%	24	79%	259	79%
≥8	Unfit	22	19%	30	17%	10	19%	62	19%
	6-CIT not recorded	3	3%	2	1%	0	2%	5	2%
VES-13									
≤2	Fit	71	62%	91	51%	15	44%	177	54%
≥3	Unfit	41	36%	80	45%	19	56%	140	43%
	VES-13 not recorded	3	3%	6	3%	0	0%	9	3%
ADL									
≥6	Fit	99	86%	149	84%	31	91%	279	86%
≤5	Unfit	13	11%	23	13%	2	6%	38	12%
	ADL not recorded	3	3%	5	3%	1	3%	9	3%
IADL									
≥8	Fit	87	76%	139	79%	22	65%	248	76%
≤7	Unfit	25	22%	32	18%	11	32%	68	21%
	IADL not recorded	3	3%	6	3%	1	3%	10	3%
G8									
≥15	Fit	55	48%	66	37%	14	41%	135	41%
≤14	Unfit	56	49%	105	59%	19	56%	180	55%
	G8 not recorded	4	3%	6	3%	1	3%	11	3%
CCI									
≤1	Fit	88	77%	125	71%	25	74%	238	73%
≥2	Unfit	13	11%	30	17%	5	15%	48	15%
	CCI not recorded	14	12%	22	12%	4	12%	40	12%

Abbreviations: 6-CIT = 6-Item Cognitive Impairment Test; ADL = Activities of Daily Living; ASA Grade = American Society of Anaesthesiologists Grade; CCI = Charlson's Comorbidity Index; ECOG PS = Eastern Cooperative Oncology Group Performance Status; IADL = Instrumental Activities of Daily Living; VES-13 = Vulnerable Elders Survey.

Table 3. Proportion of patients undergoing treatment according to fitness as defined by Complete Geriatric Assessment (N = 301)

Treatment	Patient fitness				X ² P-value
	Fit		Unfit		
	N	%	N	%	
Breast surgery	132/(132)	100%	156/(171)	91%	0.0002
Patients undergoing axillary surgery	122/(132)	92%	144/(171)	84%	0.0340
Adjuvant radiotherapy after WLE	82/(93)	88%	86/(96)	90%	0.8195
High risk patients receiving chemotherapy	39/(76)	51%	18/(91)	20%	0.0001
HER2-positive patients receiving Trastuzumab ^a	14/(21)	67%	11/(19)	58%	0.7451
ER-positive receiving endocrine therapy	102 (115)	89%	131/(151)	87%	0.7451

Abbreviations: ER = oestrogen receptor; HER2 = human epidermal growth factor receptor 2; WLE = wide local excision.

^aThree unfit patients received adjuvant Herceptin with no concomitant chemotherapy. Statistically significant P-values are shown in bold.

can be independent (Pallis *et al*, 2010). Therefore eight geriatric assessment tools were used in this current study. The specific instruments that constituted the CGA in this analysis were pre-selected because they have been either established in clinical practice or validated in published studies. Although both the G8 and VES-13 were included, it must be noted that these are normally used as screening tools to help identify elderly patients

who may benefit from further geriatric assessments (Decoster *et al*, 2015) and are not usually part of what would be considered a standard CGA by convention. However, in this study both G8 and VES-13 were utilised not only as screening tools but also as part of the CGA because their constituent items allowed for an objective, reliable and reproducible assessment of nutrition, polypharmacy, psychological status, body weight and functional mobility by the

research nurses involved in data collection in this study. Of the remaining five tools, ASA and ECOG PS were included because they are commonly used in clinical practice particularly when evaluating fitness in the elderly prior to surgery and the likelihood of tolerating adjuvant chemotherapy respectively. The ADL and IADL tools were included because both have been shown in large studies, either as part of a CGA (Repetto *et al*, 2002), or alone (van Abbema *et al*, 2017) to provide more information on not only the baseline functional capacity in the elderly but also the likelihood of functional decline after treatment with chemotherapy. The CCI was also included in the CGA in this study because previously published large trials have shown that multiple comorbidities are associated with poorer survival not only in cancer patients in general (Sogaard *et al*, 2013) but also in elderly patients with early breast cancer in particular (Patnaik *et al*, 2011).

The CGA in this study was therefore an aggregate of eight constituent assessment tools. In order to establish a clinically useful output to determine fitness to undergo adjuvant therapies, data derived from the CGA were utilised to try to discriminate a 'fit' from an 'unfit' patient. To the best of the authors' knowledge, this is not an approach that has been used in other published studies. The working definition of 'fit' that was used in this study (i.e. not more than one 'unfit' score in any of the eight assessment tools constituting the CGA) was a pragmatic one to enable an analysis of whether fitness was being used to determine treatment. A key finding from the study was that despite using this fairly stringent definition of fitness, over 40% of the study population was defined as 'fit'. This is important as patients older than 70 years of age, but who are defined as 'fit' might be expected to have a low risk of death from competing causes compared to those who are unfit but of the same age. Furthermore, it might be hypothesised that they would tolerate treatment.

In this study, all patients who were fit underwent primary breast surgery, compared to only 91% of the unfit patients ($P=0.0002$). This would seem appropriate as less fit patients may be well served by primary endocrine therapy rather than primary surgery. Overall though, the rates of primary surgery were higher in this study compared with other analyses (Morgan *et al*, 2015a). This may reflect selection bias, which might be occurring as sites may be only selecting fitter patients for the study. Furthermore, while a broad range of 24 UK sites were involved, the sites who took part might be those with a particular interest in breast cancer in older patients, and therefore may deploy a different treatment approach to centres which did not take part in the study.

A similar number of unfit and fit patients underwent adjuvant radiotherapy after breast conserving surgery (88% vs 92% respectively; $P=0.8195$). The PRIME II study randomised women aged 65 or over who had undergone breast conserving surgery for ER positive, axillary node negative early breast cancer to receive breast radiotherapy or not (Kunkler *et al*, 2015). There was a lower risk of ipsilateral breast tumour recurrence in those having radiotherapy (1.3% vs 4.1%, $P=0.0002$), but the absolute risk was low and there were no differences in regional recurrences, distant metastases, or overall survival. Therefore there is likely to be a population of older patients, with lower risks of recurrence who are less fit where the benefits of adjuvant radiotherapy are marginal. Despite this, in the current study 90% of patients defined as unfit received radiotherapy, raising the possibility that some of these patients are being over-treated.

In the AChEW study only 30% of women with high risk early breast cancer aged 70 or older were offered adjuvant chemotherapy, and 17% went on to receive it (Ring *et al*, 2013). It was hypothesised that the reason for the low number of patients being offered chemotherapy was that they were not deemed fit enough to benefit from treatment, but fitness was not measured. The current study aimed to answer this question: It showed that more fit patients compared to unfit patients received chemotherapy (51% vs

20% respectively; $P=0.0001$). However there were still a large number of fit older patients with high-risk disease who did not receive chemotherapy. The reasons for this are not clear, but may relate to physician perceptions or preferences for treatment on behalf of patients. The large UK National study: 'Bridging the Age Gap in breast cancer' (University of Sheffield, 2017) is a cluster randomised trial that utilises patient and clinician decision-aids to attempt to inform decision-making in this patient group and will continue to address this particular question.

This study has potential limitations. Firstly, the overall number of (whether high risk or not) who received adjuvant chemotherapy was higher than one would expect in either trial or non-trial populations for patients aged 70 years or older (20% overall compared with 8% for the overall population in the AChEW study). One explanation for this is would be emerging changes in practice resulting in more proactive treatment of older patients with breast cancer (Muss *et al*, 2005). However, it may also be due to selection bias, with participating sites recruiting generally fitter patients into the study. This would also explain the higher rates of surgery in this elderly patient cohort when compared to other published studies. Secondly, the study also excluded patients with cognitive impairment and thereby may have enriched the potential number of patients characterised as 'fit'. The decision to exclude patients with cognitive impairment was made in order to ensure reliability and consistency of the CGA completion, particularly when assessments were being completed over the telephone. There is increasing evidence, however, to suggest cognitive impairment does influence physician treatment choices and patient preferences in older breast cancer patients who are unfit (Morgan *et al*, 2014; 2015b). These older patients represent an important sub-group with particular unmet needs, and in which prospective studies such as the Bridging the Age Gap in Breast Cancer (University of Sheffield, 2017) have made particular provision for, with the express aim of providing answers to such questions.

In summary, early breast cancer in women aged 70 is a heterogeneous disease, with many having features of high-risk disease. An objective attempt at determining fitness of patients aged 70 and over using a CGA was achieved in the majority of patients participating in this study. Primary breast surgery was undertaken in most women, whether fit or unfit. In contrast, adjuvant chemotherapy was often not used in most women with breast cancer at high risk of recurrence, even in those deemed fit by a CGA. Therefore, fit women aged over 70 years who undergo primary surgery for early breast cancer, but who do not receive chemotherapy may represent a subgroup of undertreated patients who may benefit from adjuvant treatment. Larger national studies are attempting to better identify these patients in order to increase uptake of adjuvant chemotherapy in this group and thereby improve survival in older patients with early breast cancer.

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Hospital, Bridgend; Queen's Hospital, Burton; Royal Albert Edward Infirmary, Wigan; Royal Bournemouth Hospital, Bournemouth; Royal Glamorgan Hospital, Llantrisant; Royal Sussex County Hospital, Brighton; Russells Hall Hospital, Dudley; Sandwell General Hospital, Lyndon; Solihull Hospital, Solihull; Walsall Manor Hospital, Walsall; Wrexham Maelor Hospital, Wrexham and Ysbyty Gwynedd, Bangor.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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