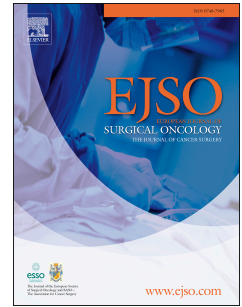


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Addressing frailty in patients with breast cancer: A review of the literature

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38

39 The aim of the NABCOP is to evaluate the care of older women diagnosed with breast cancer in
40 England and Wales, and support NHS providers to improve the quality of hospital care for these
41 women. More information can be found at: www.nabcop.org.uk

42

43

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46

47

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50

51

52 Abstract

53

54 Various studies have documented variation in the management of older patients with breast cancer,
55 and some of this variation stems from different approaches to balancing the expected benefit of
56 different treatments, with the ability of patients to tolerate them. Frailty is an emerging concept that
57 can help to make clinical decisions for older patients more consistent, not least by providing a
58 measure of 'biological' ageing. This would reduce reliance on 'chronological' age, which is not a
59 reliable guide for decisions on the appropriate breast cancer care for older patients.

60

61 This article examines the potential of frailty assessment to inform on breast cancer treatments.

62 Overall, the current evidence highlights various benefits from implementing comprehensive geriatric
63 assessment and screening for frailty in breast cancer patients. This includes a role in supporting the

64 selection of appropriate therapies and improving physical fitness prior to treatment. However, there
65 are challenges in implementing routine frailty assessments in a breast cancer service. Studies have
66 used a diverse array of frailty assessment instruments, which hampers the generalisability of
67 research findings. Consequently, a number of issues need to be addressed to clearly establish the
68 optimal timing of frailty assessment and the role of geriatric medicine specialists in the breast cancer
69 care pathway.

70

71 *203 words*

72

73 **Keywords:** *Frailty, Breast Cancer, Elderly, Review*

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80 **Introduction***

81 Clinical guidelines emphasise that breast cancer treatment should be based on clinical need and
82 patient fitness, rather than age¹. For example, the guidelines for early breast cancer issued by the UK
83 National Institute for Health and Care Excellence (NICE) recommends that women *“irrespective of
84 age, are offered surgery, radiotherapy and appropriate systemic therapy, unless significant
85 comorbidity precludes it”*². However, various UK-based population level studies report considerable
86 variation in the breast cancer treatments received by older women (often defined as age 70 years or
87 older) in comparison to younger women.

88

89 Older women are less likely to receive surgery for operable breast cancer^{3,4}. Among those older
90 women who do receive surgery, this is more likely to be a mastectomy than breast conserving
91 surgery (BCS)⁵, and of those women having BCS, they are less likely to have adjuvant radiotherapy^{6,7}.

92 Older women are also less likely to receive chemotherapy⁸. There are various possible reasons for
93 these reported differences in treatment provision. On average, older women tend to have larger
94 tumours at diagnosis⁹, which is partly a consequence of being older than the inclusion ages of
95 women (usually 50 to 70 years) in national breast screening programmes. The higher burden of
96 comorbid conditions among older women may also be a significant contributing factor, with various
97 studies showing lower rates of surgery³ and other therapies^{10,11} among women with more comorbid
98 conditions. However, these factors only explain some of the reported variation in treatment
99 patterns between younger and older women. One-third of all breast cancers diagnosed are in
100 women aged 70 years or over¹², so addressing this variation is important for population health .

101

102 The impact of ageing on health is complex and ageing can influence functional ability, physiology and
103 social wellbeing to different degrees¹³. Chronological age is increasingly viewed as a poor descriptor
104 of the ageing process. More recently, there is a much greater desire to determine “biological age”¹⁴,
105 ¹⁵. Geriatric associations have, for a while, recommended that a measure of frailty be used to report
106 on ageing and its complex sequelae^{14,16}. This approach has been progressively adopted by other
107 specialties, perhaps most evidently in relation to the management of hip fractures¹⁷. However,
108 there has been slow implementation of this recommendation in breast cancer care pathways, not

* **Abbreviations:** BCS – breast conserving surgery, CGA – comprehensive geriatric assessment, EUSOMA – European Society of Breast Cancer Specialists, ER – oestrogen receptor, FFF – fit for frailty, NABCOP – National Audit of Breast Cancer in Older Patients, PACE – Pre-operative Assessment of Cancer in the Elderly, PET – primary endocrine therapy, SIOG – International Society of Geriatric Oncology,

109 least because it has not proven straightforward to incorporate the assessment of frailty into routine
110 clinical practice⁵.

111

112 This article reviews how the identification of frailty in older patients can influence breast cancer
113 treatment received, and how frailty affects subsequent outcomes. The article also considers how
114 frailty assessment might be incorporated into standard practice within breast cancer units and what
115 challenges need to be overcome to achieve this.

116

117

118 **What is frailty?**

119 Frailty describes how a person becomes increasingly vulnerable to poor health as a consequence of
120 an age-related decline in the reserve of multiple physiological systems¹⁸. Frailty is closely associated
121 with comorbidity and disability, but each one constitutes an independent concept of ageing¹³. Frailty
122 can also be present without concurrent disability or comorbidity¹⁹, and it is not exclusive to a specific
123 chronological age cut-off²⁰. Consequently, although measures of comorbidity and functional status
124 are useful in stratifying patients with different clinical needs and health care outcomes^{21, 22}, frailty
125 adds another dimension in capturing the characteristics of an ageing population²³. Specifically,
126 because frailty is a dynamic manifestation of disease or injury and an increased vulnerability to
127 stressors, it is potentially reversible with early identification and appropriate interventions²⁴⁻²⁶.

128

129 There is no single, agreed conceptual model of frailty. There are currently two dominant concepts:
130 the 'phenotype' model and the 'cumulative deficit' model ([Appendix 1](#))^{19, 27}. The 'phenotype' model
131 was developed by Fried *et al.* and is based on the theory of frailty as a biological syndrome and a
132 "*cycle associated with declining energetics and reserves*"¹⁹. It is based on five pre-defined physical
133 frailty elements: weight loss, exhaustion, low physical activity, slowness and weakness. The
134 classification of a person as: 'not frail', 'pre-frail' and 'frail', is based on their combined performance
135 in these five elements.

136

137 In the 'cumulative deficit' model, frailty is considered as an accumulation of deficits across a number
138 of domains²⁷. These deficits are related to, but not specific to, the ageing process, and include both
139 subjective (observed during a clinical examination) and objective (e.g. biochemical tests, presence of
140 a disease) facets of adverse health and functional status²⁰. This model is the basis for several
141 objective frailty assessments, with the original frailty index developed for the Canadian Study of
142 Health and Ageing (CSHA) by Rockwood and colleagues²⁷. The CSHA frailty index consists of 92

143 deficits, with the index expressed as a proportion of the number of deficits present divided by the
144 total number possible²⁷. The index threshold for classification of frailty was based on the average
145 value of individuals with the same chronological age²⁷. Newer frailty indices, such as the Hospital
146 Frailty Risk Score²⁸, based on the ‘cumulative deficit’ model, have explored the inclusion of further
147 deficits to measure frailty. It is a feature of this model of frailty, that these newer measures
148 calculated using different deficits, are still able to identify an increasing burden of frailty among
149 older people, and demonstrate poorer health outcomes among those who are frail²⁸⁻³⁰.

150
151 Both concepts of frailty have been successfully operationalised as frailty assessments for use in
152 populations that include community residents, primary care patients and hospital in-patients. In the
153 clinical setting, the information on five specific elements of frailty (such as grip strength) provided by
154 assessments based on the phenotype model are valuable in identifying potentially reversible aspects
155 of frailty³¹. In contrast, the individual deficits within a frailty index are not of value by themselves,
156 and provide little insight into how to clinically respond to health problems at a patient level³². At
157 population level however, describing frailty as an accumulation of deficits is informative. Given that
158 this model is less prescriptive in its construction of frailty, it underpins the majority of the frailty
159 assessments used in large, primary care^{29,30} and administrative hospital datasets^{28,33}.

160
161 The conceptual basis of frailty and how frailty is best assessed is an ongoing area of research¹⁸. This
162 is necessary to ensure that the operationalisation of these frailty concepts into assessments is
163 clinically applicable towards the identification and management of frailty in any population. In
164 parallel, it is equally important to initiate the integration of frailty assessments into clinical practice.
165 This should be irrespective of disease cohort, with the aim of improving objectivity on the influence
166 of a patient’s ageing on clinical decisions.

167

168

169 **Tools for identifying frailty in patients with breast cancer**

170 In the era of multi-modal breast cancer treatment, decisions about a patient’s treatment are made
171 at various time points throughout their care pathway. In the initial stages, identifying an older
172 patient’s frailty status can inform clinical decision making, thus guidelines increasingly recommend
173 the use of formal frailty tools^{1,14}. Reliance on subjective “end-of-the-bed” opinions of patient frailty
174 is increasingly undesirable³⁴, especially given the dynamic and potentially reversible nature of frailty.
175 For example, the perception of frailty in a patient can vary depending on setting (e.g. emergency in-
176 patient vs. out-patient), the time of day or patient mood.

177

178 There are a variety of approaches to assessing frailty, and one widely recommended tool by geriatric
179 professional bodies is the Comprehensive Geriatric Assessment (CGA)^{14, 35, 36}. This provides a “*clinical*
180 *management strategy which will give a framework for the delivery of interventions which will*
181 *address relevant and appropriate issues for an individual patient*”¹⁶, without prescribing specific
182 methods for assessing these specific CGA domains (Table 1). However, the CGA typically requires
183 expertise from a geriatric medicine specialist and has been estimated by Girones *et al.* to take
184 between 30 to 40 minutes to complete³⁷.

185

186 The CGA has been used to assess the burden of frailty among breast cancer patients in several
187 studies, a selection of which are described in Table 2. These frailty assessments were performed for
188 a range of purposes including the assessment of fitness for primary surgery and the prediction of
189 adverse treatment outcomes. Irrespective of the purpose of the CGA, patients with increasing age
190 were more likely to be described as unfit or frail^{37, 38}, and had poorer survival and breast cancer
191 treatment outcomes³⁸⁻⁴⁰. Two prospective studies evaluated whether routine CGA altered breast
192 cancer treatment decisions^{41, 42} and reported different findings. In the study by Okonji *et al.*, women
193 defined as unfit or frail were less likely to undergo surgery or receive adjuvant chemotherapy⁴². In
194 contrast, Barthélémy *et al.* reported that the CGA results did not influence MDT decisions on
195 adjuvant chemotherapy⁴¹.

196

197 The variety of study designs in Table 2 also highlight the uncertainty that surrounds the application
198 of CGA in breast cancer care. First, there was no consistent definition of ‘old age’, with studies
199 having inclusion criteria that ranged from patients over 65 to 70 years. Second, there was
200 considerable heterogeneity in the patient populations: six studies only included patients with early
201 breast cancer^{37, 38, 41, 43, 44} and in two studies, patients with significant cognitive or functional
202 impairment were specifically excluded^{40, 42}. Finally, there were discrepancies between the studies in
203 the types of individual assessments used to assess CGA domains. This variation might be expected
204 given that the emphasis of the CGA is on individual domain assessment, with no preference for the
205 tools used within each domain⁴⁵. Nonetheless, this hampers the comparison of results across
206 studies as well as the ability to extrapolate whether the results can be applied in different settings⁴⁶.
207 Overall, these studies illustrate that there is little insight into how CGA results can guide
208 management decisions and what consequences this might have on outcomes.

209

210 Undertaking a CGA is labour and time intensive, and there are a range of screening tools available
211 with the aim of identifying patients who are frail and would benefit from a more comprehensive
212 assessment⁴⁷. In the UK, collaborations between professional bodies such as the Fit for frailty^{† 16, 36}
213 and NHS RightCare Frailty Toolkit^{‡ 48} clearly distinguishes between tools which screen for and those
214 that assess frailty. Some of the recommended frailty screening tools include:

- 215 • The Program of Research to Integrate Services for the Maintenance of Autonomy (PRISMA)-
216 7 questionnaire⁴⁹,
- 217 • the Clinical Frailty Scale⁵⁰,
- 218 • the Vulnerable Elders Survey (VES-13)⁵¹,
- 219 • the Edmonton Frail Scale⁵², and
- 220 • the Geriatric 8 (G8) frailty screening tool⁵³.

221 Neither Fit for Frailty, nor NHS RightCare, advocate one specific screening tool due to concerns that
222 certain instruments may have good sensitivity but poor specificity in identifying frailty, and the
223 accuracy of individual tools depend on the population assessed⁵⁴. In contrast, the International
224 Society of Geriatric Oncology (SIOG) declares a preference for the G8 tool for the identification of
225 frailty in older cancer patients⁴⁷. However, only a few of the aforementioned frailty screening tools
226 (i.e. VES-13⁵¹, Fried criteria^{55, 56}, G8^{53, 57}) have been used for patients with breast cancer, thus the
227 utility of other tools are unclear.

228
229 There are several other dominant reasons for why there is no current consensus on the most
230 appropriate frailty screening tool for use in patients with breast cancer. These are highlighted in
231 several systematic reviews of frailty assessment tools in general use. De Vries *et al.* identified and
232 reviewed 20 different frailty assessment tools⁵⁸. Although there was some consistency in the factors
233 that were included in most of the frailty assessments: physical activity, mobility, strength, energy,
234 nutritional status, cognition, mood, and social relations, there was wide heterogeneity between
235 tools⁵⁸. Aguayo *et al.* reviewed the agreement in the rating of frailty among 35 tools and only noted
236 moderate agreement in the classification of people as frail⁴⁶. Despite the conclusion of these reviews
237 and a lack of consensus on frailty tools, there is an ever-growing number of studies addressing the
238 value of frailty identification in older patients, at various stages of the breast cancer care pathway.

239
240

[†] Fit for frailty is a collaborative between British Society of Geriatrics, Age UK and Royal College of General Practitioners

[‡] NHS RightCare Frailty Toolkit was developed in collaboration with NHS England's National Clinical Director for Older People, Age UK, Getting It Right First Time (GIRFT) and NICE

241 Frailty and surgical treatment planning in early breast cancer

242 Surgery is the standard of care for patients with early invasive breast cancer, unless significant
243 burden of poor fitness precludes it^{1,2}. Elective breast surgery carries a comparably low risk of
244 mortality, and the impact of chronological age and comorbidity burden on post-operative
245 complications is negligible^{59,60}. Specifically, it is only in the presence of poor functional status and
246 cognitive impairment that multiple comorbidities is associated with post-operative mortality and
247 functional decline⁶¹. Despite this, studies repeatedly report a lower rate of surgical resection for
248 older patients with breast cancer, based on age and comorbidity profile^{3,4}. This is particularly the
249 case in patients with oestrogen receptor (ER-) positive disease for which primary endocrine therapy
250 (PET) is available as an 'alternative' treatment⁵, despite the inferiority of PET on disease-free
251 survival⁶².

252

253 The Pre-operative Assessment of Cancer in the Elderly (PACE) was developed to measure the
254 functional reserve of older cancer patients with the aim of "*reducing unacceptable denial of*
255 *potentially curative surgery*"⁶³. PACE incorporates the CGA and surgical risk assessments. Early
256 results from the PACE study provide insight on how information from a multi-domain frailty
257 assessment may influence surgical treatment decisions and short term post-operative outcomes⁶³.
258 For example, patients with poor scores had higher rates of 30-day surgical complications⁶⁰. However,
259 only 47% (of the 460 patients) in the study cohort had breast cancer, and the results were not
260 reported by cancer type. This limits the extrapolation of PACE to guide surgical decisions for patients
261 with breast cancer.

262

263 There are advocates for omitting extensive axillary surgery for older patients with early stage
264 invasive breast cancer, to minimise morbidity without compromising oncological outcomes. Large
265 longitudinal population-based studies have shown that this perspective is increasingly adopted, with
266 fewer older patients undergoing comprehensive axillary staging over time⁶⁴. Whether frailty
267 assessments can provide information to guide decisions on axillary management independent of
268 decisions on primary breast surgery for older patients, is unclear. Few studies specifically address
269 this question, though a multi-centre prospective study using the CGA reported that frailty was not
270 strongly associated with non-receipt of axillary surgery among women who were having primary
271 breast surgery⁴².

272

273 **Frailty and primary endocrine therapy**

274 The evidence base on how formal frailty assessments in older patients with breast cancer might
275 contribute towards the decision between PET and surgical treatment, or how frailty is associated
276 with breast cancer outcomes among patients taking PET, is lacking¹. In addition, the majority of
277 studies addressing treatment selection mainly examined the association between PET, or surgery,
278 and comorbidity^{4, 65}. One exception is the ongoing 'Bridging the Age Gap Study' which examines the
279 use a clinical decision support tool specifically for older patients with breast cancer⁶⁶. Long-term
280 follow-up results for this study are still outstanding.

281

282 The SIOG and European Society of Breast Cancer Specialists (EUSOMA) recommend PET for patients
283 with ER-positive disease who have "*poor predicted life expectancy or who are unfit for surgery after*
284 *medical optimisation*"⁶⁷. Framing the decision in relation to life expectancy highlights the potential
285 role for frailty assessment to complement the assessment of fitness for surgical treatment.

286 Identification of frailty creates an opportunity to provide interventions that may improve a patient's
287 frailty status, either before or after primary treatment. Given that a higher burden of frailty,
288 irrespective of method of frailty assessment, is associated with shorter life expectancy, optimisation
289 of frailty components has the potential value of improving disease-specific and overall survival.

290 Frailty assessments are also applicable in optimising patients for palliative surgical resections with a
291 view to minimising symptoms or disease progression on PET⁶⁸.

292

293 **Frailty and adjuvant therapies in breast cancer: Chemotherapy**

294 In contrast to younger patients with breast cancer, the evidence base to support chemotherapy
295 decisions in older age patients is limited. Older patients are often poorly represented in clinical
296 trials^{69, 70}, and several large international multi-centre randomised trials aimed at addressing
297 treatment in the older cohort were terminated prematurely due to insufficient accrual^{71, 72}.

298 Consequently, much of the available evidence stems from population-level studies that demonstrate
299 an association between adjuvant chemotherapy and survival benefits in older patients with high-risk
300 tumour characteristics (such as axillary nodal metastasis)^{11, 73}. However, it is not possible to confirm
301 causality from observational studies.

302

303 Guidelines emphasise that the decision to offer chemotherapy to older patients with breast cancer
304 should not be based on age⁶⁷. However, older age is associated with higher rates of chemotherapy

305 related toxicity and mortality^{70,74} and chronological age is perceived as an important patient
306 characteristic by oncologists when considering adjuvant chemotherapy⁷⁵. Few published population
307 level studies account for patient characteristics beyond chronological age and comorbidity, and this
308 has likely contributed to the lower uptake of adjuvant chemotherapy among older patients^{11,70,76}.

309

310 There is increasing support for the use of frailty assessments to identify patients who are at
311 increased risk of chemotherapy toxicity, or who require additional support to facilitate completion of
312 regimes^{77,78}. For example, in a pilot study by Extermann *et al.*, fifteen patients underwent a CGA
313 assessment prior to and during adjuvant chemotherapy. Issues identified by the CGA led to a range
314 of medical, nutritional and psychological interventions that directly influenced the care of four out of
315 the fifteen patients⁴³. Allowing for the small sample size, the study highlights the range of issues that
316 can be identified and addressed by a formal frailty assessment. In another study, Kalsi *et al.*
317 evaluated whether a frailty assessment could improve chemotherapy tolerance in patients with
318 various types of cancer. The process led to an average of six interventions per patient before or
319 during the course of systemic therapy. There was also improved tolerance to treatment regimens in
320 comparison to a control group. Collectively, these studies illustrate the value of a multidisciplinary
321 team approach in managing selected older patients with breast cancer, with a particular role for a
322 specialist geriatrician in the consideration for, and delivery of, chemotherapy.

323

324 **Frailty and adjuvant therapies in breast cancer: Radiotherapy**

325 The use of radiotherapy in older patients with breast cancer mirrors that observed for
326 chemotherapy, with lower levels of radiotherapy uptake in older age^{6,79}. This might be similarly due
327 to the lack of evidence on long-term survival benefit after radiotherapy in this cohort⁸⁰⁻⁸². Several
328 randomised-trials have reported no increased risk of complications from radiotherapy with older
329 age^{80,83}. However, radiotherapy was delivered in the adjuvant setting (after surgery) in these studies,
330 and frail patients are less likely to receive surgery. Therefore, it is unclear how these reports of
331 minimal radiotherapy complications in a cohort of fit older patients can be applied to a frail cohort.
332 There are some smaller studies examining the association between frailty and radiotherapy toxicity
333 in older (non-breast) cancer patients^{84,85}. However, these studies were inconsistent in their findings
334 on the influence of frailty, on the completion of radiotherapy treatment and toxicity^{84,85}.

335

336 It is not understood whether frailty assessments can support the delivery of radiotherapy in older
337 patients with breast cancer⁸⁶, though some small studies have suggested potential utility. For
338 example, Denkinger *et al.* suggested that the CGA was superior to other assessments of patient
339 characteristics in predicting fatigue after radiotherapy⁸⁷. In addition, because CGA covers multiple
340 frailty domains⁸⁸, it also has the potential to capture issues related to transport and travel for
341 treatment - logistical factors known to influence radiotherapy uptake⁸⁹.

342

343 **Challenges in the implementation of frailty assessments in breast cancer**

344 In the UK, there has been slow uptake towards the implementation of frailty assessments as part of
345 routine clinical practice for breast cancer^{5,90}. As examined, one reason for this could be the lack of a
346 strong evidence base, both in terms of the effects of the frailty assessment process and the types
347 and range of interventions that should be employed. However, reassuringly, this is being addressed
348 with an increasing number of studies investigating the value of frailty assessments throughout the
349 breast cancer patient pathway.

350

351 Another reason might be the lack of capacity within geriatric services to provide support for frailty
352 assessments of cancer patients. It is more realistic that breast cancer services would need to adopt a
353 screening process to identify patients who would benefit from a more extensive frailty assessment,
354 in order to minimise the requirement for specialist input. However, even if sufficient expertise can
355 be provided, the next challenge is to identify a consistent method of screening or fully assessing
356 frailty, and the 'ideal' point in a patient care pathway to apply this.

357

358 Prior to implementing a frailty assessment into the service pathway for breast cancer care, it is
359 important to be clear on the purpose of identifying frailty in a patient. If the aim of the frailty
360 assessment is to inform on the risk of complications from breast cancer treatments for each patient,
361 the focus of the assessment and interventions could be rationalised to focus on those frailty
362 domains (within the CGA) that are strongly associated with treatment-related morbidity and
363 survival. However, if the purpose of the frailty assessment is to evaluate the overall health of the
364 patient with a view to optimising their fitness for breast cancer treatments, then all the frailty
365 domains should be thoroughly assessed and optimised, where appropriate.

366

367 Finally, there are also several key issues to address in an effort to strengthen the current evidence
368 base.

369

- 370 • **There needs to be consistency in the assessment of frailty in older patients with breast**
371 **cancer.**

372 Consensus statements and guidelines should include an aim to have a position on the preferred
373 types of frailty screening and assessment tools. This should include more precise recommendations,
374 than currently exist, concerning the appropriate tools for the various frailty domains, as described by
375 the CGA, and how the results might link to interventions for optimising patients for cancer
376 treatments (e.g. the involvement of onco-geriatric specialities). Improving the consistency in
377 reporting standards will enable more robust comparisons between studies and provide valuable
378 information on patient outcomes. It will also improve the quality of studies evaluating the
379 implementation of frailty assessments in breast cancer care pathways. Applied at a population level,
380 a standardised method of reporting on frailty will also enhance the understanding of how patient
381 factors contribute to national variations and differences in patterns of treatment for breast cancer
382 between age cohorts.

383

- 384 • **The role of the frailty assessment needs to be clearly defined in the breast cancer patient**
385 **pathway**

386 While studies have begun to illustrate how information about patient frailty can influence treatment
387 decisions for older patients, there is little understanding of how frailty screening or assessment are
388 best utilised along the breast cancer care pathways of different patient groups⁹¹. A multi-faceted
389 assessment can identify and optimise health deficits for cancer treatment and individualise patient
390 management (including both early stage and advanced disease). Clear practical advice is required to
391 ensure that the results of frailty assessments are used as a guide to inform treatment decisions, and
392 not as a checklist or 'hurdle to overcome' in accessing particular cancer treatments.

393

- 394 • **The role of geriatric medicine in the breast cancer care pathway needs to be defined**

395 In the UK, few breast cancer units work in collaboration with geriatric services in their management
396 of older patients⁹. A small number of studies have shown that geriatric services can make a valuable
397 contribution towards planning and delivery of cancer therapy^{39, 60, 78, 92}. A pragmatic compromise in

398 most units could be a standardised screening process to identify patients who are frail and who
399 would benefit from onward referral for specialist geriatric input.

400

401 In summary, a formal assessment of frailty in the breast cancer care pathway has the potential to
402 improve objectivity in management decisions and identify underlying health problems in older
403 patients that can be optimised to improve the chances of successful treatment. Heterogeneity in the
404 available methods for screening and assessing frailty is an important challenge to overcome for
405 implementation into clinical practice. However, it is also important to be clear on the reason for
406 frailty assessments in the treatment pathway, and the role of the geriatric specialist in facilitating a
407 holistic approach to breast cancer care.

408

409 *3,945 words (including headings, excluding references and tables)*

410

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 668 elderly breast cancer survivors. Results of a single-center experience. *Critical Reviews in*
 669 *Oncology/Hematology*. 2010;73(3):236-45.
- 670 Table 1: Frailty domains assessed in the Comprehensive Geriatric Assessment (CGA)

671

Multi-dimensional CGA assessment components:
<ul style="list-style-type: none"> • Physical symptoms • Mental health symptoms • Level of function in daily activity: for personal care and life activities • Social support network (formal e.g. carers and informal e.g. family and friends) • Living environment (including ability to use local facilities and technological support) • Level of participation and individual concerns • Compensatory mechanisms and resourcefulness which is used by the individual in response to frailty

672

673 **Table 2: A summary of studies using the comprehensive geriatric assessment (CGA) on breast cancer patients**

674

675 *Abbreviations: ADL – Activities of Daily Living, ASA – American Society of Anaesthesiology, BMI – Body Mass Index, CCI – Charlson Comorbidity Index, Cumulative illness*
 676 *Rating Scale for Geriatrics (CIRS-G), ECOG PS –Eastern Cooperative Oncology Group performance status, ER – oestrogen receptor, GDS – Geriatric Depression Scale, iADL –*
 677 *Instrumental Activities of Daily Living, G8, MMSE – Mini Mental State Examination, MNA – mini nutritional assessment, TUG – timed up-and-go*

678

Author, year	Study population	Study objective	Number of patients, age	Details of assessment/ instruments used (where specified)	Results
Okonji <i>et al</i> , 2017 ⁴²	Multicentre prospective study (n=24) (Jan 2012 – Oct 2015) Stage I – III breast cancer, aged ≥70 years with no severe cognitive impairment	To use CGA to assess fitness for primary surgery and adjuvant treatment	326 patients Median age 77 years	Comorbidity: CCI, clinical interview Cognition: 6-Cognitive Impairment Test (6-CIT) Functional status: ADL, iADL Other: ASA grade, ECOG PS Frailty screening tools: Vulnerable Elder Survey (VES-13), G8 <u>Definition of fit:</u> ECOG PS ≤ 1, ASA grade ≤ II, 6-CIT ≤ 7, VES-13 ≤ 2, ADL ≥ 6, IADL ≥ 8, G8 ≥15 and CCI ≤ 1.	Older patients were reported as less 'fit' (35% in 70 – 74 years, 61% in 75 – 84 years, 12% in ≥ 85 years) In comparison to fit patients, unfit patients were less likely to undergo primary breast cancer resection (100% vs. 91%, p = 0.002) and receive adjuvant chemotherapy (51% vs. 20%, p=0001). Patient fitness, independent of age, did not affect the proportion of patients undergoing axillary surgery, receiving radiotherapy after wide local excision, Trastuzumab (in HER2-positive patients only) or adjuvant endocrine therapy.

<p>Stotter <i>et al</i>, 2015³⁹</p>	<p>Single centre retrospective study (Jan 2005 – May 2012)</p> <p>Women with primary early ER-positive breast cancer where there were concerns regarding fitness to receive standard treatment</p>	<p>The use of CGA to predict 3-year overall survival</p>	<p>328 patients</p> <p>Median age 82 years (range: 43 – 98 years)</p>	<p>Comorbidity: Satariano score/CCI Cognition: MMSE Mental Health: GDS Functional status: Barthel Index of ADL, IADL Other: ASA score</p>	<p>212/328 (65%) had surgical treatment after CGA assessment.</p> <p>97% of the cohort had died by 3 years.</p> <p>Comorbidity, MMSE, poor functional status and ASA grade was associated with 3-year mortality.</p> <p>CGA was predictive of 3-year survival probability (ROC of the survival model = 0.75 (95% CI: 0.67 – 0.82)).</p>
<p>Hamaker <i>et al</i>, 2014⁴⁰</p>	<p>Multi-centre randomised clinical trial (Dutch Breast Cancer Trialists' Group OMEGA study) (Apr 2007 – Sept 2011)</p> <p>Metastatic breast cancer patient, aged ≥ 65 years, good ECOG PS (0-2) and good health status</p>	<p>To evaluate the use of CGA/ screening tool for predicting chemotherapy related toxicity and overall survival.</p> <p>Patients randomised to receive (1) Doxorubicin, or (2) Capecitabine</p>	<p>78 patients</p> <p>Median age 76 years (range: 66 – 87 years)</p>	<p>Comorbidity: CCI Cognition: MMSE Mental health: GDS Functional status: iADL Number of medications used Nutritional status: BMI</p> <p><u>Cut-off scores for deficiencies/ impairment</u> CCI ≥ 2, IADL: partial dependence 14–27; full functional dependence ≤ 13, polypharmacy ≥ 5, undernutrition = $\leq 20 \text{ kg/m}^2$, MMSE ≤ 23, GDS: severe depressive symptoms ≥ 10, moderate depressive symptoms 5–9.</p> <p><u>Classification of frailty</u> ≥ 1 of full IADL dependence, comorbidity score ≥ 2, polypharmacy, cognitive impairment, undernutrition and/or moderate to severe depressive symptoms</p>	<p>Study terminated early due to poor accrual</p> <p>There was no difference in chemotherapy toxicity rates between the two arms of the study.</p> <p>Increasing number of CGA deficiencies was associated with grade 3-4 chemotherapy-related toxicity. Polypharmacy was the only individual factor within the CGA that was associated with toxicity.</p> <p>54/78 (69%) of patients died (median follow-up 32 months).</p> <p>Median survival between fit (19.9 months) vs. frail (10.3 months, $p = 0.04$) became non-significant when adjusting for age, PS and chemotherapy type ($p = 0.2$).</p>

Parks <i>et al</i> , 2014 ⁴⁴	Single-centre prospective study Women with stage I-II operable primary breast cancer, aged \geq 70 years.	To understand how CGA characteristics were associated with receipt of surgical treatment	47 patients Mean age 80 years (max 92 years)	Mental health: Hospital Anxiety and Depression Scale (HADS), Blessed Orientation-Memory-Concentration test (BOMC) Functional status: iADL, ADL, Karnofsky self-reported performance rating scale, TUG test Geriatric syndromes: falls, polypharmacy Self-reported health: Older American Resources and Services (OARS) Nutrition: self-reported weight loss, BMI Social support: MOS Social Support Survey, Seeman and Berkman Social Ties	62% of the cohort had surgical treatment Increasing age, polypharmacy, greater comorbidity and slow TUG test results were associated with a reduced likelihood of receiving surgery. No difference in quality of life score (at 6 weeks or at 6 months) between those who did and did not have surgery.
Clough-Gorr <i>et al</i> , 2012 ³⁸	Multi-centre longitudinal study Women with stage I (tumour size $>1\text{cm}$) or II-IIIa breast cancer, aged ≥ 65 years; treated with surgical resection	Secondary survival analysis on cancer specific CGA domains in relation to breast cancer outcomes and survival	660 patients 18% aged ≥ 80 years	Using cancer-specific geriatric assessment (C-SGA) consisting of 4 main domains. Clinical: CCI, BMI Psychosocial: Mental Health Index (MHI5), medical outcomes study social support scale (MOS-SSS) Self-rated health status Socio-demographic: adequate financial resources	Women with ≥ 3 C-CGA deficits had poorer 5 and 10-year all cause (HR 1.87, 1.74) and breast cancer specific (HR 1.95, 1.99) survival.
Barthélemy <i>et al</i> , 2011 ⁴¹	Single-centre prospective study (July 2006 – July 2009) Patients with primary early breast cancer, age 70 – 79 years (with one comorbidity) and all patients >79 years	To assess impact of CGA, chronological age and other prognostic factors on MDT proposal for adjuvant chemotherapy	192 patients Median age 75 years (range: 70 – 98 years)	Comorbidity: CIRS-G Cognitive function: MMSE Mental health: GDS Functional status: iADL, ADL, ECOG PS Geriatric syndromes: falls Nutritional status: BMI, MNA <u>Classification</u> Fit = no deficiencies in the domains above Frail = >1 major deficiency	Patient age and tumour characteristics were associated with MDT recommendations for adjuvant characteristics Patient CGA results were not associated with trends in MDT recommendations for adjuvant chemotherapy.

Gironés <i>et al</i> , 2009 ⁹³	Single centre cross-sectional study (Jan 2005 – June 2006) Patients treated for early primary breast cancer, aged ≥70 years (who were able to give written consent)	To assess the prevalence of comorbidity, disability and geriatric syndrome. To assess feasibility of implementing CGA in an oncology clinic	91 patients Mean age at surgery = 76 years (range: 70 – 92 years) Mean age at CGA = 80 years (range: 71 – 95 years)	Comorbidity: CCI Cognition: MMSE Mental health: GDS Functional status: iADL, ADL, ECOG PS Geriatric Syndromes: dementia, delirium, depression, falls, neglect and abuse, spontaneous bone fractures Nutrition: MNA Pharmacy: number and appropriateness of medications, risk of drug interactions Socioeconomic: living conditions, presence of a caregiver CGA was performed at follow-up visit. The median interval between diagnosis and CGA was 39 months (range 2 – 120 months).	Inclusion criteria was biased towards patients with good cognitive function. Study found low prevalence of functional limitations (4%) and cognitive impairment (16%). Hypertension and peripheral vascular disease were the most common comorbidities. Presence of comorbidity was independent of functional limitations and age. High number of prescribed medications (75% on > 6 medications). 34/91 (37%) were reported as frail.
Extermann <i>et al</i> , 2004 ⁴³	Patients treated with surgery for stage I – II breast cancer, aged ≥ 70 years; prior to initiation of adjuvant therapy	To assess the prevalence of geriatric problems, amenable to intervention, and their interaction with cancer treatment	15 patients Median age 79 years (range: 72 – 87 years)	Quality of life – Functional Assessment of Cancer Treatment- Breast (FACT-B) Functional status – iADL, ADL, ECOG PS Mental health – GDS Cognitive function – MMSE Nutrition – MNA Comorbidity – CCI, CIRS-G Regular 3 monthly assessments during follow-up period, after surgical treatment.	CGA identified problems throughout their cancer care, with opportunities for preventative interventions. The cancer care of 4/11 patients directly benefitted from the interventions.

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683 Appendix 1: A comparison of the variables included in the phenotype and cumulative deficit models
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Comprehensive Geriatric Assessment (CGA domain)	Phenotype Model Fried et al¹⁹	Cumulative deficit model Mitniski et al²⁷ (26)
Cognition / Mood		Delirium, Sleep changes, Memory problems, Mood problems, Sadness
Nutritional problems	Baseline:>10lbs lost unintentionally in prior year (Shrinking: unintentional weight loss), sarcopenia (loss of muscle mass)	Gastrointestinal symptoms
Sensory problems		Hearing or visual problems
Energy / Activity levels	Self-reported exhaustion Poor endurance: exhaustion Kcals /week: lowest 20%	Activities of daily living
Mobility / musculoskeletal problems	weakness: Grip strength - score 1 if lowest 20% (by gender, body mass index) slowness: Walking time/.15 feet: slowest 20% (by gender, height)	Mobility impairment, Gait abnormality, Difficulty in going out / cooking / getting dressed / grooming/ bathing/ toileting, Tremor (resting/ action), Dyskinesia's/ chorea, Akinesia, Limb tone abnormality, Impaired vibration sense
Genito-urinary problems		Urinary/stool incontinence, Urinary symptoms
Medical co-morbidities		History of thyroid disease, Diabetes Mellitus, Clinical abnormalities in head / neck / neurology thyroid/ breast/ lungs/ cardiovascular/ peripheral pulses/ abdomen/ rectum/ skin examination, Biochemical abnormalities of Sodium / Potassium / Urea / Creatinine/ Calcium / Phosphate / Thyroid stimulating hormone / vitamin B12 / Folate / vDRL / protein / albumin levels, Renal disease, Parkinson's disease, Hypertension, Cardiac symptoms, Cardiovascular disease, Cerebrovascular disease

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Declarations of interest: none

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