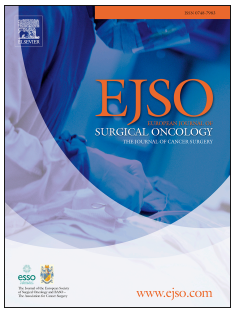

Addressing frailty in patients with breast cancer: A review of the literature

Yasmin Jauhari, Melissa Ruth Gannon, David Dodwell, Kieran Horgan, Carmen Tsang, Karen Clements, Jibby Medina, Sarah Tang, Ruth Pettengell, David Alan Cromwell

PII: S0748-7983(19)30623-7

DOI: https://doi.org/10.1016/j.ejso.2019.08.011

Reference: YEJSO 5460

To appear in: *European Journal of Surgical Oncology*

Received Date: 22 July 2019

Accepted Date: 12 August 2019

Please cite this article as: Jauhari Y, Gannon MR, Dodwell D, Horgan K, Tsang C, Clements K, Medina J, Tang S, Pettengell R, Cromwell DA, Addressing frailty in patients with breast cancer: A review of the literature, *European Journal of Surgical Oncology* (2019), doi: https://doi.org/10.1016/j.ejso.2019.08.011.

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

Author names and affiliations:

Yasmin Jauhari (Y.J.)[1 7], Melissa Ruth Gannon (M.R.G.)[1 2], David Dodwell (D.D)[5], Kieran Horgan (K.H.)[4], Carmen Tsang (C.T.)[2 3], Karen Clements (K.C.)[6], Jibby Medina (J.M.)[1], Sarah Tang (S.T.)[6], Ruth Pettengell (R.P.)[6] and David Alan Cromwell (D.A.C.)[1 2]

Institutions

[1] Clinical Effectiveness Unit, The Royal College of Surgeons of England, London, UK

[2] Department of Health Services Research & Policy, London School of Hygiene & Tropical Medicine, London, UK

[3] Centre for Surgical Research, Bristol Medical School: Population Health Sciences, University of Bristol, Bristol, UK

[4] Department of Breast Surgery, St James's University Hospital, Leeds, UK

[5] Nuffield Department of Population Health, University of Oxford, Oxford, UK

[6] Public Health England, 1st Floor, 5 St Philip's Place, Birmingham, UK

[7] St Georges Healthcare NHS Trust, London, UK

Corresponding author:

Yasmin Jauhari (yjauhari@rcseng.ac.uk)

Clinical Effectiveness Unit, The Royal College of Surgeons of England, 35 – 43 Lincoln Inn's Fields, London, WC2A 3PE

Phone: 020 7869 6606

Manuscript category: review article

Role of the funding source:

This review was undertaken as part of the work by the National Audit of Breast Cancer in Older Patients (NABCOP). The Audit is commissioned by the Healthcare Quality Improvement Partnership (HQIP) as part of the National Clinical Audit and Patient Outcomes Programme (NCAPOP), and funded by NHS England and the Welsh Government (www.hqip.org.uk/national-programmes). Neither HQIP nor the funders had any involvement in the design of this review or in the identification, and interpretation of published literature, in the writing of the report, or in the decision to submit the article for publication. The authors had full independence from the HQIP.

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

Ethics approval

Not applicable

Data sharing:

Not applicable

Abstract

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

This article examines the potential of frailty assessment to inform on breast cancer treatments. Overall, the current evidence highlights various benefits from implementing comprehensive geriatric assessment and screening for frailty in breast cancer patients. This includes a role in supporting the

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

203 words

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

Introduction*

Clinical guidelines emphasise that breast cancer treatment should be based on clinical need and patient fitness, rather than age[1]. For example, the guidelines for early breast cancer issued by the UK National Institute for Health and Care Excellence (NICE) recommends that women *"irrespective of age, are offered surgery, radiotherapy and appropriate systemic therapy, unless significant comorbidity precludes it"*[2]. However, various UK-based population level studies report considerable variation in the breast cancer treatments received by older women (often defined as age 70 years or older) in comparison to younger women.

Older women are less likely to receive surgery for operable breast cancer[3, 4]. Among those older women who do receive surgery, this is more likely to be a mastectomy than breast conserving surgery (BCS)[5], and of those women having BCS, they are less likely to have adjuvant radiotherapy[6, 7]. Older women are also less likely to receive chemotherapy[8]. There are various possible reasons for these reported differences in treatment provision. On average, older women tend to have larger tumours at diagnosis[9], which is partly a consequence of being older than the inclusion ages of women (usually 50 to 70 years) in national breast screening programmes. The higher burden of comorbid conditions among older women may also be a significant contributing factor, with various studies showing lower rates of surgery[3] and other therapies[10, 11] among women with more comorbid conditions. However, these factors only explain some of the reported variation in treatment patterns between younger and older women. One-third of all breast cancers diagnosed are in women aged 70 years or over[12], so addressing this variation is important for population health .

The impact of ageing on health is complex and ageing can influence functional ability, physiology and social wellbeing to different degrees[13]. Chronological age is increasingly viewed as a poor descriptor of the ageing process. More recently, there is a much greater desire to determine "biological age"[14, 15]. Geriatric associations have, for a while, recommended that a measure of frailty be used to report on ageing and its complex sequelae[14, 16]. This approach has been progressively adopted by other specialties, perhaps most evidently in relation to the management of hip fractures[17]. However, 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,

least because it has not proven straightforward to incorporate the assessment of frailty into routine clinical practice[5].

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

What is frailty?

Frailty describes how a person becomes increasingly vulnerable to poor health as a consequence of an age-related decline in the reserve of multiple physiological systems[18]. Frailty is closely associated with comorbidity and disability, but each one constitutes an independent concept of ageing[13]. Frailty can also be present without concurrent disability or comorbidity[19], and it is not exclusive to a specific chronological age cut-off[20]. Consequently, although measures of comorbidity and functional status are useful in stratifying patients with different clinical needs and health care outcomes[21, 22], frailty adds another dimension in capturing the characteristics of an ageing population[23]. Specifically, because frailty is a dynamic manifestation of disease or injury and an increased vulnerability to stressors, it is potentially reversible with early identification and appropriate interventions[24-26].

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

In the 'cumulative deficit' model, frailty is considered as an accumulation of deficits across a number of domains[27]. These deficits are related to, but not specific to, the ageing process, and include both subjective (observed during a clinical examination) and objective (e.g. biochemical tests, presence of a disease) facets of adverse health and functional status[20]. This model is the basis for several objective frailty assessments, with the original frailty index developed for the Canadian Study of Health and Ageing (CSHA) by Rockwood and colleagues[27]. The CSHA frailty index consists of 92

deficits, with the index expressed as a proportion of the number of deficits present divided by the total number possible[27]. The index threshold for classification of frailty was based on the average value of individuals with the same chronological age[27]. Newer frailty indices, such as the Hospital Frailty Risk Score[28], based on the 'cumulative deficit' model, have explored the inclusion of further deficits to measure frailty. It is a feature of this model of frailty, that these newer measures calculated using different deficits, are still able to identify an increasing burden of frailty among older people, and demonstrate poorer health outcomes among those who are frail[28-30].

Both concepts of frailty have been successfully operationalised as frailty assessments for use in populations that include community residents, primary care patients and hospital in-patients. In the clinical setting, the information on five specific elements of frailty (such as grip strength) provided by assessments based on the phenotype model are valuable in identifying potentially reversible aspects of frailty[31]. In contrast, the individual deficits within a frailty index are not of value by themselves, and provide little insight into how to clinically respond to health problems at a patient level[32]. At population level however, describing frailty as an accumulation of deficits is informative. Given that this model is less prescriptive in its construction of frailty, it underpins the majority of the frailty assessments used in large, primary care[29, 30] and administrative hospital datasets[28, 33].

The conceptual basis of frailty and how frailty is best assessed is an ongoing area of research[18]. This is necessary to ensure that the operationalisation of these frailty concepts into assessments is clinically applicable towards the identification and management of frailty in any population. In parallel, it is equally important to initiate the integration of frailty assessments into clinical practice. This should be irrespective of disease cohort, with the aim of improving objectivity on the influence of a patient's ageing on clinical decisions.

Tools for identifying frailty in patients with breast cancer

In the era of multi-modal breast cancer treatment, decisions about a patient's treatment are made at various time points throughout their care pathway. In the initial stages, identifying an older patient's frailty status can inform clinical decision making, thus guidelines increasingly recommend the use of formal frailty tools[1, 14]. Reliance on subjective "end-of-the-bed" opinions of patient frailty is increasingly undesirable[34], especially given the dynamic and potentially reversible nature of frailty. For example, the perception of frailty in a patient can vary depending on setting (e.g. emergency in-patient vs. out-patient), the time of day or patient mood.

There are a variety of approaches to assessing frailty, and one widely recommended tool by geriatric professional bodies is the Comprehensive Geriatric Assessment (CGA)[14, 35, 36]. This provides a "*clinical management strategy which will give a framework for the delivery of interventions which will address relevant and appropriate issues for an individual patient*"[16], without prescribing specific methods for assessing these specific CGA domains (Table 1). However, the CGA typically requires expertise from a geriatric medicine specialist and has been estimated by Girones *et al.* to take between 30 to 40 minutes to complete[37].

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

The variety of study designs in Table 2 also highlight the uncertainty that surrounds the application of CGA in breast cancer care. First, there was no consistent definition of 'old age', with studies having inclusion criteria that ranged from patients over 65 to 70 years. Second, there was considerable heterogeneity in the patient populations: six studies only included patients with early breast cancer[37, 38, 41, 43, 44] and in two studies, patients with significant cognitive or functional impairment were specifically excluded[40, 42]. Finally, there were discrepancies between the studies in the types of individual assessments used to assess CGA domains. This variation might be expected given that the emphasis of the CGA is on individual domain assessment, with no preference for the tools used within each domain[45]. Nonetheless, this hampers the comparison of results across studies as well as the ability to extrapolate whether the results can be applied in different settings[46]. Overall, these studies illustrate that there is little insight into how CGA results can guide management decisions and what consequences this might have on outcomes.

Undertaking a CGA is labour and time intensive, and there are a range of screening tools available with the aim of identifying patients who are frail and would benefit from a more comprehensive assessment[47]. In the UK, collaborations between professional bodies such as the Fit for frailty[†] [16, 36] and NHS RightCare Frailty Toolkit[‡] [48] clearly distinguishes between tools which screen for and those that assess frailty. Some of the recommended frailty screening tools include:

- The Program of Research to Integrate Services for the Maintenance of Autonomy (PRISMA)-7 questionnaire[49],
- the Clinical Frailty Scale[50],
- the Vulnerable Elders Survey (VES-13)[51],
- the Edmonton Frail Scale[52], and
- the Geriatric 8 (G8) frailty screening tool[53].

Neither Fit for Frailty, nor NHS RightCare, advocate one specific screening tool due to concerns that certain instruments may have good sensitivity but poor specificity in identifying frailty, and the accuracy of individual tools depend on the population assessed[54]. In contrast, the International Society of Geriatric Oncology (SIOG) declares a preference for the G8 tool for the identification of frailty in older cancer patients[47]. However, only a few of the aforementioned frailty screening tools (i.e. VES-13[51], Fried criteria[55, 56], G8[53, 57]) have been used for patients with breast cancer, thus the utility of other tools are unclear.

There are several other dominant reasons for why there is no current consensus on the most appropriate frailty screening tool for use in patients with breast cancer. These are highlighted in several systematic reviews of frailty assessment tools in general use. De Vries *et al*. identified and reviewed 20 different frailty assessment tools[58]. Although there was some consistency in the factors that were included in most of the frailty assessments: physical activity, mobility, strength, energy, nutritional status, cognition, mood, and social relations, there was wide heterogeneity between tools[58]. Aguayo *et al.* reviewed the agreement in the rating of frailty among 35 tools and only noted moderate agreement in the classification of people as frail[46]. Despite the conclusion of these reviews and a lack of consensus on frailty tools, there is an ever-growing number of studies addressing the value of frailty identification in older patients, at various stages of the breast cancer care pathway.

[†] 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

Frailty and surgical treatment planning in early breast cancer

Surgery is the standard of care for patients with early invasive breast cancer, unless significant burden of poor fitness precludes it[1, 2]. Elective breast surgery carries a comparably low risk of mortality, and the impact of chronological age and comorbidity burden on post-operative complications is negligible[59, 60]. Specifically, it is only in the presence of poor functional status and cognitive impairment that multiple comorbidities is associated with post-operative mortality and functional decline[61]. Despite this, studies repeatedly report a lower rate of surgical resection for older patients with breast cancer, based on age and comorbidity profile[3, 4]. This is particularly the case in patients with oestrogen receptor (ER-) positive disease for which primary endocrine therapy (PET) is available as an 'alternative' treatment[5], despite the inferiority of PET on disease-free survival[62].

The Pre-operative Assessment of Cancer in the Elderly (PACE) was developed to measure the functional reserve of older cancer patients with the aim of "*reducing unacceptable denial of potentially curative surgery*"[63]. PACE incorporates the CGA and surgical risk assessments. Early results from the PACE study provide insight on how information from a multi-domain frailty assessment may influence surgical treatment decisions and short term post-operative outcomes[63]. For example, patients with poor scores had higher rates of 30-day surgical complications[60]. However, only 47% (of the 460 patients) in the study cohort had breast cancer, and the results were not reported by cancer type. This limits the extrapolation of PACE to guide surgical decisions for patients with breast cancer.

There are advocates for omitting extensive axillary surgery for older patients with early stage invasive breast cancer, to minimise morbidity without compromising oncological outcomes. Large longitudinal population-based studies have shown that this perspective is increasingly adopted, with fewer older patients undergoing comprehensive axillary staging over time[64]. Whether frailty assessments can provide information to guide decisions on axillary management independent of decisions on primary breast surgery for older patients, is unclear. Few studies specifically address this question, though a multi-centre prospective study using the CGA reported that frailty was not strongly associated with non-receipt of axillary surgery among women who were having primary breast surgery[42].

Frailty and primary endocrine therapy

The evidence base on how formal frailty assessments in older patients with breast cancer might contribute towards the decision between PET and surgical treatment, or how frailty is associated with breast cancer outcomes among patients taking PET, is lacking[1]. In addition, the majority of studies addressing treatment selection mainly examined the association between PET, or surgery, and comorbidity[4, 65]. One exception is the ongoing 'Bridging the Age Gap Study' which examines the use a clinical decision support tool specifically for older patients with breast cancer[66]. Long-term follow-up results for this study are still outstanding.

The SIOG and European Society of Breast Cancer Specialists (EUSOMA) recommend PET for patients with ER-positive disease who have *"poor predicted life expectancy or who are unfit for surgery after medical optimisation"*[67]. Framing the decision in relation to life expectancy highlights the potential role for frailty assessment to complement the assessment of fitness for surgical treatment. Identification of frailty creates an opportunity to provide interventions that may improve a patient's frailty status, either before or after primary treatment. Given that a higher burden of frailty, irrespective of method of frailty assessment, is associated with shorter life expectancy, optimisation of frailty components has the potential value of improving disease-specific and overall survival. Frailty assessments are also applicable in optimising patients for palliative surgical resections with a view to minimising symptoms or disease progression on PET[68].

Frailty and adjuvant therapies in breast cancer: Chemotherapy

In contrast to younger patients with breast cancer, the evidence base to support chemotherapy decisions in older age patients is limited. Older patients are often poorly represented in clinical trials[69, 70], and several large international multi-centre randomised trials aimed at addressing treatment in the older cohort were terminated prematurely due to insufficient accrual[71, 72,]. Consequently, much of the available evidence stems from population-level studies that demonstrate an association between adjuvant chemotherapy and survival benefits in older patients with high-risk tumour characteristics (such as axillary nodal metastasis)[11, 73]. However, it is not possible to confirm causality from observational studies.

Guidelines emphasise that the decision to offer chemotherapy to older patients with breast cancer should not be based on age[67]. However, older age is associated with higher rates of chemotherapy

related toxicity and mortality[70, 74] and chronological age is perceived as an important patient characteristic by oncologists when considering adjuvant chemotherapy[75]. Few published population level studies account for patient characteristics beyond chronological age and comorbidity, and this has likely contributed to the lower uptake of adjuvant chemotherapy among older patients[11, 70, 76].

There is increasing support for the use of frailty assessments to identify patients who are at increased risk of chemotherapy toxicity, or who require additional support to facilitate completion of regimes[77, 78]. For example, in a pilot study by Extermann *et al*., fifteen patients underwent a CGA assessment prior to and during adjuvant chemotherapy. Issues identified by the CGA led to a range of medical, nutritional and psychological interventions that directly influenced the care of four out of the fifteen patients[43]. Allowing for the small sample size, the study highlights the range of issues that can be identified and addressed by a formal frailty assessment. In another study, Kalsi *et al.* evaluated whether a frailty assessment could improve chemotherapy tolerance in patients with various types of cancer. The process led to an average of six interventions per patient before or during the course of systemic therapy. There was also improved tolerance to treatment regimens in comparison to a control group. Collectively, these studies illustrate the value of a multidisciplinary team approach in managing selected older patients with breast cancer, with a particular role for a specialist geriatrician in the consideration for, and delivery of, chemotherapy.

Frailty and adjuvant therapies in breast cancer: Radiotherapy

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

It is not understood whether frailty assessments can support the delivery of radiotherapy in older patients with breast cancer[86], though some small studies have suggested potential utility. For example, Denkinger *et al.* suggested that the CGA was superior to other assessments of patient characteristics in predicting fatigue after radiotherapy[87]. In addition, because CGA covers multiple frailty domains[88], it also has the potential to capture issues related to transport and travel for treatment - logistical factors known to influence radiotherapy uptake[89].

Challenges in the implementation of frailty assessments in breast cancer

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

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

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

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

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

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

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

While studies have begun to illustrate how information about patient frailty can influence treatment decisions for older patients, there is little understanding of how frailty screening or assessment are best utilised along the breast cancer care pathways of different patient groups[91]. A multi-faceted assessment can identify and optimise health deficits for cancer treatment and individualise patient management (including both early stage and advanced disease). Clear practical advice is required to ensure that the results of frailty assessments are used as a guide to inform treatment decisions, and not as a checklist or 'hurdle to overcome' in accessing particular cancer treatments.

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

In the UK, few breast cancer units work in collaboration with geriatric services in their management of older patients[9]. A small number of studies have shown that geriatric services can make a valuable contribution towards planning and delivery of cancer therapy[39, 60, 78, 92]. A pragmatic compromise in

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

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

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

References

1. Biganzoli L, Wildiers H, Oakman C, Marotti L, Loibl S, Kunkler I, et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). Lancet Oncol. 2012;13.
2. National Institute for Health and Care Excellence. NICE guidelines (CG101). Early and locally advanced breast cancer: diagnosis and treatment. NICE, 2018.
3. Bates T, Evans T, Lagord C, Monypenny I, Kearins O, Lawrence G. A population based study of variations in operation rates for breast cancer, of comorbidity and prognosis at diagnosis: Failure to operate for early breast cancer in older women. European Journal of Surgical Oncology (EJSO). 2014;40(10):1230-6.
4. Richards P, Ward S, Morgan J, Lagord C, Reed M, Collins K, et al. The use of surgery in the treatment of ER-positive early stage breast cancer in England: Variation by time, age and patient characteristics. European Journal of Surgical Oncology. 2016;42(4):489-96.
5. Healthcare Quality Improvement Partnership (HQIP). National Audit of Breast Cancer in Older Patients (NABCOP): 2019 annual report. 2019.
6. Schonberg MA, Marcantonio ER, Li D, Silliman RA, Ngo L, McCarthy EP. Breast Cancer Among the Oldest Old: Tumor Characteristics, Treatment Choices, and Survival. Journal of Clinical Oncology. 2010;28(12):2038-45.
7. Lavelle K, Todd C, Moran A, Howell A, Bundred N, Campbell M. Non-standard management of breast cancer increases with age in the UK: a population based cohort of women 65 years or older. Br J Cancer. 2007;96(8):1197-203.
8. Biganzoli L, Aapro M. Elderly breast cancer patients: adjuvant chemotherapy and adjuvant endocrine therapy. Gynakol Geburtshilfliche Rundsch. 2005;45(3):137-42.
9. Healthcare Quality Improvement Partnership (HQIP). National Audit of Breast Cancer in Older Patients (NABCOP): 2018 annual report. 2018.
10. Gannon M, Jauhari Y, Medina J, Horgan K, Cromwell D, Dodwell D. Use of taxane-containing adjuvant chemotherapy regimens among older women with operable early breast cancer: data from

a population based cohort within the National Audit of Breast Cancer in Older Patients (NABCOP) Journal of Geriatric Oncology. 2018;9(6):S40-1.
11. Giordano SH, Duan Z, Kuo Y-F, Hortobagyi GN, Goodwin JS. Use and Outcomes of Adjuvant Chemotherapy in Older Women With Breast Cancer. Journal of Clinical Oncology. 2006;24(18):2750-6.
12. Cancer Research UK. Breast cancer incidence (invasive) statistics 2019 [02/07/2019]. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive#ref-1.
13. Fried LP; Ferrucci L; Darer J; Williamson JD; Anderson G;. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. J Gerontol A Biol Sci Med Sci. 2004;59(3): 255-63.
14. Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen MLG, Extermann M, et al. International Society of Geriatric Oncology Consensus on Geriatric Assessment in Older Patients With Cancer. Journal of Clinical Oncology. 2014;32(24):2595-603.
15. Soto-Perez-de-Celis E, Li D, Yuan Y, Lau YM, Hurria A. Functional versus chronological age: geriatric assessments to guide decision making in older patients with cancer. The Lancet Oncology. 2018;19(6):e305-e16.
16. British Geriatrics Society. Fit for Frailty Part 1 - Full Guide 2014 [02/07/2019]. Available from: https://www.bgs.org.uk/resources/resource-series/fit-for-frailty.
17. Neuburger J, Currie C, Wakeman R, Georghiou T, Boulton C, Johansen A, et al. Safe working in a 7-day service. Experience of hip fracture care as documented by the UK National Hip Fracture Database. Age and Ageing. 2018;47(5):741-5.
18. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. The Lancet. 2013;381(9868):752-62.
19. Fried LP, Tangen CM, Walston J, Newman AB, Hirsh C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56A.
20. Mitnitski AB, Graham JE, Mogilner AJ, Rockwood K. Frailty, fitness and late-life mortality in relation to chronological and biological age. BMC Geriatrics. 2002;2:1-8.
21. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. Journal of Chronic Diseases. 1987;40(5):373-83.
22. Braithwaite D, Satariano WA, Sternfeld B, Hiatt RA, Ganz PA, Kerlikowske K, et al. Long-term Prognostic Role of Functional Limitations Among Women With Breast Cancer. Journal of the National Cancer Institute. 2010;102(19):1468-77.
23. National Confidential Enquiry into Patient Outcome and Death. An Age Old Problem. London: 2010.
24. Xue Q-L. The Frailty Syndrome: Definition and Natural History. Clinics in geriatric medicine. 2011;27(1):1-15.
25. Gill TM, Gahbauer EA, Allore HG, Ham L. Transitions between frailty states among community-living older persons. Arch Intern Med. 2006;166.
26. Campbell JB, DM.;. Unstable disability and fluctuations of frailty. Age and Ageing. 1997;26:315 - 8.
27. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. The Scientific World. 2001;1.
28. Gilbert T, Neuburger J, Kraindler J, Keeble E, Smith P, Ariti C, et al. Development and validation of a Hospital Frailty Risk Score focusing on older people in acute care settings using electronic hospital records: an observational study. The Lancet. 2018.
29. Hippisley-Cox J, Coupland C. Development and validation of QMortality risk prediction algorithm to estimate short term risk of death and assess frailty: cohort study. BMJ. 2017;358.

30. Clegg A, Bates C, Young J, Ryan R, Nichols L, Ann Teale E, et al. Development and validation of an electronic frailty index using routine primary care electronic health record data. Age and Ageing. 2016;45(3):353-60.
31. Fried LP, Xue Q-L, Cappola AR, Ferrucci L, Chaves P, Varadhan R, et al. Nonlinear Multisystem Physiological Dysregulation Associated With Frailty in Older Women: Implications for Etiology and Treatment. The Journals of Gerontology: Series A. 2009;64A(10):1049-57.
32. Dent E, Kowal P, Hoogendijk EO. Frailty measurement in research and clinical practice: A review. European Journal of Internal Medicine. 2016;31:3-10.
33. Soong J, Poots AJ, Scott S, Donald K, Bell D. Developing and validating a risk prediction model for acute care based on frailty syndromes. BMJ Open. 2015;5(10).
34. Kirkhus L, Šaltytė Benth J, Rostoft S, Grønberg BH, Hjermstad MJ, Selbæk G, et al. Geriatric assessment is superior to oncologists' clinical judgement in identifying frailty. British Journal Of Cancer. 2017;117:470.
35. British Geriatric Society. Comprehensive Assessment of the Frail Older Patient 2019 [02/07/2019]. Available from: https://www.bgs.org.uk/resources/resource-series/comprehensive-geriatric-assessment-toolkit-for-primary-care-practitioners.
36. Turner G, Clegg A. Best practice guidelines for the management of frailty: a British Geriatrics Society, Age UK and Royal College of General Practitioners report. Age and Ageing. 2014;43(6):744-7.
37. Gironés R, Torregrosa D, Díaz-Beveridge R. Comorbidity, disability and geriatric syndromes in elderly breast cancer survivors. Results of a single-center experience. Crit Rev Oncol Hematol. 2009;17.
38. Clough-Gorr KM, Thwin SS, Stuck AE, Silliman RA. Examining five- and ten-year survival in older women with breast cancer using cancer-specific geriatric assessment. Eur J Cancer. 2012;48(6):805-12.
39. Stotter A, Reed MW, Gray LJ, Moore N, Robinson TG. Comprehensive Geriatric Assessment and predicted 3-year survival in treatment planning for frail patients with early breast cancer. British Journal of Surgery. 2015;102(5):525-33.
40. Hamaker ME, Seynaeve C, Wymenga ANM, van Tinteren H, Nortier JWR, Maartense E, et al. Baseline comprehensive geriatric assessment is associated with toxicity and survival in elderly metastatic breast cancer patients receiving single-agent chemotherapy: Results from the OMEGA study of the Dutch Breast Cancer Trialists' Group. The Breast. 2014;23(1):81-7.
41. Barthélémy P, Heitz D, Mathelin C, Polesi H, Asmane I, Litique V, et al. Adjuvant chemotherapy in elderly patients with early breast cancer. Impact of age and comprehensive geriatric assessment on tumor board proposals. Crit Rev Oncol Hematol. 2011;79.
42. Okonji DO, Sinha R, Phillips I, Fatz D, Ring A. Comprehensive geriatric assessment in 326 older women with early breast cancer. Br J Cancer. 2017.
43. Extermann M, Meyer J, McGinnis M, Crocker TT, Corcoran MB, Yoder J. A comprehensive geriatric intervention detects multiple problems in older breast cancer patients. Crit Rev Oncol Hematol. 2004;49.
44. Parks RM, Hall L, Tang S-W, Howard P, Lakshmanan R, Winterbottom L, et al. The potential value of comprehensive geriatric assessment in evaluating older women with primary operable breast cancer undergoing surgery or non-operative treatment; A pilot study. Journal of Geriatric Oncology. 2014;6(1):46-51.
45. Ferrat E, Paillaud E, Caillet P, Laurent M, Tournigand C, Lagrange J-L, et al. Performance of Four Frailty Classifications in Older Patients With Cancer: Prospective Elderly Cancer Patients Cohort Study. Journal of Clinical Oncology. 2017;35(7):766-77.
46. Aguayo GA, Donneau A-F, Vaillant MT, Schritz A, Franco OH, Stranges S, et al. Agreement Between 35 Published Frailty Scores in the General Population. American Journal of Epidemiology. 2017;186(4):420-34.

47. Decoster L, Van Puyvelde K, Mohile S, Wedding U, Basso U, Colloca G, et al. Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations†. Annals of Oncology. 2015;26(2):288-300.
48. NHS RightCare. NHS RightCare: Frailty Toolkit. Optimising a frailty system 2019 [02/07/2019]. Available from: https://www.england.nhs.uk/rightcare/wp-content/uploads/sites/40/2019/06/frailty-toolkit-june-2019.pdf.
49. Hébert R, Durand PJ, Dubuc N, Tourigny A, Group P. PRISMA: a new model of integrated service delivery for the frail older people in Canada. Int J Integr Care. 2003;3:e08-e.
50. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ : Canadian Medical Association Journal. 2005;173(5):489-95.
51. Molina-Garrido MJ, Guillen-Ponce C. Comparison of two frailty screening tools in older women with early breast cancer. Critical Reviews in Oncology / Hematology. 2011;79(1):51-64.
52. Rolfson DB, Majumdar SR, Tsuyuki RT, Tahir A, Rockwood K. Validity and reliability of the Edmonton Frail Scale. Age and Ageing. 2006;35(5):526-9.
53. Bellera CA, Rainfray M, Mathoulin-Pélissier S, Mertens C, Delva F, Fonck M, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. Annals of Oncology. 2012;23(8):2166-72.
54. Clegg A, Rogers L, Young J. Diagnostic test accuracy of simple instruments for identifying frailty in community-dwelling older people: a systematic review. Age and Ageing. 2015;44(1):148-52.
55. Magnuson A, Lei L, Gilmore N, Kleckner AS, Lin FV, Ferguson R, et al. Longitudinal Relationship Between Frailty and Cognition in Patients 50 Years and Older with Breast Cancer. Journal of the American Geriatrics Society. 2019;67(5):928-36.
56. Gilmore N, Kadambi S, Lei L, Loh KP, Mohamed M, Magnuson A, et al. Associations of inflammation with frailty in patients with breast cancer aged 50 and over receiving chemotherapy. Journal of Geriatric Oncology.
57. Soubeyran P, Bellera C, Goyard J, Heitz D, Curé H, Rousselot H, et al. Screening for vulnerability in older cancer patients: The ONCODAGE prospective multicentre cohort study. PLoS ONE. 2014;9(12).
58. de Vries NM, Staal JB, van Ravensberg CD, Hobbelen JSM, Olde Rikkert MGM, Nijhuis-van der Sanden MWG. Outcome instruments to measure frailty: A systematic review. Ageing Research Reviews. 2011;10(1):104-14.
59. Houterman S, Janssen-Heijnen MLG, Verheij CDGW, Louwman WJ, Vreugdenhil G, van der Sangen MJC, et al. Comorbidity has negligible impact on treatment and complications but influences survival in breast cancer patients. Br J Cancer. 2004;90(12):2332-7.
60. Pope D, Ramesh H, Gennari R, Corsini G, Maffezzini M, Hoekstra HJ, et al. Pre-operative assessment of cancer in the elderly (PACE): A comprehensive assessment of underlying characteristics of elderly cancer patients prior to elective surgery. Surgical Oncology. 2006;15(4):189-97.
61. Tang V, Zhao S, Boscardin J, et al. Functional status and survival after breast cancer surgery in nursing home residents. JAMA Surgery. 2018.
62. Hind D, Wyld L, Reed MW. Surgery, with or without tamoxifen, vs tamoxifen alone for older women with operable breast cancer: Cochrane review. Br J Cancer. 2007;96(7):1025-9.
63. participants P. Shall we operate? Preoperative assessment in elderly cancer patients (PACE) can help. Critical Reviews in Oncology / Hematology. 2008;65(2):156-63.
64. Beek MA, Verheuvel NC, Luiten EJT, Klompenhouwer EG, Rutten HJT, Roumen RMH, et al. Two decades of axillary management in breast cancer. British Journal of Surgery. 2015;102(13):1658-64.
65. Morgan JL, Reed MW, Wyld L. Primary endocrine therapy as a treatment for older women with operable breast cancer - A comparison of randomised controlled trial and cohort study findings. European Journal of Surgical Oncology. 2014;40(6):676-84.

66. Collins K, Reed M, Lifford K, Burton M, Edwards A, Ring A, et al. Bridging the age gap in breast cancer: evaluation of decision support interventions for older women with operable breast cancer: protocol for a cluster randomised controlled trial. BMJ Open. 2017;7(7).
67. Biganzoli L, Wildiers H, Oakman C, Marotti L, Loibl S, Kunkler I, et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). Lancet Oncol. 2012;13(4):e148-60.
68. Mustacchi G, Ceccherini R, Milani S, Pluchinotta A, De Matteis A, Maiorino L, et al. Tamoxifen alone versus adjuvant tamoxifen for operable breast cancer of the elderly: long-term results of the phase III randomized controlled multicenter GRETA trial. Annals of Oncology. 2003;14(3):414-20.
69. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomised trials. The Lancet. 1998;352(9132):930-42.
70. Muss HB, Woolf S, Berry D, et al. Adjuvant chemotherapy in older and younger women with lymph node positive breast cancer. JAMA. 2005;293(9):1073-81.
71. Leonard R, Ballinger R, Cameron D, Ellis P, Fallowfield L, Gosney M, et al. Adjuvant chemotherapy in older women (ACTION) study - what did we learn from the pilot phase? Br J Cancer. 2011;105(9):1260-6.
72. Crivellari D, Gray KP, Dellapasqua S, Puglisi F, Ribi K, Price KN, et al. Adjuvant pegylated liposomal doxorubicin for older women with endocrine nonresponsive breast cancer who are NOT suitable for a "standard chemotherapy regimen": The CASA randomized trial. The Breast. 2013;22(2):130-7.
73. Elkin EB, Hurria A, Mitra N, Schrag D, Panageas KS. Adjuvant Chemotherapy and Survival in Older Women With Hormone Receptor–Negative Breast Cancer: Assessing Outcome in a Population-Based, Observational Cohort. Journal of Clinical Oncology. 2006;24(18):2757-64.
74. Garg P, Rana F, Gupta R, Buzaianu EM, Guthrie TH. Predictors of Toxicity and Toxicity Profile of Adjuvant Chemotherapy in Elderly Breast Cancer Patients. The Breast Journal. 2009;15(4):404-8.
75. Biganzoli L, Goldhirsch A, Straehle C, Castiglione-Gertsch M, Therasse P, Aapro M, et al. Adjuvant chemotherapy in elderly patients with breast cancer: a survey of the Breast International Group (BIG). Ann Oncol. 2004;15(2):207-10.
76. Ring A, Harder H, Langridge C, Ballinger RS, Fallowfield LJ. Adjuvant chemotherapy in elderly women with breast cancer (AChEW): an observational study identifying MDT perceptions and barriers to decision making. Annals of Oncology. 2013;24(5):1211-9.
77. Wildes TM, Ruwe AP, Fournier C, Gao F, Carson KR, Piccirillo JF, et al. Geriatric assessment is associated with completion of chemotherapy, toxicity, and survival in older adults with cancer. Journal of Geriatric Oncology. 2013;4(3):227-34.
78. Kalsi T, Babic-Illman G, Ross PJ, Maisey NR, Hughes S, Fields P, et al. The impact of comprehensive geriatric assessment interventions on tolerance to chemotherapy in older people. Br J Cancer. 2015;112(9):1435-44.
79. Luu C, Goldstein L, Goldner B, Schoellhammer HF, Chen SL. Trends in Radiotherapy After Breast-Conserving Surgery in Elderly Patients with Early-Stage Breast Cancer. Annals of Surgical Oncology. 2013;20(10):3266-73.
80. Williams L, Kunkler I, King C, Jack W, van der Pol M. A randomised controlled trial of post-operative radiotherapy following breast-conserving surgery in a minimum-risk population. Quality of life at 5 years in the PRIME trial. Health Technology Assessment. 2011;15(12):64.
81. Kunkler IH, Williams LJ, Jack WJL, Cameron DA, Dixon JM. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. The Lancet Oncology. 2015;16(3):266-73.
82. Hughes KS, Schnaper LA, Bellon JR, Cirrincione CT, Berry DA, McCormick B, et al. Lumpectomy Plus Tamoxifen With or Without Irradiation in Women Age 70 Years or Older With Early Breast Cancer: Long-Term Follow-Up of CALGB 9343. Journal of Clinical Oncology. 2013;31(19):2382-7.

83. Hughes KS, Schnaper LA, Berry D, Cirrincione C, McCormick B, Shank B, et al. Lumpectomy plus Tamoxifen with or without Irradiation in Women 70 Years of Age or Older with Early Breast Cancer. New England Journal of Medicine. 2004;351(10):971-7.
84. Keenan LG, O'Brien M, Ryan T, Dunne M, McArdle O. Assessment of older patients with cancer: Edmonton Frail Scale (EFS) as a predictor of adverse outcomes in older patients undergoing radiotherapy. Journal of Geriatric Oncology. 2017;8(3):206-10.
85. Spyropoulou D, Pallis AG, Leotsinidis M, Kardamakis D. Completion of radiotherapy is associated with the Vulnerable Elders Survey-13 score in elderly patients with cancer. Journal of Geriatric Oncology. 2014;5(1):20-5.
86. O'Donovan A, Leech M, Gillham C. Assessment and management of radiotherapy induced toxicity in older patients. Journal of Geriatric Oncology. 2017.
87. Denkinger MD, Hasch M, Gerstmayer A, Kreienberg R, Nikolaus T, Hancke K. Predicting fatigue in older breast cancer patients receiving radiotherapy. Zeitschrift für Gerontologie und Geriatrie. 2015;48(2):128-34.
88. Puts MTE, Hardt J, Monette J, Girre V, Springall E, Alibhai SMH. Use of Geriatric Assessment for Older Adults in the Oncology Setting: A Systematic Review. JNCI Journal of the National Cancer Institute. 2012;104(15):1134-64.
89. Schroen AT, Brenin DR , Kelly MD, Knaus WA , Slingluff CL. Jr. Impact of Patient Distance to Radiation Therapy on Mastectomy Use in Early-Stage Breast Cancer Patients. Journal of Clinical Oncology. 2005;23(28):7074-80.
90. Harari D, Hopper A, Dhesi J, Babic-Illman G, Lockwood L, Martin F. Proactive care of older people undergoing surgery ('POPS'): Designing, embedding, evaluating and funding a comprehensive geriatric assessment service for older elective surgical patients. Age and Ageing. 2007;36(2):190-6.
91. Parks RM, Lakshmanan R, Winterbottom L, AL Morgan D, Cox K, Cheung K-L. Comprehensive geriatric assessment for older women with early breast cancer – a systematic review of literature. World Journal of Surgical Oncology. 2012;10(1):88.
92. Audisio RA, Gennari R, Sunouchi K, Nair HR, Sestini A, Pope D, et al. Preoperative Assessment of Cancer in Elderly Patients: A Pilot Study. Supportive Cancer Therapy. 2003;1(1):55-60.
93. Gironés R, Torregrosa D, Díaz-Beveridge R. Comorbidity, disability and geriatric syndromes in elderly breast cancer survivors. Results of a single-center experience. Critical Reviews in Oncology/Hematology. 2010;73(3):236-45.

Table 1: Frailty domains assessed in the Comprehensive Geriatric Assessment (CGA)

Multi-dimensional CGA assessment components:
• 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

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 *et al, 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.

Stotter *et al,* 2015[39]	Single centre retrospective study (Jan 2005 – May 2012) Women with primary early ER-positive breast cancer where there were concerns regarding fitness to receive standard treatment	The use of CGA to predict 3-year overall survival	328 patients Median age 82 years (range: 43 – 98 years)	Comorbidity: Satariano score/CCI Cognition: MMSE Mental Health: GDS Functional status: Barthel Index of ADL, IADL Other: ASA score	212/328 (65%) had surgical treatment after CGA assessment. 97% of the cohort had died by 3 years. Comorbidity, MMSE, poor functional status and ASA grade was associated with 3-year mortality. CGA was predictive of 3-year survival probability (ROC of the survival model = 0.75 (95% CI: 0.67 – 0.82)).
Hamaker *et al,* 2014[40]	Multi-centre randomised clinical trial (Dutch Breast Cancer Trialists' Group OMEGA study) (Apr 2007 – Sept 2011) Metastatic breast cancer patient, aged ≥65 years, good ECOG PS (0-2) and good health status	To evaluate the use of CGA/ screening tool for predicting chemotherapy related toxicity and overall survival. Patients randomised to receive (1) Doxorubicin, or (2) Capecitabine	78 patients Median age 76 years (range: 66 – 87 years)	Comorbidity: CCI Cognition: MMSE Mental health: GDS Functional status: iADL Number of medications used Nutritional status: BMI <u>Cut-off scores for deficiencies/ impairment</u> CCI ≥2, IADL: partial dependence 14–27; full functional dependence ≤13, polypharmacy ≥5, undernutrition = ≤20 kg/m^2, MMSE ≤23, GDS: severe depressive symptoms ≥10, moderate depressive symptoms 5–9. <u>Classification of frailty</u> ≥1 of full IADL dependence, comorbidity score ≥2, polypharmacy, cognitive impairment, undernutrition and/or moderate to severe depressive symptoms	Study terminated early due to poor accrual There was no difference in chemotherapy toxicity rates between the two arms of the study. 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. 54/78 (69%) of patients died (median follow-up 32 months). 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).

Parks *et al*, 2014[44]	Single-centre prospective study Women with stage I-II operable primary breast cancer, aged ≥ 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 *et al,* 2012[38]	Multi-centre longitudinal study Women with stage I (tumour size >1cm) 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.
Barthélémy *et al,* 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 *et al*, 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 *et al,* 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.

683 Appendix 1: A comparison of the variables included in the phenotype and cumulative deficit models
684 of frailty
685

Comprehensive Geriatric Assessment (CGA domain)	**Phenotype Model Fried et al[19]**	**Cumulative deficit model Mitniski et al[27] (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

686

Declarations of interest: none