Introduction

Elderly cancer patients represent a major public health issue. Indeed, the number of elderly patients living with cancer has increased in the last years, due to a longer life expectancy and to the possibility to diagnose cancer early and to treat it accordingly.

Breast cancer is the most common malignancy among women and has the highest incidence in the aging population: it is estimated that 21% of newly diagnosed patients are over 70 years of age. It has been extensively reported that breast cancer-related mortality increases with age, regardless of disease stage (1,2). Overall survival is reduced in patients who are diagnosed when over 55, even when adjusting life expectancy for comorbidities (3,4). These findings can be explained by under-/over-treatment, decreased tolerance to standardized therapy and decreased patient compliance. Optimal treatment of this patient group remains unclear, since elderly patients are often excluded from clinical trials. Despite the importance of the issue, there is little solid evidence regarding the management and treatment protocols for this specific group of patients. Treatment of breast cancer in elderly women in clinical practice is mostly based on randomized clinical trials which have actually excluded these patients from the...
studied population (5). Furthermore, no specific guidelines were available until 2007, when the International Society of Geriatric Oncology (SIOG) created the first dedicated task force to provide precise recommendations to treat geriatric breast cancer patients (6). Despite this effort, several issues still remain unsolved. For example, a review on Southwest Oncology Group’s therapeutic trials revealed that in studies about breast cancer, women aged 65 or older constituted only 9% of the enrolled population, despite the fact that 49% of women with breast cancer belongs to this age group (7). Also, patients over 70 made up only 20% of subjects enrolled in US Food and Drug Administration registration trials from 1995 to 1999, although they made up 46% of the US cancer population in that period.

Breast cancer biology changes according to patients’ age but the mechanisms underlying such differences have not yet been understood. Most studies demonstrate that older women are more likely to have hormone receptor-positive, HER2-negative, low-risk tumor histology disease, with no lymph node involvement, which generally carries a more favorable prognosis. Scientific societies have generally considered cancer in the elderly as less aggressive when compared to younger women and alternative approaches lead to over- or (most likely) under-treat in many cases. However, in the past few years, it has been observed that there has been an increase in more aggressive cancer forms in the geriatric population, and it is estimated that 15–18% of breast cancers in elderly patients is triple negative (8).

Despite the conflicting information regarding the relation between breast cancer biology and aging, in recent years data are accruing that suggest that the intrinsic biological characteristics of the tumor should be used to predict the risk of relapse and guide therapeutic choices. For example, Oncotype DX (Genomic Health) is a 21-gene assay that can predict breast cancer recurrence, chemotherapy efficacy and overall survival. The predictive effect of gene signature was ultimately not age-dependent (9). Similar results were reached using a 70-gene signature test (MammaPrint) in the MINDACT STUDY (10). Even though the results of these studies show that it is reasonable to forgo chemotherapy in women with early breast cancer and favorable tumor biology, it has to be reminded that older women were underrepresented in both studies.

The biological and clinical differences between younger and older patients with breast cancer show that elderly patients should not undergo standard protocols, but should be treated and managed in different ways.

In this article we review the evidence supporting the need for comprehensive geriatric assessment as a guide to treatment choices in older women with breast cancer.

### Screening for frailty

Elderly patients are a heterogeneous group due to differences in comorbid conditions, functional capacity and social support, but it is not clear how much each of these aspects is relevant in cancer patients because of under-representation of geriatric population in clinical trials (7). The large variety in characteristics within this population, together with the lack of evidence on the most suitable therapeutic approach and the limited data on older patients’ preferences, make treatment decision-making for these patients generally difficult. Treatment choices for elderly cancer patients should respect the goals of care of the individual patient, and should take into consideration associated conditions and functional capacity. Therefore, all older breast cancer patients should undergo a pre-treatment evaluation, including an assessment of organ function and comorbidity. Such characteristics are important to evaluate the patients’ ability to tolerate treatment (i.e., surgery, chemotherapy) and to guide the oncologist in deciding which treatment is more appropriated. Thus, the aim of the evaluation should be identification of frail or pre-frail patients, that should undergo a more specific geriatric assessment; indeed, it is important to determine which other forms of oncological treatments should be offered, to increase patients’ survival, compliance and treatment tolerance.

Frailty is an extremely common condition in elderly patients. This geriatric syndrome is associated with an increased risk for falls, hospitalization and mortality. For a longtime it has been considered synonymous to disability and comorbidity, while it can be more accurately conceptualized as a distinct entity with protean manifestations, with the concurrent presence of multiple symptoms being necessary for its presentation. Fried et al. (11) proposed the best current working definition of frailty: a clinical syndrome defined by the presence of 3 or more of the following symptoms: (I) unintentional weight loss (4–5 kg in 1 year); (II) self-reported exhaustion; (III) weakness (grip strength <20% in the dominant hand); (IV) slow walking speed (<20% for time to walk 15 feet), and (V) low levels of physical activity (<20% for caloric expenditure). Clinical signs of this condition are represented by undernutrition, sarcopenia, osteopenia and balance and
gait disorders. The presence of 2 of the above-mentioned symptoms defines a ‘pre-frail’ process, while the presence of 3 corresponds to the frailty state.

Frailty can be conceptualized as the loss of functional homeostasis, which is the ability of an individual to cope with a stressor without losing function (12). It is an extended process of increasing vulnerability, predisposing to functional decline and ultimately leading to death (13). A continuum exists in the transition from robustness to functional decline. The frailty process is characterized by a loss of physiological reserves, so that the capacity to repair damages to the body is progressively impaired and recovering from illnesses or stressors becomes always more difficult. Many factors contribute to this process, such as age, gender, lifestyle, socioeconomic background, comorbidities and affective, cognitive and/or sensory impairments (14). Three stages in the frailty process can be described: a pre-frail process, the frailty state and frailty complications (15). The dynamics of the frailty process are presented in Figure 1, as modified from (15).

In the pre-frail state physiological reserves are sufficient to allow the organism to respond adequately to an insult (i.e., acute disease, injury or stress) with a chance of complete recovery but also a risk to progress into a frail condition. The frailty state, instead, is characterized by its clinical manifestations and is by no means silent: anorexia, weight loss, generalized weakness (fatigue), gait disorders and fear of falling, causing functional dependence and reduced time spent in outdoor activities, subtle cognitive decline, delirium, and polypharmacy are present (16); yet, if not specifically investigated, these symptoms can be misdiagnosed. The frailty state is characterized by slow and incomplete recovery when exposed to stressors (such as acute diseases or injuries), due to progressive loss of resilience.

Complications of the frailty process are related to this progressive loss of hemostatic reserve, so that capacity of recovery is impossible. The clinical picture is characterized by falls (with consequent fractures and bed rest), progressive functional decline leading to disability, malnutrition polypharmacy, a high-risk of hospitalization, infections, institutionalization and death (17). Cognitive impairment can become more evident, finally leading to overt dementia. As shown in Figure 1, the transition from the pre-frail process (latent phase) to the frail state (clinically apparent) is generally provoked by a trigger event, such as injury, acute disease and/or psychological stress, new drugs and surgery. In particular, for elderly breast cancer patients, the “stress tests” that may unveil frailty are surgery, systemic and/or radio-therapy and the tumor itself. As frailty is a progressive condition that begins with a preclinical stage, there are opportunities for early detection and prevention (18). Frailty differs from ageing and, unlike ageing, it can be prevented and possibly reversed. The identification of frailty in cancer patients is important for oncologists to guide the decision making.

**Comprehensive geriatric assessment**

A comprehensive geriatric assessment (CGA) has been suggested as a possibly useful approach in dealing with the elderly and frail elderly cancer patients. It is defined as a multidimensional, interdisciplinary diagnostic process focusing on determining an older person’s parameters of function, comorbidity, nutrition, medication, socioeconomic status, and geriatric syndromes. Its aim is to develop a coordinated and integrated plan for treatment and long-term follow-up and it can help guide management of reversible comorbidities and geriatric syndromes; also, it is an objective way to assess life expectancy among older adults. Moreover, the CGA allows to identify the deficits that would not be apparent from the history and physical examination alone (19). It is not uncommon in clinical practice to meet elderly patients who do not show overt frailty characteristics (falls, fatigue, polypharmacy or comorbidity), but through the CGA they appear to be in a pre-frail condition, which exposes them to a greater risk of complications and adverse events.

The CGA evaluates in particular: the functional and

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**Figure 1** Pre-frailty, frailty and disability.
the psycho-cognitive areas, the socio-economic and the nutritional areas, the presence of polypharmacy, comorbidities, frailty and geriatric syndromes (20-26).

Assessing patients’ functional state is helpful to evaluate the presence of disability as well as identifying those patients at greater risk of developing disability and preventing worsening of their performance indexes. It has been shown that the functional status of the subject is an independent prognostic factor of complications, regardless of oncological or other comorbidities (27,28). Rehabilitation and occupational therapy program, as well as promotion of regular physical activity, could reduce the incidence of disability (29).

Malnutrition is a common condition in the elderly population (30). Analyzing the subject’s nutritional status is critical in preventing many complications such as infections and occurrence of pressure ulcers (31), all conditions that may lead to the extension of the hospitalization period and may affect the prognosis. In addition to Mini Nutritional Assessment (MNA), serum albumin, Body Mass Index (BMI), and the identification of unintended weight loss can help identify individuals at risk of malnutrition susceptible to dietetic interventions (32).

Evaluation of the cognitive area is also important because mild cognitive impairment (MCI) or dementia can affect the prognosis. The presence of either of these conditions permits to identify those patients who are at greater risk of delirium. Setting up a program of cognitive activity, sleep hygiene, dehydration prevention and the adoption of special measures to improve visual and hearing disorders could be helpful to prevent delirium and cognitive impairment (33).

Depression is a common condition in elderly patients (34) and it causes an increase in mortality and a reduction of the adherence to therapy. It is often atypical and may also be the first non-specific symptom of an associated pathology. By identifying a mood disorder, it is possible to carry out pharmacological therapies and correct a possible cause of cognitive and functional status reduction.

Finally, analyzing the social support of elderly patients is crucial for long-term management. Good social support ensures better treatment adherence and reduced hospitalization (and therefore associated the complications) (35). Patients with low levels of social support can be addressed to the social services, to the appropriate facilities for the continuation of care or to a caregiver, also necessary for the recovery and maintenance of autonomy.

The usefulness of a geriatric assessment is broadly recognized in oncology: the International Society of Geriatric Oncology (SIOG) (36) and the National Comprehensive Cancer Network (NCCN) recommend the incorporation of geriatric assessment in treatment planning (37). Performing CGA in elderly patients with cancer can allow the identification of suspected health conditions, still unrecognized with usual clinical work-up, in order to plan targeted interventions to reverse the problem. CGA also permits prediction of adverse outcomes; a better estimate of residual life expectancy and lethality of the malignancy in the context of competing comorbidities and general health problems. There is strong evidence in the elderly population that increasing administration of CGA to detect potentially reversible conditions (comorbidities, depression, and nutrition) and guide their focused management improves compliance, treatment tolerability, quality of life (QoL), survival (38) and physical function, while decreasing the risk of hospitalization and nursing home placement. CGA has the potential to evaluate the pros and cons of performing or omitting specific oncologic interventions; it identifies geriatric syndromes and age-related problems which cannot be easily detected by routine clinical exams in approximately half of older cancer patients.

There is currently no standard method for geriatric assessment. Important domains of CGA are functional status, fatigue, comorbidity, cognition, mental health status, social support, nutrition, and geriatric syndromes (e.g., dementia, delirium, falls, incontinence, osteoporosis or spontaneous fractures, neglect or abuse, failure to thrive, constipation, polypharmacy, pressure injuries and sarcopenia). Various tools are available to investigate these domains, and the superiority of one tool over another has not been proven yet. The choice of the instrument might rely on local preference, aim of the tool or available resources. In Table 1 we listed the tools that we propose for the evaluation of elderly patients with breast cancer.

Table 1

The domains covered by the evaluation are based on the International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer (36).

While comprehensive geriatric assessment is the gold standard, it can be time consuming and may not be feasible in a busy oncology practice. As a result, some experts prefer the use of a screening tool (assessment of autonomy, malnutrition, depression, cognition, and comorbidity) to identify vulnerable patients for whom a CGA could potentially optimize cancer treatment. Some of these screening tools include Vulnerable Elders Survey (VES-13), abbreviated Comprehensive Geriatric Assessment


<table>
<thead>
<tr>
<th>Domain</th>
<th>Tool</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening for frailty</td>
<td>G-8</td>
<td>(39-41)</td>
</tr>
<tr>
<td></td>
<td>VES-13</td>
<td></td>
</tr>
<tr>
<td>Comorbidity</td>
<td>CIRS-G</td>
<td>(23,24)</td>
</tr>
<tr>
<td>Physical activity and performance</td>
<td>Physical Activity Scale for the Elderly (PASE)</td>
<td>(42-45)</td>
</tr>
<tr>
<td></td>
<td>Short Physical Performance Battery (SPPB)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Timed Up and Go Test (TUG)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hang-grip strength</td>
<td></td>
</tr>
<tr>
<td>Functional Status</td>
<td>ADLs (Katz index)</td>
<td>(46-48)</td>
</tr>
<tr>
<td></td>
<td>IADL (Lawton scale)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lawton-Brody IADL Scale</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ECOG PS</td>
<td></td>
</tr>
<tr>
<td>Cognition</td>
<td>Mini Mental State Examination</td>
<td>(21)</td>
</tr>
<tr>
<td>Depression</td>
<td>Geriatric Depression Scale</td>
<td>(22,49)</td>
</tr>
<tr>
<td></td>
<td>Distress thermometer</td>
<td></td>
</tr>
<tr>
<td>Nutritional status/body composition</td>
<td>Body-mass Index</td>
<td>(25,30,32)</td>
</tr>
<tr>
<td></td>
<td>Mini Nutritional Assessment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DEXA scan (for muscle mass and bone mass)</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>Numeric Rating Scale</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Visual Analogue Scale</td>
<td></td>
</tr>
<tr>
<td>Fatigue, Nausea, Dyspnea and other</td>
<td>Edmonton Symptom Assessment Scale</td>
<td>(50,51)</td>
</tr>
<tr>
<td>symptoms</td>
<td>modified Medical Research Council dyspnea scale (mMRC)</td>
<td></td>
</tr>
<tr>
<td>Falls</td>
<td>History of self-reported falls (one or more in last 90 days)</td>
<td></td>
</tr>
<tr>
<td>Quality of Life</td>
<td>FACT-B</td>
<td>(52,53)</td>
</tr>
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<td></td>
<td>EQ-SD</td>
<td></td>
</tr>
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(aCGA), Fried Frailty Criteria, Barber Questionnaire (BQ) and the most validated Geriatric8 (G8) (39-41,54). Hurria and colleagues have developed the cancer-specific geriatric assessment (CSGA), that assess cancer patients across seven domains (functional status, comorbidity, polypharmacy, cognitive and nutritional function, psychological status, social support), which is self-administered.

All these screening tools should not replace CGA in evaluation of older cancer patient, because none of these are successful in identifying impairment in all domains of covered by CGA, but they can successfully be used to identify frail patient who would benefit from a CGA before initiating therapy. Among these instruments, G8 has the highest sensitivity; it consists of eight items: a selection of seven items from the MNA questionnaire (food intake, weight loss, body mass index, motor skills, psychological status, number of medications and self-perception of health) and an indication of age in three categories (<80, 80–85, and >85).

A two-step approach has recently been proposed by a
geriatric oncology task force to improve the management of older cancer patients (55). The first step is screening all older cancer patients using G8 screening tool. Those patients who result as “fit” at this screening assessment should be considered similar to younger patients and treated accordingly. Instead, patients resulting as frail or “unfit” should require a more in-depth evaluation, the CGA, which is the second step, aimed to design the optimal treatment for this patient group. These patients should not automatically be excluded from the standard oncological treatment because they may still benefit from it but they may need specifically tailored interventions, designed and developed on the basis of the CGA. Because frailty is a transitional state in dynamic progression, it is important to screen breast cancer patients during standard treatment to prevent and, where possible, reverse this process (Figure 2).

**QoL in older breast cancer patients**

QoL is one of the most important outcome measures in cancer researches due to the medical and public health advances that have determined an interest in measuring quality of treatment not only on the basis of live-sparing and increased life span but also on the basis of QoL in treated patients. It has been shown that assessing QoL in cancer patients could contribute to improve treatment outcomes and could even have a prognostic value (27). The concept of health-related quality of life covers a broad number of aspects that can affect physical and mental health. When assessed on the individual level, health related QoL includes perceptions of physical and mental health, that can be determined by risk factors, health conditions, functional status, social support, and socio-economic status. On a community level, health related QoL includes all factors that can influence health perception and functional capacity, such as use of resources, policies, and practices that have implication for health. Self-assessed health status has been proven a more powerful predictor of mortality and morbidity than many objective measures of health (56): patient-reported QoL has also been found to predict response to treatment (57) and adherence to prescribed therapies, which is especially relevant to older patients.
women with early breast cancer who should undergo a long treatment course with aromatase inhibitors (58).

Focusing on HRQoL as an outcome can be useful to allow a more complete and appropriate use of social, mental, and medical services, which is fundamental for a complete management particularly for elderly patients: very few studies have addressed the issue of what happens to this frail population after undergoing treatment.

The gold standard should be that patients self-report their HRQoL. Patient reported outcomes (PROs) is an “umbrella term” that refers to “self-reporting” status by the patient, covering a whole range of potential measurements which are directly reported by the patient without the filter of interpretation by a clinician or anyone else. PRO data ideally should be collected via self-administered questionnaires (59), which the patients fill in themselves. Patient interviews are an acceptable alternative to self-collection (59), however they will only qualify as a PRO, if the interviewer is registering the patient’s point of view without making a professional assessment or judgment of the impact of treatments on the patient’s health status. PRO measures give a picture of the impact of disease as well as treatments on physical and mental health, taken from the patient perspectives, without the intermediation of health workers. They also allow for a direct appraisal of the impact of symptoms and conditions on functional capacity. Measures can be related to absolute or relative changes in signs, symptoms, functions or multidimensional concepts.

The interest in QoL in breast cancer patients is rising because of the increasing number of women with breast cancer, the overall survival rate in cancer patients, and the meaning that breast cancer holds for a woman’s identity. Several valid instruments were used to measure QoL in breast cancer patients, which could be divided into general QoL questionnaires, body-image-related questionnaires, breast-reconstruction-specific questionnaires and chemotherapy specific questionnaires. Among these, FACT-B is a 44-item questionnaire that comprises 5 domains of FACT G [Physical Well-Being, Emotional Well-Being, Social Well-Being (SWB), Functional Well-Being and Relationship with Doctor] in addition to the Breast Cancer Subscale (BCS), which complements the general scale with nine items specific to QoL in breast cancer. In comparison with QLQ-BR23, FACT-B is shorter and covers fewer symptoms and treatment-related side effects, but it allows for a total QoL score, broader coverage of the SWB domain, and the opportunity for patients to provide individualized weighting for the various QoL domains (52).

The assessment of burdening symptoms of disease is essential to the implementation of effective supportive measures (60). The aim of these measures is to offer relief and allowing for better adherence to prescribed treatments and improving quality of life.

Conclusions
Geriatric oncology is an emerging field that is bringing important new notions to the world of oncology. Individualized treatment plans for older women with breast cancer should consider comorbidities, functional status, life expectancy, quality of life, patient's preferences, and available socioeconomic resources. Increasing representation of older women in clinical trials and incorporating geriatric assessment and multidimensional supportive care are potential ways to improve the outcomes for older patients with breast cancer.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References


58. Pinheiro LC, Wheeler SB, Reeder-Hayes KE, et al. Investigating associations between health-related quality of life and endocrine therapy underuse in women with early-air...
