Review

ClinicalPractice

Comprehensive geriatric assessment in the older cancer patient: coming of age in clinical cancer care

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Practice points

- Based on the enclosed discussion, we recommend the following approach for the evaluation of all older patients with cancer:
  - All cancer patients, ≥65 years of age, should undergo a screening assessment for age-dependent functional impairment using screening tools, such as the G8, VES-13 or their combined use for even greater sensitivity.
  - Patients with abnormal screening tests should have a comprehensive geriatric assessment (CGA) performed by trained professionals.
  - The request for a CGA should indicate the type of malignancy and therapeutic considerations, such as surgery, radiation and/or chemotherapy. In the case of chemotherapy, contemplated agents should be identified so that potential interactions can be evaluated.
  - Results of the CGA and consultation should be shared with primary care physicians, and surgeons, specific tumor-focused oncologists and other specialists involved in case management.
  - Trained professionals should use results of CGA and other diagnostic tests to discuss with patients and caregivers, prognosis, recommended therapies, alternatives, likelihood of response, probability of adverse effects, suggestions for prehabilitation and remedial recommendations, as well as plans for social arrangements and rehabilitation.
  - The CGA should be repeated periodically during therapy and follow-up to detect new onset of remediable changes, especially those that can facilitate completion of therapy.
  - The CGA should be repeated at yearly intervals after completion of therapy to follow resolution of problems and/or development of late-onset adverse effects.

Cancer care at the extremes of life, in the young and the old, is characterized by unique issues associated with pediatrics and geriatric medicine, accentuated by the special vulnerabilities of these groups. In response to these needs, the field of pediatric oncology has been well honed to deal with the special problems associated with juvenile cancer patients. While most adult oncologists consider themselves well prepared to deal with older cancer patients, the current expansion of the geriatric population – their variable levels of fitness, frailty and vulnerability, the fact that cancer is primarily a disease of older adults, the significant expansion of agents and approaches to treat cancer, as well as their resultant toxicities and complications – has led to the development of specialized geriatric oncologists. Moreover, the special characteristics and needs of these patients have led to the evolution of new guidelines for evaluation, management and the conduct of research in older patients with cancer.

Future Medicine part of fsg

Introduction

Cancer incidence rises exponentially in the final decades of life such that 60% of newly diagnosed malignancies and 70% of cancer deaths occur in patients over 65 years of age [1–4]. The age-adjusted cancer incidence rate is tenfold greater in the population over 65 years and the age-adjusted cancer mortality rate is 16-fold greater in the population over 65 years, compared with those under 65 years [1–4]. While these statistics clearly indicate the need for geriatric considerations in caring for most cancer patients, the situation is magnified by expansion of the elderly population such that in the USA, the number of patients older than 65 is expected to increase from 35 million in 2000 to 88.5 million by 2050, at which time many of these patients will be older than age 85 years [5,6]. In fact, based on the anticipated increase in the number of older individuals with cancer and the expansion of the population over 65 [7], plans are already underway to prepare for an 'epidemic of cancer in the aging population' [8].

At the same time, there has also been an explosion in understanding the metabolic and molecular alterations associated with cancer. Many of these serve as targets for the vastly expanded armamentarium of agents and procedures available for treatment. These include multiple new cytotoxics, targeted thereapeutics and immunotherapeutics, each with its own mechanism(s) of action, adverse effects and possible long-term toxicities. Many of the new cancer therapeutic agents, such as imatinib and ibrutinib, may be chronically administered on a life-long basis [9–11]. In addition, the pharmacology and pharmacokinetics of these new agents may be significantly affected by the vast array of agents now employed to treat many of the conditions associated with aging [12,13]. Moreover, approaches to therapy that were previously administered to young patients only, such as hematopoietic stem cell transplant (HCT), are now being offered to patients in the geriatric age range [14–18].

As a result of these advances, there is a compelling need to better understand the clinical, molecular and physiologic effects of cancer in the elderly, as well as the factors that determine therapeutic response, toxicity and tolerance in the elderly patient with cancer [19–25]. It is also necessary to determine how unique geriatric conditions and/or comorbidities may predispose to effects of chemotherapy leading to specific toxicities such as peripheral neuropathies, heart failure or post-chemotherapy cognitive impairment (chemobrain). Of even greater significance is the need to identify prognostic factors in the elderly that may be predictive of short-term mortality. Thus, it is important to distinguish between chronologic age, physiologic age and associated geriatric conditions and comorbidities to more effectively decide when and with what to treat older cancer patients. In planning treatment for the older patient with cancer, it is also critical to determine how the patient's status may be improved, to define what remedial measures might be instituted and to identify appropriate social support arrangements that may improve opportunities for better outcomes [19–25].

The comprehensive geriatric assessment

The comprehensive geriatric assessment (CGA) has been developed as a multidisciplinary framework to evaluate the impact of age-associated physiologic factors, in contrast with chronologic age, that may affect health and disease in older adults. Here, we discuss application of the CGA to evaluate the issues outlined above in older patients with cancer. The CGA, as applied to cancer patients, is the coordinated use of a group of validated geriatric assessment tools, which, when used together, provide: a multidimensional evaluation of an older individual's ability to tolerate and respond to therapy; the probability of impending early death; the likelihood that the patient will develop and/or recover from adverse effects of therapy; and the identity of risk factors where remedial steps may be taken to potentially improve outcomes [19–25].

As suggested, the CGA is not a single specific test, but consists of a number of validated instruments that can be most effectively used to evaluate impact and needs in a series of domains, including functional status, cognition, comorbidities, polypharmacy, psychosocial function, social support and nutritional status, all shown to affect outcome in older individuals and specifically in older patients with cancer. While the CGA continues to evolve, to be modified and to be improved both in its content and its ability to evaluate specific situations, a relatively standardized format has gained general acceptance [26].

When administered by a trained, experienced professional, a CGA does not provide a single score, but rather a descriptive analysis and scaling of multiple factors that have been shown to impact outcomes, especially adverse effects in older patients. By evaluating the multiple distinctive factors that may influence the ability of an older patient to cope physically, psychologically and sociologically with cancer and its potential therapeutic interventions, the CGA provides the clinician with a much more useful guide than the single parameter of chronological age alone. This is especially important since individuals of identical chronological age may have vastly different physiologic reserves and different results on the CGA. Even among patients with increased risk factors, there may be fundamental differences such as cardiovascular versus cognitive, leading to different toxicities. Likewise,

comorbidities such as osteoarthritis or congestive heart failure are expected to have drastically different effects on outcomes. Moreover, the CGA provides the basis for implementation and research on remedial strategies to improve outcomes, as well as for stratifying patients on clinical trials to evaluate new procedural and/or therapeutic initiatives.

When used by a skilled clinician, experienced in dealing with elderly cancer patients along with tumor-specific surgeons and oncologists, results of the CGA should be considered along with an understanding of the specific tumor, its stage, pathophysiology, prognosis and expected effects of available therapeutics to realistically discuss with patients, their families and caregivers, the probable risks, benefits and rationale for therapeutic strategies and/or patient care. Results of the CGA and plans for therapeutic initiatives should be useful also to primary care physicians and specific tumor-oriented surgeons and oncologists in planning for shared care approaches as part of a multidisciplinary cancer team, as well as for palliative therapy and symptom management [27–29]. Moreover, in implementing these approaches it is clear that specific disease-oriented surgeons and oncologists will require greater training in utilizing the results of the CGA and availability of geriatricians and geriatric oncologists to assist in their interpretation and implementation. Of critical importance in this regard, is the consideration of both the patients and families risk aversion and risk taking philosophy, as well as their coping capacities, for which validated assessment tools are still in need of development. In addition, these parameters should be used to assess, in anticipatory fashion, the need for adjusting social arrangements. For example, the family of a cancer patient, about to undergo chemotherapy with the potential for developing post-chemotherapy cognitive impairment would be well advised to make appropriate social arrangements to accommodate changes before complications occur.

Components of the CGA
The instruments generally employed in the CGA are outlined below.

Functional status
Functional status is subdivided into an assessment of ability to perform activities of daily living (ADL); an assessment of instrumental activities of daily living (IADL); an assessment of mobility using the Gait Speed or Timed Up and Go (TUG); an assessment of risk for falls; and an assessment of visual and auditory acuity (Sufficiency). The ADL assessment evaluates a patient's ability to independently care for self by conducting basic activities such as bathing, dressing, maintaining continence, going to the toilet and feeding [26,30]. The IADL tool was designed to assess the ability of the elderly patient to manage the diversity of activities required to maintain independence in community interactions and includes shopping, managing medications, housekeeping, preparing meals, laundry, transportation and managing finances [26,31–32]. These scales are useful for predicting adverse effects of therapy, since low scores, indicating lack of independence, are associated with toxicity and reduced survival in older patients with cancer [26,33–35]. Importantly, results of the ADL and IADL assessment provide an important guide for arranging patient support activities. However, it should be noted that low ADL scores should not be considered an absolute contraindication to cancer therapy since some can be compensated for with appropriate support services, and more importantly, some may be reversible with treatment of the cancer [36].

Evaluation of mobility provides both an indication of ability to maintain independence, as well as an assessment of overall function and fitness. The TUG test measures the time it takes for a patient to stand up from an armchair, walk 10 ft to a marker on the floor, turn, walk back to the chair and sit down [37]. Community-dwelling elderly who perform normally in the TUG are usually independently mobile, whereas those with compromised performance in the TUG commonly have difficulties in ADLs and are at increased risk for falls potentially leading to fractures and other complicating conditions [37,38]. Normal Gait speed, tested in a standardized manner, has also been shown to predict improved survival in older patients, whereas reduced gait speed has negative implications [39,40]. Reduction in gait speed has been associated with an elevated risk for mortality in older individuals [39,40]. While vision and hearing are not traditionally part of the CGA Functional Assessment, poor vision/total blindness or poor hearing/total deafness have been identified as significant impediments to cancer therapy [41].

Cognitive function
The Mini Mental State (MMS) is a screening instrument to evaluate cognitive difficulties in orientation, registration, attention, calculation, recall and language [42]. Since the MMS does not identify potential causes of disorders such as depression or dementia, abnormalities in the MMS should be pursued with neuropsychiatric consultation since dementia in the geriatric population is an independent prognostic factor for survival [43]. Moreover, patients with cancer and cognitive impairment are at risk for noncompliance and nonadherence to therapeutic regimens as well as for delirium [44] and early death [45].

Comorbidities & geriatric syndromes

Not surprisingly, many older patients are likely to have a series of disorders and treatments that could potentially affect tumor growth, therapeutic efficacy and tolerance. In a recent US Census Bureau survey, 36% of individuals ≥65 years of age had at least one chronic condition that would be classified as a comorbidity and many had three or more [6]. Of even greater concern, The American Association of Retired Persons estimates that more than 88% of older Americans, ≥65 years of age, have at least one chronic illness [46]. The Charlson Comorbidity Index provides a prospective approach to enumerate comorbid conditions, characterize their severity and estimate their impact on risk of death. Thus, increased numbers and severity of comorbid conditions adversely affects survival [26,47]. Comorbidities also are associated with functional difficulties in older long-term cancer survivors [48]. In addition to a quantitative estimate, it is important to consider unique effects of some comorbidities. For example, diabetes has been show to adversely affect recurrence and survival in patients with colon and breast cancer [26,49]. However, at the same time, some of these comorbidities provide the basis for supportive interventions such as diabetes control.

A number of geriatric syndromes, as opposed to distinct comorbidities, have been identified that can adversely affect disease progression and therapeutic tolerance. These include dementia, delirium, depression, distress, osteoporosis, falls, fatigue, frailty and urinary incontinence. These syndromes are important to identify both because of their deleterious effects in the older cancer patient and also because they may be remediable with therapeutic attention. Of particular note is the possibility that some neuropsychologic disorders may be due to cytokine abnormalities associated with tumor progression, which may be improved with exercise and/or with tumor targeted therapy [50].

Polypharmacy

The use of increased and excessive numbers of prescribed and nonprescribed medications, especially cardiovascular, analgesic and psychotropic agents [51], as well as potentially inappropriate medications (PIM) used by the elderly, provides the basis for increased risk of drug interactions and adverse drug effects. Polypharmacy is defined as concurrent use of five or more drugs, while Beers Criteria provides a useful tool to determine inappropriate medication used by the elderly [52–54]. In a study of 500 older, aged ≥65, cancer patients about to receive ambulatory chemotherapy for solid tumors, participants were found to take a mean of 5 ± 4 daily medications and 29% of patients were identified as taking PIM. In another recent report of patients ≥65 years

of age, presenting to a major cancer center, with newly diagnosed cancer, the use of polypharmacy was 80% and inappropriate medication use 41% [55]. Interestingly, neither polypharmacy nor PIM was associated with grade 3–5 toxicity or risk of hospitalization during chemotherapy [56]. Polypharmacy and inappropriate medication use is, however, associated with poor performance status [55], increased risk of hip fracture [57] and increased mortality in older adults [58].

Problems associated with polypharmacy in the elderly may be further amplified by administration of chemotherapy along with agents employed to control side effects, especially those that may inhibit or induce CYP450. For example, agents that commonly affect CYP450 isoforms include proton pump inhibitors, tricyclic antidepressants and some antibiotics, which may alter pharmacokinetics, efficacy and toxicity of chemotherapeutic agents such as imatinib, irinotecan, paclitaxel and vinca alkaloids [12–13,59].

Psychological status

Emotional disorders in the elderly, particularly depression, which is estimated to be present in 5–20% of the elderly, may interfere with acceptance or adherence to therapeutic strategies, management of side effects and personal care. The Geriatric Depression Scale (GDS) is a multiquestion, self-rating instrument, validated in the aged, and capable of distinguishing the mildly and severely depressed from normal [60,61]. As with MMS, patients with abnormalities in the GDS should be referred for neuropsychiatric evaluation.

Social support

Compared with patients in socially supportive relations, social isolation and the perception of loneliness increases the risk for mortality, especially in the elderly [62,63]. Thus, interpersonal relations and support services are important to assess in older patients with cancer both to identify the need for companionship and to plan supportive care. The Medical Outcomes Study (MOS) Social Support Survey provides a multidimensional tool to evaluate emotional/informational, tangible, effective and positive social interactions. Adequacy of the MOS Social Support Survey correlates with improved functioning and wellbeing, whereas low scores indicate the need for support services to improve health outcomes [64].

Nutritional status

The Mini Nutritional Assessment is a validated approach to assess nutritional deficiency and/or malnutrition, which is a common problem occurring in 15–60% of elderly patients due to disease, poor eating habits or inadequate social support systems [65]. Nutri-

tional deficiency/malnutrition may be particularly problematic in the elderly where it can lead to sarcopenia, frailty, functional decline and death. The MNA components include an assessment of height, weight, weight loss, questions regarding lifestyle and medication, assessment of dietary adequacy and food intake, and self-perception of health and nutrition. Low scores in the MNA are useful to identify patients at risk for weight loss or development of low serum albumin. These results should be used to plan and institute corrective nutritional interventions [65].

Summary CGA components

The multidimensional assessment plan outlined above is comprehensive and provides multiple indicators to determine prognosis, risks and benefits associated with cancer in the elderly, as well as the basis for initiating interventions to improve outcomes. It is certainly more objective and reproducible than unstructured physician estimates. For example, in a comparison of physician impression to CGA evaluation in 200 patients, ≥70 years of age, with a variety of hematologic and non-hematologic malignancies, the CGA was found to be most effective at identifying patients as fit, vulnerable or frail [66]. As reported below, the CGA and in some cases, use of selected elements, has been validated in a number of clinical settings, to predict adverse events and/or early mortality in older patients with or without malignancy

Applications of CGA
Application of CGA to estimate survival

In a study of frail, chronically ill patients, ≥70 years of age, who qualified for nursing home placement, risk for 1-year and 3-year mortality was associated with male gender, progressive increase in age, ADL dependence in toileting, dressing and comorbidities, especially cancer, congestive heart failure, chronic obstructive pulmonary disease and renal failure or insufficiency [67]. More specific to cancer, Walter et al. [68] developed and validated an assessment tool for predicting 1-year mortality in patients ≥70 years of age hospitalized on a general medical service at major teaching or regional medical centers. Among 3163 patients, 1-year mortality was associated with male gender, dependence at discharge for assistance with ADL, comorbid conditions, particularly congestive heart failure and cancer, with advanced disease being worse than localized, and bloodwork showing creatinine greater than 3.0 mg/dl or low albumin, less than 3.0 g/dl. In another report of 348 patients, ≥70 years of age, undergoing chemotherapy for a variety of malignancies, risk of early death, within 6 months of starting chemotherapy, was associated with advanced disease, poor nutritional

status indicated by low MNA score, male gender, and impaired mobility, indicated by slow TUG test. In the multivariate analysis, early death was not predicted by ECOG performance status or geriatric evaluation of factors including ADL, IADL, MMS or Geriatric Depression Scale. Interestingly, the planned administration of reduced versus standard dose chemotherapy was not associated with early death [69].

Application of CGA in specific malignancies
Solid tumors

Addressing survival with specific malignancies, a study of 566 patients, ≥75 years of age, with advanced non-small-cell lung cancer (NSCLC), median survival was 30 weeks. Multivariate assessment for prognostic factors associated with shortened survival included reduced quality of life, measured by EORTC QLQ-C30 and abnormal IADL, as well as reduced performance status and number of metastatic sites. Neither baseline ADL nor Charleson comorbidity index added to the prognostic value of the assessment [33]. In another study of patients, ≥70 years of age, with NSCLC undergoing treatment with carboplatin–gemcitabine or carboplatin–paclitaxel, results of the CGA were associated with development of neuropsychiatric toxicity, ability to tolerate full dose chemotherapy and overall survival, however, they did not correlate with quality of life [70].

Applying a CGA and quality of life assessment before and after a cautiously modified dose regimen of cyclophosphamide, vincristine and prednisone for treatment of diffuse large B-cell lymphoma (DLBCL) and peripheral T-cell non-Hodgkin's Lymphoma in frail, elderly patients, ≥70 years of age, Soubeyran et al. [71] demonstrated an association of abnormal CGA, particularly impaired ADL and IADL with early death. However, since survival of older patients with diffuse large cell lymphoma (DLCL) has been improved by more aggressive chemoimmunotherapy regimens containing cyclophosphamide, hydroxydaunomycin, vincristine and prednisone (CHOP) with added rituximab [72,73], there is a critical need to distinguish which elderly patients are likely to benefit from full dose chemotherapy and which are likely to show decline. Accordingly, in a series of patients with DLCL, ≥65 years of age, treated with chemoimmunotherapy, CGA was shown to be more effective than clinical judgment for predicting response, progression-free survival and overall survival [74].

CGA has been recommended to guide clinical decisions for managing a variety of issues in older patients with breast cancer. In an approach to evaluation of older women with breast cancer, Mandelblatt et al. showed that evaluation of burden of illness, includ-

ing life expectancy, self-rated health and physical function, and number of chronic conditions affected decisions regarding surgical treatment and subsequent chemotherapy [75]. Use of the CGA and assessment of quality of life has also been suggested to identify older women with breast cancer who should undergo surgery compared with those who might derive optimal benefits, while minimizing adverse effects, from alternative approaches including primary endocrine therapy and/or primary radiotherapy [76].

In older women, ≥65 years of age, undergoing first-line palliative chemotherapy for metastatic breast cancer, a pretreatment study of CGA abnormalities found that increasing numbers of comorbidities coupled with increasing age and diminished performance status was associated with grade 3/4 chemotoxicity. Polypharmacy was also independently predictive of grade 3/4 chemotoxicity [77]. Using a detailed battery of neuropsychiatric tests in a series of 164 breast cancer patients, ≥60 years of age and matched controls, executive function was lower in patients compared with controls. Cognitive impairment was not associated with disease compared with controls, but was more common in older patients and those with greater comorbidity, especially diabetes and cardiovascular disease [78].

It has also been suggested that the CGA be used to provide an objective determination for use of adjuvant therapy in older patients with breast cancer. For example, in a survey of breast cancer oncologists at two major US Cancer Centers, Hurria *et al.* showed that both the use and type of adjuvant chemotherapy for hypothetical breast cancer patients, ≥70 years of age, was widely variable but generally decreased with increase in age or decreased functional status [79]. The study clearly demonstrated the potential usefulness of the CGA to objectively stratify patients for trials of adjuvant therapy, to determine whether or not a patient would tolerate adjuvant therapy and to determine which patients might be remediated to improve their risk/benefit ratio. In a small series of 15 women, ≥70 years of age, with early-stage breast cancer, Extermann *et al.* showed that 3-month follow-up with CGAs were useful in detecting and providing the basis for remediation and/or resolution of new-onset or previously missed geriatric conditions, psychosocial risks, nutritional disorders and inappropriate medications that contributed to improved treatment and prognosis [80].

The CGA was used to distinguish fit from vulnerable patients among a group of head and neck cancer patients, ≥65 years of age at two Belgian Medical Center, prior to undergoing curative therapy with radiation ± cisplatin. Vulnerable patients compared with fit, showed a statistically nonsignificant trend towards greater toxicity. Moreover, all patients who died during therapy had been identified as vulnerable [81].

Hematologic malignancies

Klepin *et al.* developed a modified CGA that could be administered at the bedside to evaluate older patients with AML about to undergo induction chemotherapy [82]. In these AML patients >60 years of age, the modified geriatric assessment was predictive of shorter overall survival [83]. The authors suggested use of geriatric assessment for stratification of AML patients being entered onto AML clinical therapeutic trials.

In a series of 166 patients, ≥50 years of age, preparing for allogeneic HCT, the CGA was found to be more successful than other instruments in identifying undetected vulnerabilities, particularly comorbidities and reduced mental health. Results of tumor response and toxicity were not provided, however, the report suggested using the CGA to evaluate prognostic and therapeutic potential in HCT [84].

Application of CGA to predict outcomes

While the CGA has been extensively studied to evaluate factors affecting toxicity and survival, its use to evaluate response to therapeutic regimens has been more limited. However, as noted above, CGA was shown to be more effective than physician judgment in predicting response, progression free survival and overall survival in older patients administered chemoimmunotherapy for DLCL [74]. In another study, a prospective evaluation of patients, >70 years of age, with advanced ovarian cancer, treated with six cycles of carboplatin and cyclophosphamide, components of the multivariate CGA along with performance status, successfully predicted tolerance as demonstrated by absence of severe toxicity and efficacy as determined by lack of tumor progression [85].

Other uses for the CGA

The CGA has also been evaluated as a preoperative assessment tool for inpatients undergoing cancer surgery. Of 175 patients, ≥70 years of age, undergoing abdominal surgery for colorectal cancer, preoperative CGA, which classified patients as fit, intermediate or frail, was significantly associated with severe postoperative morbidity including pulmonary, cardiac, anastomatic leakages, delirium and need for reoperation [86]. In another study of 111 patients, ≥65 years of age, undergoing either laparoscopic or open abdominal surgery for cancer, preoperative CGA was predictive for prolonged hospital stay or the need to be discharged to a skilled nursing facility. However, there was no association with morbidity or mortality within 90 days or need for readmission within 30 days. Prolonged

hospital stay was associated with weight loss ≥10%, polypharmacy ≥5 daily oral medications and distant disease. Weight loss ≥10% and Eastern Cooperative Oncology Group performance score ≥2 were associated with need for nursing facility admission [87]. Interestingly, on the basis of these findings the authors recommended preoperative use of the CGA in geriatric oncologic patients for prehabilitation to improve postoperative course and for planning needs for extended postoperative care [87].

Prehabilitation & rehabilitation in the older cancer patient

The practice of prehabilitation therapy has been beneficially employed in areas such as orthopedic and cardiovascular surgery [88] and has more recently been applied to cancer care, especially in older patients [89,90]. Cancer prehabilitation is defined as the care that occurs between the time of cancer diagnosis and the beginning of acute treatment [88–90], which on average may be expected to be approximately 4 weeks. Prehabilitation may also take place during administration of neoadjuvant therapy, in the period before surgery in diseases such as breast cancer. Based on CGA findings and associated diagnostic tests to identify specific impairments, a prehabilitation program should consist of a multimodal approach incorporating both physical and psychological interventions to improve a patient's health, to reduce the incidence of current and anticipated future impairments, to potentially reduce costs and to improve long-term outcomes [89,90].

Obvious targets for improvement in a prehabilitation program include nutritional status [91] including improving protein balance, vitamin D deficiency and hyperglycemia, the latter associated with diabetes. Specific attention should be focused on improving anemia by correcting nutritional deficiencies of iron, folic acid and B12 or by transfusion when necessary [92]. Pharmacological interventions to improve heart failure should be initiated promptly and exercise programs to increase cardiovascular fitness, in both the prehabilitative and rehabilitative periods, should be implemented [93]. Introduction of aerobic and/or resistance exercise training in prehabilitative programs, has been shown to reduce fatigue and improve functional capacity in breast cancer patients [94]. Prehabilitation using inspiratory muscle training in older, although not specifically cancer patients, reduced risk of post-surgical pulmonary complications including atelectasis [93]. Another study found improved cardiovascular fitness in patients undergoing preoperative exercise training prior to pulmonary resection for lung cancer [95].

Using a multimodal program including nutrition counseling, protein supplementation, anxiety reduc-tion and a moderate aerobic exercise program coupled with resistance training resulted in improved postoperative walking capacity, emotional status and greater functional exercise capacity in the post-operative recovery period [96].

There is obviously a need for high quality clinical trials to evaluate the risk benefit ratios of these and other suggested prehabilitative interventions, including the risk of the approximately 4 week period required to conduct prehabilitative programs before initiating definitive therapy and, the possibility of adverse effects being associated directly with the interventions themselves. In addition to effects on short term outcomes, benefits need to be assessed on long term outcomes, including response to therapy, remission duration as well as cancer specific and all-cause mortality. Research is needed also to more fully evaluate the potential of prehabilitative programs to reverse frailty [97] and prevent functional decline [98,99].

In another approach to investigate older cancer patients for postsurgical outcomes, a modified CGA extended by including the American Society of Anesthesiologists surgical risk assessment and the Brief Fatigue Index were combined to form the Preoperative Assessment in Cancer in the Elderly (PACE). Studying 460 older patients undergoing surgery for breast cancer, gastrointestinal cancer and genitourinary cancer showed that PACE abnormalities were associated with 50% increase in rates of postoperative complications [100].

As noted above, repeated CGAs have been recommended to identify risks where appropriate remedial interventions may allow for continuation of care and provide the basis for improving treatment and prognosis [80]. In a meta-analysis of 28 trials analyzing 4959 subjects, the CGA was shown to be effective at identifying patients who benefited from Geriatric Evaluation and Management Unit programs to reduce morbidity and improve physical and cognitive function and survival [101].

With increasing success of cancer therapy and more targeted therapies capable of controlling as opposed to curing cancer, there in an increasing need for rehabilitation programs for patients with either curable malignancies or those with the potential for prolonged survival. Balduci and Fossa suggested use of the CGA to identify older cancer patients that could benefit from rehabilitation programs to prevent long-term complications of cancer therapy and prolong functional independence [102].

Adaptability & change in the CGA
The CGA has been easy to administer in the USA and in multiple countries, including Belgium, England,

should have a CGA and results should be analyzed relative to morbidity, mortality and outcomes [108]. Moreover, consideration needs to be given to morphometric assessment of bone density, muscle mass and obesity using MRI and physiologic assessment of pulmonary and cardiovascular status using pulmonary function and stress testing, since each of these conditions can impact outcomes in older patients with cancer. To further define the potential usefulness of the CGA and associated tests in decision-making regarding selection of therapeutic agents and strategies for treating cancer in the elderly, we suggest that results of the CGA be used to randomize older cancer patients with impact evaluated on clinical outcomes including tumor response, progression-free survival and overall survival.

The CGA has been demonstrated to be superior to best 'guestimate', even by experienced clinicians, when used to evaluate the older cancer patient for functional status as compared with chronological age [74] . It is clearly useful for determining risk of adverse effects associated with tumors and/or their treatments. With more use to stratify patients entering into clinical trials, the CGA will become even more useful for determining likelihood of success for therapeutic regimens. While it is unlikely that any laboratory test will ever replace clinical assessment to determine general aspects of physiologic factors and frailty, psychosocial or cognitive functions, it is reasonable to speculate that future development of objective biomarkers, as recently reviewed [115], will provide more precise indicators of overall and specific systems as well as indicators of targets for specific therapeutic strategies. Although a detailed discussion of such objective assessments is beyond the scope of this article, a few possibilities are worth noting as potential biomarkers. For example, biomarkers such as peripheral blood leukocyte telomere length and telomerase activity [116] and p16^{INK4a} [117–121] might be useful to quantitatively assess senescence status and reserve capacity compared with chronological age.

Components of DNA repair pathways and DNA damage response, reactive oxidative stress and defense systems and Sir2 protein status could also be used for predicting response and risk of adverse effects from chemotherapy, radiation therapy and other stresses [122–125]. Signal metabolites and peptides such as circulating levels of the C-terminal fragment of Agrin [126] in association with elevated C-reactive protein and IL-6 [127] along with imaging studies to quantitate sarcopenia and cachexia would be useful to evaluate need for and results of therapeutic strategies [127,128]. Circulating cytokines including C-reactive protein, TNF-α, IL-1β, IL-6 and PAI-1 may be associated with increased risk for mortality in older patients [129,130]. In a recent report of older men with anxiety and depression, associated with androgen deprivation therapy for prostate cancer, an exercise regimen was shown to improve quality of life in association with changes in inflammatory cytokines, suggesting the possibility that assessment of circulating cytokines might provide an indication and target for remediation of psychological disturbances in older cancer patients [50,131]. The potential biomarkers noted in this paragraph and others, including myokines [132] will require considerable investigation before they are validated for clinical use. Nonetheless, this research is clearly justified as we prepare for the epidemic of cancer accompanying the graying of the population [8].

Since the incidence of cancer increases with age and the geriatric population continues to expand, it is critical to develop strategies, procedures and professional personnel to provide optimal care for older patients with cancer. An important component of this care is to distinguish chronologic from functional age and to evaluate physiologic reserves, risk of treatment complications, probability that the older patient can cope with and recover from their primary disease and therapeutic interventions, probability of survival and to identify remediable conditions that could improve therapeutic tolerability, quality of life and overall survival. Although the CGA tool continues to be developed and will be further strengthened by the addition of objective tests as outlined above, it has matured and has been validated to a sufficient degree to recommend its routine application for older patients with cancer. Screening tests, such as the G8 and/or VES-13 should be administered to all cancer patients, aged ≥65 years. Those found to be at risk in the screening test, should be further evaluated with a full CGA and the results used by health professionals, patients, families and caregivers to develop specific strategies for medical care, and social and psychological support to improve cancer outcomes for older adults.

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References

Papers of special note have been highlighted as: • of interest

1   Yancik R. Cancer burden in the aged: an epidemiologic and demographic overview. *Cancer* 80(7), 1273–1283 (1997).

2   Ries LAG, Eisner MP, Kosary CL *et al.* (Eds). *SEER Cancer Statistics Review, 1973–1998*, National Cancer Institute, MD, USA (2001).

3   Yancik R. NIA/NCI Report of the Cancer Center Workshop: exploring the role of cancer centers for integrating aging and cancer research (June 13–15 2001). www.cancerandaging.uiowa.edu

4   Berger NA, Savvides P, Koroukian SM *et al.* Cancer in the elderly. *Trans. Am. Clin. Climatol. Assoc.* 117, 147–155; discussion 155–146 (2006).

5   Vincent Grayson K. The next four decades the older population in the United States: 2010 to 2050 (2010). www.census.gov/prod/2010pubs/p25-1138.pdf

6   United States, Administration on Aging, Administration for Community Living. Profile of Older Americans (2013). www.aoa.gov/Aging_Statistics/Profile/2013/docs/2013_Profile.pdf

7   Rose JH, O'Toole EE, Koroukian S, Berger NA. *Geriatr. Oncol.* and primary care: promoting partnerships in practice and *research. J. Am. Geriatr. Soc.* 57(Suppl. 2), S235–S238 (2009).

8   Shih YC, Hurria A. Preparing for an epidemic: cancer care in an aging population. *Am. Soc. Clin. Oncol. Educ. Book* 133–137 (2014).

9   Druker BJ, Guilhot F, O'Brien SG *et al.* Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N. Engl. J. Med.* 355(23), 2408–2417 (2006).

10   Druker BJ. Perspectives on the development of imatinib and the future of cancer *research. Nat. Med.* 15(10), 1149–1152 (2009).

11   Byrd JC, Jones JJ, Woyach JA, Johnson AJ, Flynn JM. Entering the era of targeted therapy for chronic lymphocytic leukemia: impact on the practicing clinician. *J. Clin. Oncol.* 32(27), 3039–3047 (2014).

12   Scripture CD, Sparreboom A, Figg WD. Modulation of cytochrome P450 activity: implications for cancer therapy. *Lancet Oncol.* 6(10), 780–789 (2005).

13   Levien TL. Cytochrome P450 drug interactions (2003). www.ildcare.eu

14   Dinsmore R, Kirkpatrick D, Flomenberg N *et al.* Allogeneic bone marrow transplantation for patients with acute lymphoblastic leukemia. *Blood* 62(2), 381–388 (1983).

15   Blume KG, Forman SJ, Nademanee AP *et al.* Bone marrow transplantation for hematologic malignancies in patients aged 30 years or older. *J. Clin. Oncol.* 4(10), 1489–1492 (1986).

16   Ringden O, Horowitz MM, Gale RP *et al.* Outcome after allogeneic bone marrow transplant for leukemia in older adults. *JAMA* 270(1), 57–60 (1993).

17   Kusnierz-Glaz CR, Schlegel PG, Wong RM *et al.* Influence of age on the outcome of 500 autologous bone marrow transplant procedures for hematologic malignancies. *J. Clin. Oncol.* 15(1), 18–25 (1997).

18   Popplewell LL, Forman SJ. Is there an upper age limit for bone marrow transplantation? *Bone Marrow Transpl.* 29(4), 277–284 (2002).

19   Reuben DB. Geriatric assessment in oncology. *Cancer* 80(7), 1311–1316 (1997).

20   Balducci L, Extermann M. Management of cancer in the older person: a practical approach. *Oncologist* 5(3), 224–237 (2000).

•   **Comprehensive discussion of the need for multidimensional assessment of older cancer patients and practical guide to its implementation.**

21   Balducci L, Beghe C. The application of the principles of geriatrics to the management of the older person with cancer. *Crit. Rev. Oncol. Hematol.* 35(3), 147–154 (2000).

22   Bernabei R, Venturiero V, Tarsitani P, Gambassi G. The comprehensive geriatric assessment: when, where, how. *Crit. Rev. Oncol. Hematol.* 33(1), 45–56 (2000).

23   Zagonel V. Importance of a comprehensive geriatric assessment in older cancer patients. *Eur. J. Cancer* 37(Suppl. 7), S229–S233 (2001).

24   Carreca I, Balducci L, ExtermAnn. M. Cancer in the older person. *Cancer Treat. Rev.* 31(5), 380–402 (2005).

25   Kim J, Hurria A. Determining chemotherapy tolerance in older patients with cancer. *J. Natl Compr. Cancer Netw.* 11(12), 1494–1502 (2013).

26   Hurria A, Wildes T, Blair SL *et al.* Senior adult oncology, version 2.2014: clinical practice guidelines in oncology. *J. Natl Compr. Cancer Netw.* 12(1), 82–126 (2014).

•   **Complete treatise on domains of CGA and their relevance in specific tumor systems.**

27   Owusu C, Studenski SA. Shared care in *Geriatr. Oncol.*: primary care providers' and medical/oncologist's perspectives. *J. Am. Geriatr. Soc.* 57(Suppl. 2), S239–S242 (2009).

28   O'Toole E, Step MM, Engelhardt K, Lewis S, Rose JH. The role of primary care physicians in advanced cancer care: perspectives of older patients and their oncologists. *J. Am. Geriatr. Soc.* 57(Suppl. 2), S265–S268 (2009).

29   Cohen HJ. A model for the shared care of elderly patients with cancer. *J. Am. Geriatr. Soc.* 57(Suppl. 2), S300–S302 (2009).

30   Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. The index of Adl: a standardized measure of biological and psychosocial function. *JAMA* 185, 914–919 (1963).

31   Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* 9(3), 179–186 (1969).

32   Lawton MP. Scales to measure competence in everyday activities. *Psychopharmacol. Bull.* 24(4), 609–614 (1988).

33   Maione P, Perrone F, Gallo C *et al.* Pretreatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non-small-cell lung cancer receiving chemotherapy: a prognostic analysis of the multicenter Italian lung cancer in the elderly study. *J. Clin. Oncol.* 23(28), 6865–6872 (2005).

34   Hurria A, Togawa K, Mohile SG *et al.* Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. *J. Clin. Oncol.* 29(25), 3457–3465 (2011).

35   Extermann M, Boler I, Reich RR *et al.* Predicting the risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. *Cancer* 118(13), 3377–3386 (2012).

36   Monfardini S, Basso U. Oncological causes of frailty in older cancer patients. *Eur. J. Cancer* 43(8), 1230–1231 (2007).

37   Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J. Am. Geriatr. Soc.* 39(2), 142–148 (1991).

38   Teno J, Kiel DP, Mor V. Multiple stumbles: a risk factor for falls in community-dwelling elderly. A prospective study. *J. Am. Geriatr. Soc.* 38(12), 1321–1325 (1990).

39   Studenski S, Perera S, Patel K *et al.* Gait speed and survival in older adults. *JAMA* 305(1), 50–58 (2011).

40   Klepin HD, Geiger AM, Tooze JA *et al.* Physical performance and subsequent disability and survival in older adults with malignancy: results from the health, aging and body composition study. *J. Am. Geriatr. Soc.* 58(1), 76–82 (2010).

41   Owusu C, Koroukian SM, Schluchter M, Bakaki P, Berger NA. Screening older cancer patients for a Comprehensive Geriatric Assessment: a comparison of three instruments. *J. Geriatr. Oncol.* 2(2), 121–129 (2011).

•   **Useful comparison of CGA to commonly used oncology assessment tools, VES-13, ECOG-PS and KPS.**

42   Folstein MF, Folstein SE, Mchugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12(3), 189–198 (1975).

43   Wolfson C, Wolfson DB, Asgharian M *et al.* A reevaluation of the duration of survival after the onset of dementia. *N. Engl. J. Med.* 344(15), 1111–1116 (2001).

44   Extermann. M. Older patients, cognitive impairment, and cancer: an increasingly frequent triad. *J. Natl Compr. Cancer Netw.* 3(4), 593–596 (2005).

45   Stilley CS, Bender CM, Dunbar-Jacob J, Sereika S, Ryan CM. The impact of cognitive function on medication management: three studies. *Health Psychol.* 29(1), 50–55 (2010).

46   Barrett L. Chronic conditions among older Americans 2009. In: *Beyond 5009: Chronic Care: A Call To Action For Health Reform.* AARP, Public Policy Institute, Washington DC, USA (2009).

47   Charlson ME, Pompei P, Ales KL, Mackenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J. Chronic Dis.* 40(5), 373–383 (1987).

48   Deimling GT, Arendt JA, Kypriotakis G, Bowman KF. Functioning of older, long-term cancer survivors: the role of cancer and comorbidities. *J. Am. Geriatr. Soc.* 57(Suppl. 2), S289–S292 (2009).

49   Meyerhardt JA, Catalano PJ, Haller DG *et al.* Impact of diabetes mellitus on outcomes in patients with colon cancer. *J. Clin. Oncol.* 21(3), 433–440 (2003).

50   Kamen C JM, Heffner K, Peoples A *et al.* Standardized, progressive exercise program (EXCAP) to reduce psychological distress and improve inflammatory cytokines of distress among prostate cancer survivors. Presented at: *2014 ASCO Annual Meeting*, Chicago, IL, USA, 30 May–3 June 2014.

51   Jyrkka J, Enlund H, Korhonen MJ, Sulkava R, Hartikainen S. Patterns of drug use and factors associated with polypharmacy and excessive polypharmacy in elderly persons: results of the Kuopio 75+ study: a cross-sectional analysis. *Drugs Aging* 26(6), 493–503 (2009).

52   Beers MH, Ouslander JG, Rollingher I, Reuben DB, Brooks J, Beck JC. Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. *Arch. Intern. Med.* 151(9), 1825–1832 (1991).

53   Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. *Arch. Intern. Med.* 157(14), 1531–1536 (1997).

54   American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *J. Am. Geriatr. Soc.* 60(4), 616–631 (2012).

55   Prithviraj GK, Koroukian S, Margevicius S, Berger NA, Bagai R, Owusu C. Patient characteristics associated with polypharmacy and inappropriate prescribing of medications among older adults with cancer. *J. Geriatr. Oncol.* 3(3), 228–237 (2012).

56   Maggiore RJ, Dale W, Gross CP *et al.* Polypharmacy and potentially inappropriate medication use in older adults with cancer undergoing chemotherapy: effect on chemotherapy-related toxicity and hospitalization during treatment. *J. Am. Geriatr. Soc.* 62(8), 1505–1512 (2014).

57   Lai SW, Liao KF, Liao CC, Muo CH, Liu CS, Sung FC. Polypharmacy correlates with increased risk for hip fracture in the elderly: a population-based study. *Medicine (Baltimore)* 89(5), 295–299 (2010).

58   Jyrkka J, Enlund H, Korhonen MJ, Sulkava R, Hartikainen S. Polypharmacy status as an indicator of mortality in an elderly population. *Drugs Aging* 26(12), 1039–1048 (2009).

59   Kivistö KT, Kroemer HK, Eichelbaum M. The role of human cytochrome P450 enzymes in the metabolism of anticancer agents: implications for drug interactions. *Br. J. Clin. Pharmacol.* 40(6), 523–530 (1995).

60   Yesavage JA, Brink TL, Rose TL *et al.* Development and validation of a geriatric depression screening scale: a preliminary report. *J. Psychiatr. Res.* 17(1), 37–49 (1982).

61   Yesavage JA, Sheikh JI. 9/Geriatric Depression Scale (GDS). *Clin. Gerontol.* 5(1–2), 165–173 (1986).

62   Shankar A, McMunn A, Banks J, Steptoe A. Loneliness, social isolation, and behavioral and biological health indicators in older adults. *Health Psychol.* 30(4), 377–385 (2011).

63   Perissinotto CM, Stijacic Cenzer I, Covinsky KE. Loneliness in older persons: a predictor of functional decline and death. *Arch. Intern. Med.* 172(14), 1078–1083 (2012).

64   Sherbourne CD, Stewart AL. The MOS social support survey. *Soc. Sci. Med.* 32(6), 705–714 (1991).

65   Vellas B, Guigoz Y, Garry PJ *et al.* The Mini Nutritional Assessment (MNA) and its use in grading the nutritional state of elderly patients. *Nutrition* 15(2), 116–122 (1999).

66   Wedding U, Kodding D, Pientka L, Steinmetz HT, Schmitz S. Physicians' judgement and comprehensive geriatric assessment (CGA) select different patients as fit for chemotherapy. *Crit. Rev. Oncol. Hematol.* 64(1), 1–9 (2007).

67   Carey EC, Covinsky KE, Lui LY, Eng C, Sands LP, Walter LC. Prediction of mortality in community-living frail elderly people with long-term care needs. *J. Am. Geriatr. Soc.* 56(1), 68–75 (2008).

68   Walter LC, Brand RJ, Counsell SR *et al.* Development and validation of a prognostic index for 1–year mortality in older adults after hospitalization. *JAMA* 285(23), 2987–2994 (2001).

69   Soubeyran P, Fonck M, Blanc-Bisson C *et al.* Predictors of early death risk in older patients treated with first-line chemotherapy for cancer. *J. Clin. Oncol.* 30(15), 1829–1834 (2012).

•   **Clear demonstration of how CGA components can predict early death in older patients receiving first line chemotherapy.**

70   Biesma B, Wymenga AN, Vincent A *et al.* Quality of life, geriatric assessment and survival in elderly patients with non-small-cell lung cancer treated with carboplatin-gemcitabine or carboplatin-paclitaxel: NVALT-3 a phase III study. *Ann. Oncol.* 22(7), 1520–1527 (2011).

71   Soubeyran P, Bellera C, Goyard J *et al.* Validation of the G8 screening tool in geriatric oncology : The ONCODAGE project. *ASCO Meeting Abstracts* 29(15 Suppl.), 9001 (2011).

72   Feugier P, Van Hoof A, Sebban C *et al.* Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. *J. Clin. Oncol.* 23(18), 4117–4126 (2005).

73   Kouroukis CT, Browman GP, Esmail R, Meyer RM. Chemotherapy for older patients with newly diagnosed, advanced-stage, aggressive-histology non-Hodgkin lymphoma: a systematic review. *Ann. Intern. Med.* 136(2), 144–152 (2002).

74   Tucci A, Ferrari S, Bottelli C, Borlenghi E, Drera M, Rossi G. A comprehensive geriatric assessment is more effective than clinical judgment to identify elderly diffuse large cell lymphoma patients who benefit from aggressive therapy. *Cancer* 115(19), 4547–4553 (2009).

75   Mandelblatt JS, Bierman AS, Gold K *et al.* Constructs of burden of illness in older patients with breast cancer: a comparison of measurement methods. *Health Serv. Res.* 36(6 Pt 1), 1085–1107 (2001).

76   Tang SW, Hurria A, Morgan DA, Cheung KL. Is surgery always indicated in older women with breast cancer? *Minerv. Chir.* 65(5), 555–568 (2010).

77   Hamaker ME, Seynaeve C, Wymenga AN *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. *Breast* 23(1), 81–87 (2014).

78   Mandelblatt JS, Stern RA, Luta G *et al.* Cognitive impairment in older patients with breast cancer before systemic therapy: is there an interaction between cancer and comorbidity? *J. Clin. Oncol.* 32(18), 1909–1918 (2014).

79   Hurria A, Naeim A, Elkin E *et al.* Adjuvant treatment recommendations in older women with breast cancer: a survey of oncologists. *Crit. Rev. Oncol. Hematol.* 61(3), 255–260 (2007).

80   Extermann M, Meyer J, Mcginnis M *et al.* A comprehensive geriatric intervention detects multiple problems in older breast cancer patients. *Crit. Rev. Oncol. Hematol.* 49(1), 69–75 (2004).

81   Pottel L, Lycke M, Boterberg T *et al.* Serial comprehensive geriatric assessment in elderly head and neck cancer patients undergoing curative radiotherapy identifies evolution of multidimensional health problems and is indicative of quality of life. *Eur. J. Cancer Care* 23(3), 401–412 (2014).

82   Klepin HD, Geiger AM, Tooze JA *et al.* The feasibility of inpatient geriatric assessment for older adults receiving induction chemotherapy for acute myelogenous leukemia. *J. Am. Geriatr. Soc.* 59(10), 1837–1846 (2011).

83   Klepin HD, Geiger AM, Tooze JA *et al.* Geriatric assessment predicts survival for older adults receiving induction chemotherapy for acute myelogenous leukemia. *Blood* 121(21), 4287–4294 (2013).

84   Muffly LS, Boulukos M, Swanson K *et al.* Pilot study of comprehensive geriatric assessment (CGA) in allogeneic transplant: CGA captures a high prevalence of vulnerabilities in older transplant recipients. *Biol. Blood Marrow Transplant.* 19(3), 429–434 (2013).

85   Freyer G, Geay JF, Touzet S *et al.* Comprehensive geriatric assessment predicts tolerance to chemotherapy and survival in elderly patients with advanced ovarian carcinoma: a GINECO study. *Ann. Oncol.* 16(11), 1795–1800 (2005).

86   Kristjansson SR, Nesbakken A, Jordhoy MS *et al.* Comprehensive geriatric assessment can predict complications in elderly patients after elective surgery for colorectal cancer: a prospective observational cohort study. *Crit. Rev. Oncol. Hematol.* 76(3), 208–217 (2010).

87   Badgwell B, Stanley J, Chang GJ *et al.* Comprehensive geriatric assessment of risk factors associated with adverse outcomes and resource utilization in cancer patients undergoing abdominal surgery. *J. Surg. Oncol.* 108(3), 182–186 (2013).

88   Santa Mina D, Clarke H, Ritvo P *et al.* Effect of total-body prehabilitation on postoperative outcomes: a systematic review and meta-analysis. *Physiotherapy* 100(3), 196–207 (2014).

89   Silver JK, Baima J. Cancer prehabilitation: an opportunity to decrease treatment-related morbidity, increase cancer treatment options, and improve physical and psychological health outcomes. *Am. J. Phys. Med. Rehabil.* 92(8), 715–727 (2013).

•   **Survey of multimodal prehabilitative interventions to decrease treatment-related morbidity and improve outcomes.**

90   Silver JK. Cancer rehabilitation and prehabilitation may reduce disability and early retirement. *Cancer* 120(14), 2072–2076 (2014).

91   Martindale RG, Mcclave SA, Taylor B, Lawson CM. Perioperative nutrition: what is the current landscape? *JPEN. J. Parenter. Enteral Nutr.* 37(5 Suppl.), s5–s20 (2013).

92   Berger Na, Rosenblum D. Geriatric hematology. In: *Clinical Hematology*, Young NS Gerson S, High KA (Eds). Elsevier, Amsterdam, The Netherlands, 944–955 (2006).

93   Jack S, West M, Grocott MP. Perioperative exercise training in elderly subjects. *Best Pract. Res. Clin. Anaesthesiol.* 25(3), 461–472 (2011).

94   De Paleville DT, Topp RV, Swank AM. Effects of aerobic training prior to and during chemotherapy in a breast cancer patient: a case study. *J. Strength Cond. Res.* 21(2), 635–637 (2007).

95   Jones LW, Peddle CJ, Eves ND *et al.* Effects of presurgical exercise training on cardiorespiratory fitness among patients undergoing thoracic surgery for malignant lung lesions. *Cancer* 110(3), 590–598 (2007).

96   Li C, Carli F, Lee L *et al.* Impact of a trimodal prehabilitation program on functional recovery after colorectal cancer surgery: a pilot study. *Surg. Endosc.* 27(4), 1072–1082 (2013).

97   Hubbard RE, Story DA. Patient frailty: the elephant in the operating room. *Anaesthesia* 69(Suppl. 1), 26–34 (2014).

98   Cheema FN, Abraham NS, Berger DH, Albo D, Taffet GE, Naik AD. Novel approaches to perioperative assessment and intervention may improve long-term outcomes after colorectal cancer resection in older adults. *Ann. Surg.* 253(5), 867–874 (2011).

99   Gill TM, Baker DI, Gottschalk M, Peduzzi PN, Allore H, Van Ness PH. A prehabilitation program for the prevention of functional decline: effect on higher-level physical function. *Arch. Phys. Med. Rehabil.* 85(7), 1043–1049 (2004).

100   Pope D, Ramesh H, Gennari R *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. *Surg. Oncol.* 15(4), 189–197 (2006).

101   Stuck AE, Siu AL, Wieland GD, Adams J, Rubenstein LZ. Comprehensive geriatric assessment: a meta-analysis of controlled trials. *Lancet* 342(8878), 1032–1036 (1993).

102   Balducci L, Fossa SD. Rehabilitation of older cancer patients. *Acta Oncol.* 52(2), 233–238 (2013).

103   Taira N, Sawaki M, Takahashi M, Shimozuma K, Ohashi Y. Comprehensive geriatric assessment in elderly breast cancer patients. *Breast Cancer* 17(3), 183–189 (2010).

104   Kanesvaran R, Wang W, Yang Y *et al.* Characteristics and treatment options of elderly Chinese patients with cancer as determined by Comprehensive Geriatric Assessment (CGA). *J. Geriatr. Oncol.* 5(2), 171–178 (2014).

105   Kanesvaran R, Li H, Koo KN, Poon D. Analysis of prognostic factors of comprehensive geriatric assessment and development of a clinical scoring system in elderly Asian patients with cancer. *J. Clin. Oncol.* 29(27), 3620–3627 (2011).

106   Overcash JA, Beckstead J, Extermann M, Cobb S. The abbreviated comprehensive geriatric assessment (aCGA): a retrospective analysis. *Crit. Rev. Oncol. Hematol.* 54(2), 129–136 (2005).

107   Hurria A, Gupta S, Zauderer M *et al.* Developing a cancer-specific geriatric assessment: a feasibility study. *Cancer* 104(9), 1998–2005 (2005).

108   Hurria A, Cirrincione CT, Muss HB *et al.* Implementing a geriatric assessment in cooperative group clinical cancer trials: CALGB 360401. *J. Clin. Oncol.* 29(10), 1290–1296 (2011).

•   Demonstration of usefulness of including a geriatric assessment tool for inclusion of older patients in cooperative group clinical trials.

109   Saliba D, Orlando M, Wenger NS, Hays RD, Rubenstein LZ. Identifying a short functional disability screen for older persons. *J. Gerontol. Series A, Biol. Sci. Med. Sci.* 55(12), M750–M756 (2000).

110   Min LC, Elliott MN, Wenger NS, Saliba D. Higher vulnerable elders survey scores predict death and functional decline in vulnerable older people. *J. Am. Geriatr. Soc.* 54(3), 507–511 (2006).

111   Min L, Yoon W, Mariano J *et al.* The vulnerable elders-13 survey predicts 5–year functional decline and mortality outcomes in older ambulatory care patients. *J. Am. Geriatr. Soc.* 57(11), 2070–2076 (2009).

112   Bellera CA, Rainfray M, Mathoulin-Pelissier S *et al.* Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. *Ann. Oncol.* 23(8), 2166–2172 (2012).

113   Decoster L, Van Puyvelde K, Mohile S *et al.* Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations dagger. *Ann. Oncol.* doi:10.1093/annonc/mdu210 (2014) (Epub ahead of print).

•   Overview of screening test used to indicate need for full CGA.

114   Pottel L, Boterberg T, Pottel H *et al.* Determination of an adequate screening tool for identification of vulnerable elderly head and neck cancer patients treated with radio(chemo) therapy. *J. Geriatr. Oncol.* 3(1), 24–32 (2012).

115   Hubbard JM, Cohen HJ, Muss HB. Incorporating biomarkers into cancer and aging research. *J. Clin. Oncol.* 32(24), 2611–2616 (2014).

•   Discussion of candidate biomarkers to assess functional age and reserve status in older cancer patients.

116   Ornish D, Lin J, Chan JM *et al.* Effect of comprehensive lifestyle changes on telomerase activity and telomere length in men with biopsy-proven low-risk prostate cancer: 5–year follow-up of a descriptive pilot study. *Lancet Oncol.* 14(11), 1112–1120 (2013).

117   Cawthon RM, Smith KR, O'brien E, Sivatchenko A, Kerber RA. Association between telomere length in blood and mortality in people aged 60 years or older. *Lancet* 361(9355), 393–395 (2003).

118   Burd CE, Sorrentino JA, Clark KS *et al.* Monitoring tumorigenesis and senescence *in vivo* with a p16(INK4a)-luciferase model. *Cell* 152(1–2), 340–351 (2013).

119   Krishnamurthy J, Torrice C, Ramsey MR *et al.* Ink4a/Arf expression is a biomarker of aging. *J. Clin. Invest.* 114(9), 1299–1307 (2004).

120   Liu Y, Sanoff HK, Cho H *et al.* Expression of p16(INK4a) in peripheral blood T-cells is a biomarker of human aging. *Aging Cell* 8(4), 439–448 (2009).

121   Sanoff HK, Deal AM, Krishnamurthy J *et al.* Effect of cytotoxic chemotherapy on markers of molecular age in patients with breast cancer. *J. Natl Cancer Inst.* 106(4), dju057 (2014).

122   Aoi W, Sakuma K. Oxidative stress and skeletal muscle dysfunction with aging. *Curr. Aging Sci.* 4(2), 101–109 (2011).

123   De Boer J, Andressoo JO, De Wit J *et al.* Premature aging in mice deficient in DNA repair and transcription. *Science* 296(5571), 1276–1279 (2002).

124   Gorbunova V, Seluanov A, Mao Z, Hine C. Changes in DNA repair during aging. *Nucl. Acids Res.* 35(22), 7466–7474 (2007).

125   Lombard DB, Chua KF, Mostoslavsky R, Franco S, Gostissa M, Alt FW. DNA repair, genome stability, and aging. *Cell* 120(4), 497–512 (2005).

126   Drey M, Sieber CC, Bauer JM *et al.* C-terminal agrin fragment as a potential marker for sarcopenia caused by degeneration of the neuromuscular junction. *Exp. Gerontol.* 48(1), 76–80 (2013).

127   Schaap LA, Pluijm SM, Deeg DJ, Visser M. Inflammatory markers and loss of muscle mass (sarcopenia) and strength. *Am. J. Med.* 119(6), 526.e529–517 (2006).

128   Pahor M, Manini T, Cesari M. Sarcopenia: clinical evaluation, biological markers and other evaluation tools. *J. Nutr. Health Aging* 13(8), 724–728 (2009).

129   Cohen HJ, Harris T, Pieper CF. Coagulation and activation of inflammatory pathways in the development of functional decline and mortality in the elderly. *Am. J. Med.* 114(3), 180–187 (2003).

130   De Martinis M, Franceschi C, Monti D, Ginaldi L. Inflammation markers predicting frailty and mortality in the elderly. *Exp. Mol. Pathol.* 80(3), 219–227 (2006).

131   Berger NA. Benefits of exercise in the elderly and in older cancer patients and survivors. Presented at: *2014 ASCO Annual Meeting*. Chicago, IL, USA, 31 May 2014.

132   Fiuza-Luces C, Garatachea N, Berger NA, Lucia A. Exercise is the real polypill. *Physiology* 28(5), 330–358 (2013).