Evaluating the Older Patient with Cancer: Understanding Frailty and the Geriatric Assessment

Abstract

The majority of cancer incidence and mortality occurs in individuals aged older than 65 years, and the number of older adults with cancer is projected to significantly increase secondary to the aging of the US population. As such, understanding the changes accompanying age in the context of the cancer patient is of critical importance. Age-related changes can impact tolerance of anticancer therapy and can shift the overall risk-benefit ratio of such treatment. A challenge in implementing evidence-based approaches in older adults is the under-representation of this group in oncology clinical trials. In addition, although older adults are particularly vulnerable to the side effects of cancer therapy, few oncology studies to date have incorporated a measure of health status other than the Eastern Cooperative Oncology Group or Karnofsky performance scales. Novel metrics such as frailty indices or the geriatric assessment recognize heterogeneity among older adults, and may allow for risk-adapted approaches to therapy. It is increasingly recognized that several laboratory markers may predict morbidity and mortality in older adults; these biologic variables may further aid in stratifying this group of patients based on risk. This review describes key studies from the geriatric literature that provide principles for assessing health status in the older patient, and ways that these principles can be applied to oncology care in an older population are proposed.

Introduction

Estimates from the US Census Bureau predict a rapid rise in the number of individuals aged older than 65 years. Furthermore, the number of individuals over the age of 65 years and 85 years is projected to double to nearly 62 million and 10 million, respectively, by the year 2030 and centenarians are anticipated to be the fastest-growing group within this demographic. Of particular concern in this population is the association between cancer and aging. It is estimated that 1,479,350 new cases of cancer were diagnosed in 2009, and 562,340 deaths occurred. Of these, it is projected that approximately 60% of cancer incidence and 70% of cancer-related mortality will occur in individuals aged older than 65 years, with even more pronounced figures reported for specific diseases.

Several unique concerns arise in the older adult with cancer. With increasing age, physiologic reserve decreases; however, the pace of this decline varies with each individual. Similarly, variations in functional status, cognition, and comorbidity accompany increased age, and may affect life expectancy, risk of subsequent functional decline, hospitalization, and other morbidity. These age-related changes can influence tolerance to cancer therapy, as well as the overall risk-benefit ratio of cancer treatment. The rate of these changes also varies between individuals.

Although older adults have been identified as being vulnerable to side effects from cancer therapy, few oncology studies to date have specifically incorporated baseline metrics for measuring health conditions other than functional status (Eastern Cooperative Oncology Group [ECOG] or Karnofsky performance status [PS]) to...
identify individuals most at risk. Furthermore, older adults have been under-represented in oncology clinical trials, and only a few studies published to date have focused on individuals who are considered physically unable to receive standard cancer therapy.12,13 Because the oncology literature provides little data regarding the subject, general principles from the geriatric literature can be used to guide the oncologist in identifying those patients who are frail and at high risk for functional decline, hospitalization, institutionalization, and mortality.

In this review, we describe key studies from the geriatric literature, and propose an application of these studies to care in an older oncology population. We also discuss potential biologic markers of aging, which provide an insight into clinical manifestations.

Understanding Frailty

Until recently, a consistent definition of frailty remained elusive. However, emerging data are providing a uniform definition of frailty within the geriatric population. A position statement from the American Medical Association defined the term “frailty” as characterizing “the group of patients that presents the most complex and challenging problems to the physician and all health care professionals,” because these are the individuals who have a higher susceptibility to adverse outcomes, such as institutionalization or mortality.14-16

Clinical Manifestations of Frailty

Phenotype Derived from the Cardiovascular Health Study

Data from the Cardiovascular Health Study (CHS) have been used to construct a widely cited definition of frailty.15 Based on a proposed “cycle of frailty” (Fig. 1), the investigators posited that 5 variables estimated a “phenotype of frailty”: 1) shrinking (weight loss), 2) weakness, 3) poor endurance, 4) slowness, and 5) low physical activity. Measurable parameters for each of these variables were developed, and are described in Table 1. With data from 5317 patients assessed, approximately 7% of the study population was considered frail (meeting greater than 3 frailty criteria), and 47% were considered to be prefrail (meeting 1–2 frailty criteria). There was an association noted between frailty and 5 adverse outcomes: 1) hospitalization, 2) falls, 3) worsening activity of daily living (ADL) disability, 4) worsening mobility disability, and 5) death (P < .0001 for all) (Fig. 2). Patients currently undergoing treatment for cancer were excluded from enrollment. Nevertheless, the number of patients with cancer (not receiving active treatment) did not differ significantly between the frail, prefrail, and nonfrail groups (14%, 15%, and 16%, respectively; P = .42). As such, the effects of a cancer diagnosis on frailty are difficult to assess in this study. However, distinct demographic characteristics associated with the “frail population” were identified, including older age, female gender, and African American race.17

Women’s Health and Aging Studies

The Women’s Health and Aging Studies (WHAS) I and II were used to further validate the results of the CHS.18 In the WHAS studies, previously established criteria were used to stratify women into 1 of 3 tertiles...
of disability.\textsuperscript{19} WHAS I enrolled women aged 65 years and older who were in the most disabled tertile among the community-dwelling population (N=1002). In contrast, WHAS II enrolled women ages 70 to 79 years who were in the 2 least disabled tertiles (N=436). With a slight modification of the 5 criteria derived from the CHS (Table 2), there was agreement to within 7% in the frequency of frailty in the 2 studies. Furthermore, the criteria predicted mortality in the WHAS experience. The Three-City Study conducted in France, however, yielded different results.\textsuperscript{20} Using the same criteria, a similar proportion of frail individuals (7%) was identified in a population of 6078 community-dwelling older men and women. Although frailty was found to be associated strongly with the need for assistance with ADLs and instrumental ADLs (IADLs) (Table 3), it failed to predict adverse outcomes such as hospitalization or mortality.

In an effort to simplify the CHS model, the Study of Osteoporotic Fractures (SOF) index was examined. The SOF index includes just 3 components (weight loss, inability to rise from a chair, and poor energy). In separate analyses of 3130 older males and 6701 older females, the SOF index demonstrated predictive capabilities for morbidity and mortality similar to a slightly modified CHS frailty index.\textsuperscript{21,22} Retornaz et al assessed the 5 CHS frailty markers (Table 1) in addition to mood and cognition in 50 chemotherapy recipients aged 70 years and older.\textsuperscript{23} Although this analysis did not provide data regarding clinical outcome based on these measures, it did appear that the use of this wide panel of frailty markers identified a distinct group of patients compared with the assessment of ADL and IADL dependency alone. In fact, 42% of patients included in the study had no ADL or IADL disability, but nonetheless had more than 1 frailty marker.

Bylow et al described a theoretical framework for the development of frailty in the setting of androgen deprivation therapy (ADT) for prostate cancer.\textsuperscript{24} Existing data support an association between ADT and each of the 5 CHS frailty markers. For example, unintentional lean weight loss (as a consequence of sarcopenia) frequently occurs in older adults receiving ADT.\textsuperscript{25} Sarcopenia consequently leads to increases in weakness and decreases in mobility, 2 separate components of the CHS frailty model. Finally, ADT has been associated with both fatigue and lowered physical activity, which are the remaining components of the model.\textsuperscript{26} Prospective studies are needed to validate this theoretical framework.

\begin{table}[h]
\centering
\caption{Frailty Criteria Proposed in the Cardiovascular Health Study\textsuperscript{15}}
\begin{tabular}{|l|l|}
\hline
\textbf{FRAILTY CRITERIA} & \textbf{CHARACTERISTIC} \\
\hline
Shrinking & \begin{itemize}
  \item Weight loss (unintentional) of \geq 10 lbs in prior y OR
  \item Weight loss at follow-up of \geq 5% of body weight in prior y (by direct measurement of weight).
\end{itemize} \\
Weakness & \begin{itemize}
  \item Grip strength in the lowest 20% at baseline, adjusted for gender and BMI.
\end{itemize} \\
Poor endurance and energy & \begin{itemize}
  \item Poor endurance and energy as indicated by self-report of exhaustion.
  \item Self-reported exhaustion, identified by 2 questions from the CES-D scale, is associated with stage of exercise reached in graded exercise testing as an indicator of VO$_2$ max and is predictive of cardiovascular disease.
\end{itemize} \\
Slowness & \begin{itemize}
  \item Slowest 20% of the population was defined at baseline based on time to walk 15 ft, adjusting for gender and standing height.
\end{itemize} \\
Low physical level of activity & \begin{itemize}
  \item Weighted score of Kcal expended per wk was calculated at baseline, based on each participant’s report.
  \item Lowest quintile of physical activity was identified for each gender.
\end{itemize} \\
\hline
\end{tabular}
\end{table}

\textsuperscript{BMI, body mass index; CES–D, Center for Epidemiologic Studies Depression Scale; VO$_2$ max, maximum oxygen consumption; Kcal, kilocalories.}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Incidence of Adverse Outcomes Associated With Frailty. The 3-year outcomes denoted here were adapted from Table 6 in Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56:M146–M157.\textsuperscript{15}}
\end{figure}
Canadian Study of Health and Aging

Data from the Canadian Study of Health and Aging (CSHA) were used to validate a separate set of frailty criteria derived from the Geriatric Status scale. This tool utilizes both functional and cognitive criteria in the definition of frailty (Table 4). The CSHA included 9008 adults aged 65 years and older, with a baseline assessment and 5-year follow-up for adverse outcomes. In this model, the prevalence of frailty was lower than that identified by the CHS; specifically, frailty was identified in 0.7%, 2%, and 4%, respectively, of patients ages 65 to 74 years, 75 to 84 years, and 85+ years.

### TABLE 2. Frailty Defined by the Women’s Health and Aging Study and the Cardiovascular Health Study

| FRAILTY CRITERIA | CHS | WHAS |
|------------------|-----|------|
| Weight loss      | Lost >10 lbs unintentionally in last y | ● %10 weight loss compared with weight at age 60 y OR ● BMI at examination <18.5 kg/m² |
| Exhaustion       | Self-report of either: ● Feeling everything I did was an effort in the last wk ● Could not get going in the last wk | Self-report of any: ● Low usual energy level (0-3; range, 0-10)* ● Felt unusually tired in the last mo ● Felt unusually weak in the past mo |
| Low energy expenditure | MLTA questionnaire (short version) ● Evaluating all 18 items ● <270 Kcals per wk on activity scale | MLTA questionnaire (short version) ● Evaluating 6 of 18 items: - Walking - Strenuous household chores - Strenuous outdoor chores - Dancing - Bowling - Exercise ● <90 Kcals per wk on activity scale |
| Slowness         | Walking 15 ft (4.57 m): ● Time ≥7 s for height ≥159 cm ● Time ≥6 s for height >159 cm | Walking 4 m: ● Walking speed (m/s) same as the CHS criteria |
| Weakness         | Grip strength (in kg) in dominant hand, measured by a Jamar handheld dynamometer: ● ≥17 for BMI =23 kg/m² ● ≥17.3 for BMI of 22.1-26 kg/m² ● ≥18 for BMI of 26.1-29 kg/m² ● ≥21 for BMI >29 kg/m² | Grip strength: ● Same as CHS criteria |
| Overall frailty status | Robust: met none of the criteria Intermediate: met 1 or 2 criteria Frail: met ≥3 criteria |

CHS indicates Cardiovascular Health Study; WHAS, Women’s Health and Aging Study; BMI, body mass index; MLTA, Minnesota Leisure Time Activity; Kcals, kilocalories.

*Rated on a scale of 0-10, in which 0 indicates no energy and 10 indicates the most energy that you have ever had.

### TABLE 3. ADLs and Instrumental ADLs

| ADLS | IADLS |
|------|-------|
| ● Bathing | ● Ability to use telephone |
| ● Dressing | ● Shopping |
| ● Toileting | ● Food preparation |
| ● Transferring | ● Housekeeping |
| ● Continence | ● Laundry |
| ● Feeding | ● Mode of transportation |
| ● Ability to take own medications | ● Ability to handle finances |

ADLs indicates activities of daily living; IADLs, instrumental ADLs.

### TABLE 4. Frailty Markers Proposed in Canadian Study of Health and Aging

| MARKERS | CHARACTERISTICS |
|---------|----------------|
| 0       | ● Able to walk without assistance ● Able to perform ADLs without assistance |
| 1       | ● Bladder incontinence only |
| 2 (Mild frailty) | 1 or more of the following (2 if incontinent): ● Needs assistance with mobility or ADLs ● Cognitive impairment without dementia ● Bowel or bladder incontinence |
| 3 (Moderate/severe frailty) | 2 or more of the following (3 if incontinent): ● Totally dependent for transfers ● Totally dependent for 1 or more ADLs ● Bowel or bladder incontinence ● Diagnosis of dementia |

ADLs indicates activities of daily living.
and 85 years and older. Similar to the previous studies, frailty served to predict mortality, and was associated with poor self-ratings of health, more comorbid illness, and increased social isolation. Data pertaining to specific comorbidities, including cancer diagnosis, were not reported in this analysis.

**Balducci Frailty Criteria**

Although the above frailty models provide important prognostic information for the geriatric population at large, to the best of our knowledge, data applicable to oncology patients are lacking. Frailty criteria for older adults with cancer have been proposed, combining elements of existing definitions. For example, the Balducci criteria are derived in part from observations reported in a study by Winograd et al assessing predictors of mortality and institutionalization among male patients aged 65 years and older at the Palo Alto Veterans Affairs Medical Center.27 Winograd et al identified functional impairment, comorbidity, and the presence of geriatric syndromes as predictors. The Balducci frailty criteria (Table 5) supplement these predictors with a criterion of age older than 85 years, given the purported high incidence of functional and cognitive changes in this demographic.28

Mohile et al evaluated the Balducci frailty criteria using data from the 2003 Medicare Beneficiary Survey.29 With analysis restricted to 12,480 community-dwelling individuals aged 65 years and older, a total of 2349 patients (19%) were identified with a cancer diagnosis (excluding skin cancer). Dementia or memory loss, inability to perform ADLs, and geriatric syndromes were assessed by self-report. Subjects satisfying the Balducci criteria for frailty were ultimately found to be more common in the cancer group versus the noncancer group (80% vs 73%; \( P < .001 \)). Eight cancer subtypes were also examined in this multivariate analysis: lung, colon, breast, cervical/uterine, prostate, bladder, ovarian, or “other.” Ultimately, a diagnosis of colon cancer (odds ratio [OR], 1.40; 95% confidence interval [95% CI], 1.02-1.93 \( [P = .04] \)), breast cancer (OR, 1.32; 95% CI, 1.01-1.72 \( [P = .04] \)), prostate cancer (OR, 1.45; 95% CI, 1.16-1.80 \( [P = .001] \)), and bladder cancer (OR, 2.04; 95% CI, 1.21-3.43 \( [P = .007] \)) were found to be significantly associated with frailty. Furthermore, it was found that a cancer diagnosis (compared with no cancer diagnosis) was associated with poorer self-rated health (OR, 1.46; 95% CI, 1.29-1.65 \( [P < .001] \)).

**Using a Geriatric Assessment to Predict Morbidity and Mortality**

Although composite criteria for frailty have been devised to characterize older adults, the comprehensive geriatric assessment contains domains with independent predictive capabilities, including an evaluation of functional status, comorbid medical conditions, cognitive function, psychological state, social support, nutritional status, and geriatric syndromes. Each of these domains predicts the risk of morbidity and mortality in older adults. The domains of the geriatric assessment are described below.

**Functional Status**

Functional status is a strong predictor of morbidity and mortality in the geriatric population.30 Although functional status can be measured in many different ways, a commonly used tool for evaluating functional status is the ability to complete ADLs and IADLs. ADLs are those basic self-care skills required to maintain independence in the home, such as the ability to bathe, dress, toilet, transfer, maintain continence, and feed oneself.31 IADLs are those skills required to maintain independence in the community, such as the ability to use the telephone, shop, prepare meals, do housekeeping or laundry, take transportation, take medications, and handle finances.32 Available guidelines recommend assessment of the ability to complete ADLs and IADLs on an annual basis in patients aged older

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**TABLE 5. Balducci Criteria for Frailty**

| FRAILTY CRITERIA | CHARACTERISTICS |
|------------------|----------------|
| Age              | ≥85 y          |
| ADLs             | Dependence for 1 or more |
| Comorbidity      | 3 or more      |
| Geriatric syndromes | One or more of the following:  |
|                  | Delirium       |
|                  | Dementia       |
|                  | Depression     |
|                  | Osteoporosis   |
|                  | Incontinence   |
|                  | Falls          |
|                  | Neglect and abuse |
|                  | Failure to thrive |

ADLs indicates activities of daily living.
Comorbidity

The extent of comorbidity increases with age, and increasing comorbidity may substantially affect morbidity and mortality in older adults with cancer.46-47 This was illustrated in an observational study of 17,712 patients with a new primary diagnosis of cancer, in which survival was found to be inversely related to age and comorbid medical conditions had an impact on survival independent of cancer stage.46 Similar findings have been noted in disease-specific studies. For example, in a retrospective cohort study of 29,733 patients aged 67 years and older with nonmetastatic colorectal cancer, comorbid conditions were found to be significantly associated with mortality (P < .001).48 A similar impact of comorbidity on survival was demonstrated in a study of 936 women with early stage breast cancer. Patients with 3 or more of 7 selected comorbid medical conditions were 20 times more likely to die from causes other than breast cancer, and patients with severe comorbidity were uniformly found to have higher morbidity rates compared with patients who had no comorbidity conditions.49

Comorbidity may also have a substantial impact on tolerance of anticancer therapy. A prospective assessment comparing vinorelbine alone or in combination with gemcitabine in patients aged older than 70 years identified an association between a Charlson Comorbidity Index (CCI) score of 2 or higher and treatment discontinuation.50 Similarly, an assessment of 162 patients aged older than 60 years who were treated with dose-dense chemotherapy for stage I to III breast cancer suggested that a CCI score of 1 or higher was associated with an increased risk of grade 3 and 4 toxicities. It is interesting to note that 22% of patients in this study discontinued therapy prior to the planned 8 cycles of treatment.51 Certain comorbidities may also have a specific impact on treatment tolerance. For example, hypertension may lead to an increased rate of both trastuzumab-related and anthracycline-related cardiomyopathy.52,53

Comorbidity also has practical implications for cancer screening. Guidelines from the US Preventive Services Task Force (USPSTF) and the American Cancer Society (ACS) advocate consideration of comorbid illness and associated prognosis when implementing screening for colorectal and breast cancer.54 For example, ACS guidelines indicate that screening...
for colorectal cancer may be discontinued in those patients with severe comorbidity that would preclude treatment.55 Similarly, USPSTF guidelines for breast cancer suggest that screening may be unnecessary in women with comorbid conditions that limit life expectancy.56 An inherent challenge in implementing these guidelines is the determination of an accurate prognosis.

Psychological State
A link between depression and aging has been established in several epidemiologic studies. It is estimated that 12% to 20% of community-dwelling persons aged 65 years and older experience significant depressive symptoms.57-59 Similarly, the link between depression and cancer has long been acknowledged.60 Depressive symptoms are particularly prominent among older, terminally ill, cancer patients. In one report, increasing age was paralleled by an increasing likelihood for thoughts of hurting oneself or feeling “better off dead.”61,62 The incidence of suicide has, in fact, been noted to be higher among older adults with cancer compared with older adults diagnosed with another medical illness.63 The use of psychosocial interventions may be effective in this population, and the majority of randomized controlled trial (RCT) data assessing psychosocial interventions support this strategy.64 These services may be underutilized in an older population. A study of 326 patients with metastatic gastrointestinal or lung cancer demonstrated that 100% of patients aged younger than 40 years with depressive symptoms were referred for psychosocial oncology care.65 In contrast, only 22% of patients aged 70 years and older with depressive symptoms were similarly referred. With regard to pharmacotherapy, a review of RCTs for depression interventions identified the use of selective serotonin reuptake inhibitors (SSRIs) for 6 weeks and longer as an effective strategy in depressed patients with cancer.64 However, the potential for interaction between anticancer agents (eg, tamoxifen) and SSRIs is an important consideration.66

Social Support
In older adults, studies have identified an association between social isolation and mortality.19,67,68 Available social support may also play a role in the diagnosis and treatment of the older adult with cancer. A Surveillance, Epidemiology, and End Results (SEER)—Medicare database review assessed women aged 65 years and older with a diagnosis of breast cancer.69 Those who were unmarried had a higher likelihood than married women of being diagnosed with stage II to IV breast cancer versus stage I disease. Furthermore, unmarried women with stage I or II breast cancer were less likely to receive chemotherapy. To the best of our knowledge, limited data exist to guide interventions for older adults with cancer who lack social support. In one study, unmarried patients or those living alone were more frequently referred for psychosocial oncology care; however, as previously noted, other studies indicate that these services are underutilized among older adults with depressive symptoms.65

Cognitive Function
Declines in cognitive function are associated with both increasing age and an increased risk for all-cause mortality.70,71 In the setting of oncology, cognitive impairment may be associated with a delay in the diagnosis of cancer. For example, a SEER—Medicare review examining 17,507 individuals aged 67 years and older with invasive colon cancer found that a diagnosis of colon cancer after death (ie, by autopsy or death certificate) was more than twice as likely to occur in patients with dementia.72 A diagnosis of cognitive impairment may also alter clinical decision-making in geriatric oncology. A review of the New Mexico Tumor Registry identified a correlation between decreased mental status (assessed via a screening test of cognitive function) and nonreceipt of definitive surgery in 669 cancer patients aged 65 years and older.73 The risk of cognitive impairment with anticancer therapy appears to have a strong bearing on patient decision-making as well. In a survey of patients aged 60 years and older with cancer, congestive heart failure, or chronic obstructive pulmonary disease and a limited life expectancy, the majority of patients (89%) said they would refuse life-prolonging therapy if it resulted in severe cognitive impairment.74

Polypharmacy
Older adults may be particularly susceptible to polypharmacy, given the increased number of comorbidities in this population.75 Polypharmacy raises the
likelihood of adverse drug reactions (ADRs) in older cancer patients, and has been associated with increased mortality.\textsuperscript{76,77} Certain drug classes are implicated in a higher frequency of ADRs, including anticoagulants (specifically warfarin) and benzodiazepines.\textsuperscript{78} Notably, both medications are frequently used in the treatment of oncology patients (warfarin for cancer-related thrombosis, and benzodiazepines for the management of anxiety or chemotherapy-related emetogenesis).\textsuperscript{62,63} Pharmacist-based medication review programs may reduce polypharmacy and the associated frequency of ADRs, although follow-up is needed to determine whether such programs have a substantial impact on clinical outcome in older adults with cancer.\textsuperscript{79}

**Nutrition**

Several studies in community-dwelling older adults have identified an association between a low body mass index (BMI) and an increased risk of mortality (relative to a normal BMI), underscoring the importance of adequate nutrition.\textsuperscript{80,81} Adequate nutrition is particularly important in patients with cancer. In an analysis of 3047 patients enrolled in ECOG protocols across multiple malignancies, weight loss was associated with lower response rates to chemotherapy and decreased survival.\textsuperscript{82} The observation of poorer clinical outcome in patients with cancer and concomitant weight loss has also been made in disease-specific studies of patients with small cell lung cancer and gastrointestinal malignancies.\textsuperscript{83,84}

The nutritional evaluation of older patients should be expanded in the setting of cancer to include treatment-related considerations. For example, treatment-induced nausea, vomiting, or mucositis can impede oral intake. Furthermore, cancer-related fatigue can hinder the patient’s ability to shop for food and cook, thereby compromising nutritional status. Various screening tools assess nutritional status in the older adult, beyond BMI alone. These tools are listed in Table 6.\textsuperscript{85}

**Geriatric Syndromes**

Geriatric syndromes (Table 5) are of particular relevance in the cancer patient, and appear to increase with age.\textsuperscript{86,87} In the study of Medicare beneficiaries by Mohile et al, a significant association was found between a diagnosis of cancer and a geriatric syndrome (OR, 1.27; 95% CI, 1.15–1.41).\textsuperscript{29} These syndromes have, in turn, been linked to multiple adverse clinical outcomes.\textsuperscript{88} Interventions have been devised to combat the progression of geriatric syndromes, and data from a randomized study indicate that these interventions result in improved functional abilities and mental well-being in vulnerable older adults.\textsuperscript{89}

**Geriatric Assessment in Oncology Practice**

The geriatric assessment has emerged as a useful oncology tool. It adds information to more generalized measures of functional status usually employed in oncology, such as the Karnofsky or ECOG PS. Repetto et al juxtaposed assessment by ECOG PS and by geriatric assessment in a cohort of 363 patients admitted with a diagnosis of a solid or hematologic malignancy.\textsuperscript{90} Elements of the geriatric assessment used in this study included demographic characteristics, physical function, disability, depression, and cognitive status. Components of the geriatric assessment and ECOG PS were found to be strongly associated. For example, the presence of ADL or IADL dependence conferred a 5-fold higher risk of poor PS (ECOG PS of 2 or higher). However, no association between comorbidity and PS was observed in this study. Presumably, these data suggest that although some domains of the geriatric assessment (ie, disability assessment) may serve as a surro-

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**Table 6. Screening Tools to Assess Nutritional Status**

| TOOL                                | COMPONENTS                                                                 |
|-------------------------------------|---------------------------------------------------------------------------|
| Malnutrition Universal Screening Tool | BMI                                                                       |
|                                     | Weight loss within the past 3-6 mo                                        |
|                                     | No nutritional intake in ≥5 d                                              |
|                                     | Acute illness                                                             |
| Short Nutritional Assessment Questionnaire | Involuntary weight loss                                                      |
|                                     | Loss of appetite                                                           |
|                                     | Use of tube feeding or supplemental drinks                                |
| Mini Nutritional Assessment         | Reduction in food intake                                                  |
|                                     | Weight loss                                                               |
|                                     | BMI                                                                       |
|                                     | Mobility                                                                  |
|                                     | Acute psychological distress or acute disease                             |
|                                     | Neuropsychological problems: dementia                                      |
|                                     | or depression                                                             |
| Nutritional risk score              | Undernutrition (BMI, % weight loss, change in food intake)                |
|                                     | Severity of disease                                                       |

BMI indicates body mass index.
The geriatric assessment may further aid in predicting treatment toxicity. A prospective analysis conducted at several French institutions over a 12-year interval (1988–2000) included 83 patients aged 70 years and older with advanced ovarian carcinoma who were treated with carboplatin and paclitaxel. A geriatric assessment was performed prior to the initiation of therapy. Ultimately, several elements of the geriatric assessment predicted the occurrence of severe toxicity with chemotherapy, including depression ($P = .003$) and intake of 6 or more nonchemotherapy medications per day ($P = .043$).

The geriatric assessment has also been correlated with outcomes from surgical resection of solid tumors. Using the Pre-operative Assessment of Cancer in the Elderly (PACE) tool, which combines traditional elements of the geriatric assessment with surgery-specific metrics, a cohort of 460 patients aged older than 70 years who underwent cancer-related surgery were evaluated preoperatively. On univariate analysis, ADL or IADL dependence and poor ECOG PS (higher than 2) were found to be associated with a longer hospital stay. On multivariate analysis, components of the PACE tool were found to correlate with postoperative complications, including increased fatigue score (according to the Brief Fatigue Inventory), ECOG PS (greater than 2), and IADL dependence.

As a logical extension of the prognostic and predictive capabilities of the geriatric assessment, the tool has been applied prospectively to guide the treatment of older adults with cancer. In a study of 245 patients with cancer who were aged 65 years and older, a self-administered questionnaire including all domains of the geriatric assessment was used to guide referrals to a multidisciplinary team consisting of social workers, psychiatrists, nutritional services, ophthalmologists, otolaryngologists, and rehabilitation specialists. In addition, referrals were made to community resources (ie, visiting nurses or home health aides) on the basis of the questionnaire, and communication was initiated with the patient’s primary care provider to assist in managing comorbid medical conditions that could be exacerbated by the cancer. The self-administered format of the geriatric assessment appeared to be feasible, with patients completing the questionnaire within an average of 15 minutes. The Cancer and Leukemia Group B (CALGB) is leading an effort to evaluate the feasibility of incorporating a primarily self-administered geriatric assessment into its ongoing protocols (CALGB 360401). Efforts such as these may ultimately aid in prospectively validating the stratification of treatment by geriatric assessment result.

**Biological Markers of Frailty**

Emerging laboratory research has identified molecular markers that may be associated with frailty. With increasing age, levels of the proinflammatory cytokine interleukin-6 (IL-6) and C-reactive protein (CRP) demonstrate concomitant increases. Both appear to play a role in the development of the frailty criteria established in the CHS, including weight loss. Hubbard et al assessed frailty characteristics and cytokine levels in 3 groups of patients: 1) 40 patients housed in an inpatient geriatric ward (median age, 85 years), 2) 40 patients attending a day hospital (median age, 83 years), and 3) 30 healthy controls (median age, 23 years). Increases in IL-6 and CRP were paralleled by a decrease in BMI and increasing frailty. In separate studies, increases in IL-6 and CRP have been associated with other domains of the frailty assessment, including poor walking speed and grip strength. In addition, D-dimer and other coagulation markers may play a prog-
nostic role in this population. An assessment of IL-6 and D-dimer in 1723 older adults indicated that higher circulating levels of these markers were correlated with an increased risk of mortality.\textsuperscript{101} Furthermore, D-dimer, factor VIII, and CRP levels in 4735 patients enrolled in the CHS were found to be associated with clinical frailty.\textsuperscript{102}

Levels of insulin-like growth factor 1 (IGF-1) decline with advancing age, and there is some indication that this molecular mediator may also play a key role in the pathogenesis of frailty.\textsuperscript{103,104} In the WHAS I study, low IGF-1 and high IL-6 levels were associated with a marked increase in walking limitation. Furthermore, in the subset of patients with low IGF-1 and high IL-6 levels, an increase in mortality was observed; at 5 years of follow-up, approximately 46% of these patients had died compared with 23% of patients with high IGF-1 and low IL-6 levels.\textsuperscript{105} Levels of CXC chemokine ligand 10 (CXCL10) have also been associated with the development of frailty.\textsuperscript{106} CXCL10 is a proinflammatory chemokine associated with several autoimmune diseases, such as multiple sclerosis and autoimmune thyroiditis.

The molecular markers noted to predict frailty may also play a prognostic role in the setting of cancer. For example, elevated CRP has been associated with poorer survival in patients with localized renal cell carcinoma, and high D-dimer has been shown to predict poorer survival and disease progression in patients with metastatic colorectal cancer.\textsuperscript{107,108} In addition, IL-6 may be associated with a poorer prognosis in patients with breast cancer, perhaps by up-regulating levels of angiogenic mediators such as vascular endothelial growth factor.\textsuperscript{109} Elevated IL-6 has also been linked to worsened clinical outcome in patients with advanced non–small cell lung cancer, and may be useful in differentiating hormone-refractory prostate cancer from hormone-sensitive disease or benign prostatic conditions.\textsuperscript{110,111} Ultimately, these molecular markers may guide therapy for the older adult with cancer. Several of these markers (IL-6, IGF-1, and CXCL10) serve as targets for anticancer agents currently in development.\textsuperscript{73,112,113}

**Frailty as a Dynamic Process: The Potential for Intervention**

Regardless of the schema used to classify frailty, the imperative is to find ways to identify transitions between clinical states (ie, from normal to prefrail, or from prefrail to frail) because these intermediaries offer opportunities for intervention. Data from the CHS did identify a greater risk for the development of frailty in those patients characterized as prefrail.\textsuperscript{115} For example, patients classified as prefrail at baseline (demonstrating 1 or 2 frailty characteristics) were found to have more than double the risk of becoming frail at 3 to 4 years of follow-up (OR, 2.63; 95% CI, 1.94-3.56 \([P < .001]\)). A prospective exploration of this phenomenon was reported by Gill et al, in which 754 community-dwelling individuals aged 70 years and older were assessed for frailty at 18-month intervals for a total of 54 months.\textsuperscript{114} Using the CHS frailty markers, it was noted that greater than half of the patients (58%) experienced a transition in frailty status during the evaluation period. Transitions between nonfrail and prefrail states were consistent throughout the study period; in contrast, the probability of going from the frail to the prefrail state decreased over time; only 2 patients had their status change from frail to nonfrail. With extended follow-up, the probability of death in the frail group increased over time. The likelihood of death in this group of patients compared with the nonfrail or prefrail groups was 3 to 5 times higher, depending on the study period. This suggests that frailty represents a dynamic process, underscoring the potential for developing strategies to impede its progression.

Efforts are currently ongoing in the search for ways to reduce the progression of functional decline. A randomized trial in frail adults comparing those receiving intensive, home-based physical and occupational therapy with those undergoing a less rigorous educational program indicated that the level of disability (defined by ADL dependence) declined more rapidly in the patients in the latter group.\textsuperscript{115} Intervention studies have aimed to mitigate functional decline in oncology patients through various targeted approaches. One such study identified 641 overweight patients aged 65 years and older with breast, colorectal, or prostate cancer.\textsuperscript{116} These patients were randomly assigned to receive either a 12-month, home-based program of telephone counseling with mailed materials promoting sound physical activity and dietary practices or the same intervention after a 12-month period (representing the “delayed” arm). In comparison with the delayed intervention, immediate use of the intervention led to a lesser decline in physical function, as classified by the Short-Form 36 metric.\textsuperscript{117,118}
Emerging data have suggested that pharmacologic interventions might decrease the risk of frailty. An analysis of nonfrail participants (ages 65–79 years) enrolled in the Women’s Health Initiative Observational Study demonstrated a significant association between the use of low-dose statins for a prolonged period and a decrease in the risk of frailty, as defined by CHS criteria ($P = .02$).\(^\text{119}\) The authors postulate that reductions in inflammatory mediators (ie, IL-6 and CRP) associated with statin therapy could lead to declines in frailty characteristics. These data are particularly provocative in the face of studies that have reported an association between breast cancer and statin use.\(^\text{120-124}\)

**Conclusions**

Several definitions of frailty have been described to date, including those derived from the CHS, the CSHA, and empiric criteria as defined by Balducci et al.\(^\text{15,16,28}\) The challenge for the oncologist is to incorporate elements from these definitions into a framework optimized for the older adult with cancer. The geriatric assessment may serve as the framework, because this tool includes components with independent prognostic implications for the older cancer patient. Assessing changes in molecular markers associated with frailty, such as IL-6, CRP, and D-dimer, may augment the algorithms used to stratify risk.

We are beginning to recognize that frailty is a dynamic process. This critical observation creates a window of opportunity for interventions. The geriatric oncology population would be an ideal one in which to study transitions in frailty, in which treatment and/or cancer may be associated with either transient or permanent functional decline. A better understanding of frailty in an oncology population may assist in identifying older adults who are candidates for palliative therapy, as well as those patients who may benefit from standard treatment. Ultimately, these data would guide the incorporation of frailty status into algorithms for therapeutic decision-making in cancer care, a much-needed step toward designing the best care for vulnerable adults.
25. Mauras N, Hayes V, Welch S, et al. Testosterone deficiency in young men: marked alterations in whole body protein kinetics, strength, and adiposity. J Clin Endocrinol Metab. 1998;83:1886-1892.

26. Higano CS. Side effects of androgen deprivation therapy: monitoring and minimizing toxicity. Urology. 2003;61:32-38.

28. Balducci L, Gerety MB, Chung M, et al. Screening for frailty: criteria and predictors of outcomes. J Am Geriatr Soc. 1991;39:778-784.

29. Balducci L, Extermann M. Management of the frail person with advanced cancer. Crit Rev Oncol Hematol. 2000;33:143-148.

31. Katz S, Ford AB, Moskowitz RW, et al. Social functional status as a predictor of mortality: results of a prospective study. Am J Med. 1992;93:663-669.

33. Rubenstein LV, Calkins DR, Greenfield S, et al. Health status assessment for elderly patients. Report of the Society of General Internal Medicine Task Force on Health Assessment. J Am Geriatr Soc. 1989;37:205-210.

34. Applegate WB, Blass JP, Williams TF. Comorbidity and disability in elderly Mexican and Mexican American adults: findings from Mexico and the Southwestern United States. J Aging Health. 2006;18:315-329.

35. Rubenstein LV, Calkins DR, Greenfield S, et al. Health status assessment for elderly patients. Report of the Society of General Internal Medicine Task Force on Health Assessment. J Am Geriatr Soc. 1989;37:562-569.

37. Applegate WB, Blass JP, Williams TF. Instruments for the functional assessment of older patients. N Engl J Med. 1990;322:1207-1214.

39. Patel KV, Peek MK, Wong R, et al. Comorbidity and disability in elderly Mexican and Mexican American adults: findings from Mexico and the Southwestern United States. J Aging Health. 2006;18:315-329.

41. Katz S, Ford AB, Moskowitz RW, et al. Social functional status as a predictor of mortality: results of a prospective study. Am J Med. 1992;93:663-669.

42. Audiosio RA, Ramesh H, Longo WE, et al. Depressive symptoms and the cost of health services in HMO patients aged 65 years and older: a 4-year prospective study. JAMA. 1990;264:2524-2528.

43. Yancik R, Ershler W, Satariano W, et al. Depression, hopelessness, and desire for hastened death in terminally ill patients with cancer. JAMA. 2000;284:2907-2911.

44. Walker J, Waters RA, Murray G, et al. Better off dead: suicidal thoughts in cancer patients. J Clin Oncol. 2002;20:4725-4750.

45. Miller M, Mogun H, Azrael D, et al. Cancer and the risk of suicide among Americans. J Clin Oncol. 2008;26:4720-4724.

46. Dy SM, Lorenz KA, Naeim A, et al. Evidence-based recommendations for cancer fatigue, anorexia, depression, and dyspnea. J Clin Oncol. 2008;26:3886-3895.

47. Ellis J, Lin J, Walsh A, et al. Predictors of referral for specialized oncosphychosocial oncology care in patients with metastatic cancer: the contributions of age, distress, and marital status. J Clin Oncol. 2009;27:699-705.

48. Stearns V, Johnson MD, Rae JM, et al. Active tamoxifen metabolite plasma concentrations after castration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine. J Natl Cancer Inst. 1993;95:1759-1764.

49. Seeman TE, Kaplan GA, Knudson L, et al. Social network ties and mortality among the elderly in the Alameda County Study. Am J Epidemiol. 1987;126:714-723.

50. Tomaka J, Thompson S, Palacios R. The relation of social isolation, loneliness, and social support to disease outcomes among the elderly. J Aging Health. 2008;20:359-384.

51. Osborne C, Ostor GV, Du X, et al. The influence of marital status on the stage at diagnosis, treatment, and survival of older women with breast cancer. Breast Cancer Res Treat. 2005;93:41-47.

52. Eagles JM, Beattie JA, Restall DB, et al. Relation between cognitive impairment and early death in the elderly. BMJ. 1990;300:239-243.

53. Laskow C, Wollson DB, Asgharian M, et al. A reevaluation of the duration of survival after the onset of dementia. N Engl J Med. 2001;344:1111-1116.

54. Gupta SK, Lamont EB. Patterns of presentation, diagnosis, and treatment in older patients with colon cancer and colon cancer in the elderly. J Am Geriatr Soc. 2004;52:1681-1687.

55. Goodwin JS, Hunt WC, Samet JM. Determinants of cancer therapy in elderly patients. Cancer. 1993;72:594-601.

56. Fried TR, Bradley EH, Towle VR, et al. Understanding the characteristics of seriously ill patients. N Engl J Med. 2002;346:1061-1066.

57. Yancik R, Ershler W, Satariano W, et al. Report of the national institute on aging task force on cancer and aging. J Gerontol A Biol Sci Med Sci. 2007;62:275-280.

58. Flood KL, Carroll MB, Le CV, et al. Polypharmacy in hospitalized older adult cancer patients: experience from a prospective, observational study of an oncology-
acute care for elders unit. Am J Geriatr Pharmacother. 2009;7:151-158.

77. Espino DV, Bazaldua OV, Palmer RF, et al. Suboptimal medication use and mortality in an older adult community-based cohort: results from the Hispanic EPESE Study. J Gerontol A Biol Sci Med Sci. 2006;61:170-175.

78. Hanlon JT, Pieper CF, Hajjar ER, et al. Incidence and predictors of all and preventable adverse drug reactions in frail elderly persons after hospital stay. J Gerontol A Biol Sci Med Sci. 2006;61:511-515.

79. Vinks TH, Egberts TC, de Lange TM, et al. Pharmacist-based medication review reduces potential drug-related problems in the elderly: the SMOG controlled trial. Drugs Aging. 2009;26:123-135.

80. Reynolds MW, Fredman L, Langenberg P, et al. Comprehensive geriatric assessment: a feasibility study. J Am Geriatr Soc. 2004;52:399-404.

81. Fagiolini U, Crasci A, Scraff L, et al. Increased cytokine production in mononuclear cells in elderly people. Eur J Immunol. 1994;24:2371-2378.

82. Roubenoff R, Harris TB, Abad LW, et al. Monocyte cytokine production in an elderly population: effect of age and inflammation. J Gerontol A Biol Sci Med Sci. 1998;53:M275-283.

83. Hubbard RE, O'Mahony MS, Calver BL, et al. Nutrition, inflammation, and leptin levels in aging and frailty. J Am Geriatr Soc. 2008;56:279-284.

84. Taaffe DR, Harris TB, Ferrucci L, et al. Cross-sectional and prospective relationships of C-reactive protein (C-cre) and interleukin-6 (IL-6) with physical performance in elderly persons: MacArthur studies of successful aging. J Gerontol A Biol Sci Med Sci. 2000;55:M275-283.

85. Cohen HH, Harris TJ, Pfeifer C. Coagulation and activation of inflammatory pathways in the development of functional decline and mortality in the elderly. Am J Med. 2009;126:148-153.

86. Garwood E, Kumar A, Baehner FL, et al. Statin use and breast cancer risk in a large population-based cohort. Breast Cancer Res Treat. 2008;109:573-579.

87. Kuoppala J, Lumminpää A, Pulkka E, et al. Statin use and breast cancer: a randomized controlled trial. Breast Cancer Res Treat. 2008;109:573-579.

88. Bialkowski S, van Dam FS, Muller MJ, et al. Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma. Cancer. 1999;85:640-650.

89. Schagen SB, van Dam FS, Muller MJ, et al. Cognitive dysfunction and chemotherapy: neuropsychological findings in perspective. Clin Breast Cancer. 2002;2(suppl 3):S100-S108.

90. Schagen SB, Muller MJ, Boogerd W, et al. Cognitive dysfunction and chemotherapy: neuropsychological findings in perspective. Clin Breast Cancer. 2002;2(suppl 3):S100-S108.

91. Popeck G, Nelis L, Sloane R, et al. Effects of home-based diet and exercise on functional outcomes among older, overweight long-term cancer survivors: RE-NEW: a randomized controlled trial. JAMA. 2009;301:1883-1891.

92. Wall JR, Sherrbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30:473-483.

93. McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-item short-form health survey (SF-36). II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care. 1993;31:247-263.

94. Nordstroem P, Ingemansson S, Johansson K, et al. Health-related quality of life in the elderly: a cross-sectional and longitudinal study of the MOS 36-Item Short Form Health Survey (SF-36) in an elderly population. Eur J Cancer. 2001;37:233-241.

95. Papadakis MA, Gudy D, Tierney MJ, et al. Insulin-like growth factor 1 and functional status in healthy older men. J Am Geriatr Soc. 1995;43:12.

96. Rehfeldt KE, Kjellman C, Thomsen S, et al. Cross-sectional and longitudinal associations between circulating interleukin-6 and physical performance in elderly persons. J Gerontol A Biol Sci Med Sci. 2004;59:M111-115.

97. Blackwell K, Wurtz H, Lieberman G, et al. Circulating D-dimer levels are better predictors of overall survival and disease progression than carcinomaembryonic antigen levels in patients with metastatic colorectal carcinoma. Cancer. 2004;101:77-82.

98. Ramsey S, Lamb GW, Aitchison M, et al. Evaluation of an inflammation-based prognostic score in patients with metastatic renal cell cancer. Cancer. 2007;109:205-212.

99. Caruso C, Lio D, Cavallone L, et al. Aging, longevity, inflammation, and cancer. Ann N Y Acad Sci. 2004;1028:1-13.

100. Drachenberg DE, Elgamal AA, Rowbotham R, et al. Circulating levels of interleukin-6 in patients with hormone refractory prostate cancer. Prostate. 1999;41:127-133.

101. Songur N, Kuru B, Kalkan F, et al. Serum interleukin-6 levels in patients with malnutrition and survival in patients with advanced non–small cell lung cancer. Tu-mori. 2004;90:196-200.

102. Schagen SB, van Dam FS, Muller MJ, et al. Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma. Cancer. 1999;85:640-650.

103. Schagen SB, Muller MJ, Boogerd W, et al. Cognitive dysfunction and chemotherapy: neuropsychological findings in perspective. Clin Breast Cancer. 2002;2(suppl 3):S100-S108.