

ARTICLE TITLE: Frailty and Cancer: Implications for Oncology Surgery, Medical Oncology, and Radiation Oncology

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After reading the article "Frailty and Cancer: Implications for Oncology Surgery, Medical Oncology, and Radiation Oncology," the learner should be able to:

1. Describe the associations of frailty with adverse clinical outcomes among patients being treated for cancer.
2. Review strategies for assessing frailty in an oncology setting.
3. Discuss implications of frailty in planning surgical, medical, and radiation anticancer therapies.

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Frailty and Cancer: Implications for Oncology Surgery, Medical Oncology, and Radiation Oncology

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Abstract: The concept of frailty has become increasingly recognized as one of the most important issues in health care and health outcomes and is of particular importance in patients with cancer who are receiving treatment with surgery, chemotherapy, and radiotherapy. Because both cancer itself, as well as the therapies offered, can be significant additional stressors that challenge a patient's physiologic reserve, the incidence of frailty in older patients with cancer is especially high—it is estimated that over one-half of older patients with cancer have frailty or prefrailty. Defining frailty can be challenging, however. Put simply, frailty is a state of extreme vulnerability to stressors that leads to adverse health outcomes. In reality, frailty is a complex, multidimensional, and cyclical state of diminished physiologic reserve that results in decreased resiliency and adaptive capacity and increased vulnerability to stressors. In addition, over 70 different measures of frailty have been proposed. Still, it has been demonstrated that frail patients are at increased risk of postoperative complications, chemotherapy intolerance, disease progression, and death. Although international standardization of frailty cutoff points are needed, continued efforts by oncology physicians and surgeons to identify frailty and promote multidisciplinary decision making will help to develop more individualized management strategies and optimize care for patients with cancer. *CA Cancer J Clin* 2017;67:362–377. © 2017 American Cancer Society.

Keywords: complications, Comprehensive Geriatric Assessment, Frailty Index, phenotypic frailty, survival

Practical Implications for Continuing Education

- > The concept of frailty has become increasingly recognized as one of the most important issues in health care and health outcomes and is of particular importance in patients with cancer who are undergoing surgery, chemotherapy, and radiotherapy. However, defining frailty can be challenging.
- > Frailty is a complex, multidimensional, and cyclical state of diminished physiologic reserve that results in decreased resiliency and adaptive capacity and increased vulnerability to stressors.
- > It has been demonstrated that frail patients are at increased risk of postoperative complications, chemotherapy intolerance, disease progression, and death. Although international standardization of frailty cutoff points is needed, continued efforts by oncology physicians and surgeons to identify frailty and promote multidisciplinary decision making will help to develop more individualized management strategies and optimize care for patients with cancer.

Introduction

Over the last few decades, the concept of frailty has become increasingly recognized as one of the most important issues in health care and health outcomes. Approximately 10% to 20% of patients ages 65 years and older present with frailty, and that incidence doubles in those ages 85 years and older.^{1,2} As the population continues to age, the burden of frailty is anticipated to become even greater.

TABLE 1. Adverse Health Outcomes Associated With Frailty

General risks
Falls
Disability
Comorbid conditions
Cognitive decline
Hospitalization
Functional dependence
Institutionalization
Health care-associated complications
Social withdrawal
Death
Cancer-specific risks
Chemotherapy intolerance
Treatment-associated complications
Disease recurrence/progression

Frailty is of particular importance in cancer. The elderly make up a significant proportion of patients diagnosed with cancer and account for approximately 80% of cancer deaths each year.³ Given that both cancer itself as well as the therapies offered can be significant additional stressors that challenge a patient's physiologic reserve, the incidence of frailty in older patients with cancer is especially high.⁴ Indeed, over one-half of older patients with cancer have frailty or prefrailty, and these patients are at increased risk of postoperative complications, chemotherapy intolerance, disease progression, and death (Table 1).⁵⁻¹³

This article will elaborate on the concept of frailty with a focus on cancer and will examine the important and

dynamic role frailty plays in the management and outcomes of patients with cancer in the context of 3 primary treatment modalities: surgery, chemotherapy, and radiation.

Defining Frailty

Several definitions of frailty have been proposed, and although no single operational definition can satisfy all, a clear conceptual framework for frailty has been established. Put simply, frailty is a state of extreme vulnerability to stressors that leads to adverse health outcomes (Table 1).⁵⁻¹³ In reality, however, frailty is a complex, multidimensional, and cyclical state of diminished physiologic reserve that results in decreased resiliency and adaptive capacity and increased vulnerability to stressors (Fig. 1).¹³⁻¹⁶ It is a condition marked by a decline in multiple physiologic systems, often in an age-related fashion (although not exclusively) and has been described as both a predisability state as well as coexisting with, although decidedly distinct from, disability and chronic disease (Fig. 2).^{16,17} Frailty has also been associated with the concept of health deficits, which, when accumulated over time, heighten an individual's vulnerability to adverse health outcomes.^{2,18-20}

The term "prefrailty" is sometimes used to describe patients who may be at risk for frailty. Although no exact definition exists, these patients typically have some components of a frailty measure but not enough to meet the defined frailty cutoff.²¹⁻²³ Similar to frailty, although prefrailty is often thought of as an age-related condition, it is critical to recognize that it also can exist in young patients.

Measuring Frailty

Current recommendations state that all patients older than 70 years and those with significant weight loss (>5%) because of chronic illness should be screened for frailty.²⁴ Which frailty

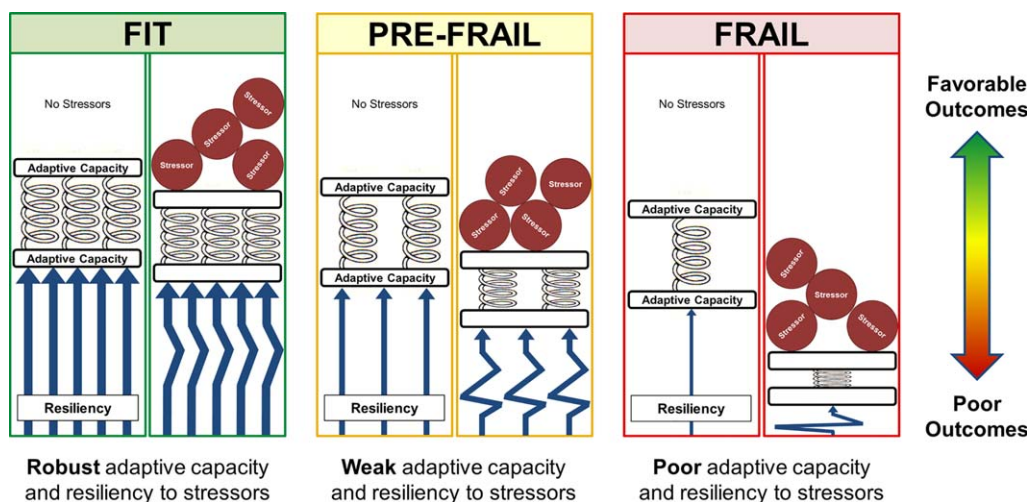


FIGURE 1. A Model for Defining Frailty. Fit patients have robust adaptive capacity and resiliency to stressors, which leads to more favorable outcomes. Prefrail patients have weakened adaptive capacity and resiliency to stressors, and frail patients have poor adaptive capacity and resiliency to stressors. Prefrail and frail patients are at greater risk of poor outcomes following surgery, chemotherapy, and radiotherapy. Figure adapted from: Robinson TN, Walston JD, Brummel NE, et al. Frailty for surgeons: review of a National Institute on Aging conference on frailty for specialists. *J Am Coll Surg.* 2015;221:1083-1092.¹³

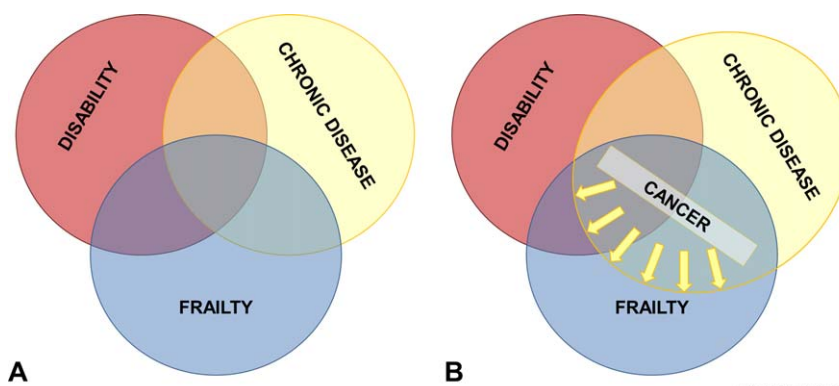


FIGURE 2. The Overlapping Existence of Frailty With Disability and Chronic Disease (A). When chronic disease includes cancer, patients are at greater risk of having disability and frailty (B).

measure is optimal for screening and assessment, however, is not clear. Over 70 different tools exist to measure frailty, few of which have been validated, and they range from a single item being measured to more than 90 items. They also vary in their intended purpose, with some frailty measures being designed as screening tools to risk-stratify patients, and others as more formal frailty assessments with the intention to guide treatment strategy and modify outcomes. In addition, it can be challenging to distinguish between certain frailty measures, which tend to have a broader and more multidimensional scope, and other, more focused risk-assessment tools, such as comorbidity indices, because they can have several overlapping features. A brief overview of several of the most commonly used frailty assessment tools are listed below.

Individual Assessment Tools

Using a single-item assessment tool is a quick and easy way to quantify a patient’s level of frailty. The most commonly used single-item tools that have been shown to be reliably predictive of frailty and other specific outcomes are gait speed (the measured time it takes for the patient to walk a 5-meter distance), a Timed Up-and-Go score (the measured time it takes for the patient to rise from a chair, walk 10 feet, turn around, and return to being seated), and sarcopenia (muscle wasting based on morphometric measurements, including lean muscle area, volume, and density).²⁵⁻³⁴ Although these single-item measurements make up some of

the components of other, more robust assessment tools and can be attractive to use in a busy and time-constrained environment, they can also lack sensitivity and specificity and, when in isolation, should be used with caution.

The FRAIL Scale

Developed by the Geriatric Advisory Panel of the International Academy of Nutrition and Aging, the FRAIL scale is a validated screening tool consisting of 5 straightforward questions (Table 2).^{25,35} Because it can be self-administered and does not require a face-to-face examination, this tool can be an efficient and cost-effective way to screen large groups of patients for frailty. However, the FRAIL scale is used most frequently in a primary care or community settings, and it has not been studied extensively as a screening tool in patients with cancer.^{36,37}

The Vulnerability Elders Survey-13

The Vulnerability Elders Survey-13 (VES-13) is a self-administered survey that consists of 13 items: 1 item for age and 12 that assess health, functional capacity, and physical performance (Table 3).^{38,39} The VES-13 is a practical screening tool that has been reported as a reliable marker of frailty in patients with cancer, although it may be inaccurate because of patient overestimation of their own competencies.⁴⁰⁻⁴³

Phenotypic Frailty

Phenotypic frailty is one of the most widely used frailty measurement tools in oncology and has been recognized as one of the optimal strategies for assessing elderly patients preoperatively by the American College of Surgeons (ACS) and the American Geriatric Society.⁴⁴ Phenotypic frailty, also known as physical frailty, is based on the idea that frailty is a result of age-related biological changes across multiple domains, such as nutrition and energy metabolism. When these changes manifest as clinical signs and symptoms, such as weight loss and decreased energy level, they result in the development of a frail phenotype, which can be

TABLE 2. The FRAIL Scale^a

F	Fatigue (Do you feel tired most or all the time?)
R	Resistance (Can you climb 1 flight of stairs without difficulty?)
A	Ambulation (Can you walk 1 block without assistance?)
I	Illness (Do you have greater than 5 illnesses?)
L	Loss of weight (Have you lost > 5% of your usual weight in the last year?)

^aScoring: 0 indicates robust; 1-2, prefrail; ≥ 3, frail.

TABLE 3. Vulnerable Elders Survey-13

CATEGORY	POINTS ^a
Age, y	
<75	0
75-84	1
≥85	3
Self-rated health	
Good, very good, or excellent	0
Fair or poor	1
Physical disability	
1) Stooping, crouching, or kneeling	
2) Lifting or carrying objects as heavy as 10 lbs	
3) Reaching or extending arms above shoulder level	
4) Writing or handling and grasping small objects	
5) Walking one-quarter of a mi	
6) Doing heavy housework	
No. of items done with difficulty:	
0 items	0
1 item	1
≥2 items	2
Functional disability	
1) Shopping for personal items	
2) Managing money	
3) Walking across the room	
4) Doing light housework	
5) Bathing or showering	
No. of items requiring assistance because of health/physical condition	
0 items	0
≥1 items	4

^aScoring: ≥ 3 points indicates frail.

concretely measured.^{10,16} Phenotypic frailty focuses on 5 criteria—size (weight), strength, energy, speed, and activity—and requires a combination of questionnaires and in-office assessments (Table 4).^{6,10,11,16,21,22,45,46}

The Frailty Index and the Modified Frailty Index

The Frailty Index was developed from the Canadian Health and Aging Study and is based on a cumulative deficit model.⁴⁷ This model proposes that the accumulation of medical, social, and functional deficits over a person's lifetime leads to a non-specific, age-associated vulnerability, or frailty (Fig. 3).^{13,18,19}

The original proposed Frailty Index includes 70 items, which range from vague to very specific signs, symptoms, diseases, and disabilities. The number of deficits present (ie, health problems or abnormal characteristics) are added, then divided

by the total number assessed to obtain a frailty score.⁴⁷ Although many of the included items can be found in patient charts, several require more cumbersome and labor-intensive assessments, which makes the Frailty Index less attractive in routine clinical practice. More recently, Obeid et al proposed a modified Frailty Index (mFI), which maps the 70 variables from the original Frailty Index to 11 preexisting variables from the National Surgical Quality Improvement Program (NSQIP) database, and has since been endorsed by the ACS (Table 5).^{29,48}

The Comprehensive Geriatric Assessment

One of the most extensively studied and used tools in oncology, the Comprehensive Geriatric Assessment (CGA), is a multidimensional and multidisciplinary assessment process to identify and manage elderly patients.^{49,50} By using principles similar to those used in the cumulative deficit model, the CGA focuses on several domains of a patient's medical, psychosocial, and functional capabilities and, when used as a screening tool (based on the number of abnormal domains), can be a reliable measure of frailty in patients with cancer.⁴² According to the International Society of Geriatric Oncology guidelines, the domains of a CGA should include functional status, comorbidity, cognition, mental health status, nutrition, social status and support, fatigue, polypharmacy, and geriatric syndromes.⁵⁰ However, with 64 instruments of measurement, each of which contain anywhere from a single item to over 2 dozen items, administering a full CGA can take hours to complete and is often impractical. Furthermore, which and how many tools are most appropriate to adequately measure these domains is unclear, and the cutoffs imposed to define frailty vary greatly from study to study.⁵

Because of these challenges, some have advocated for a 2-step approach, using simpler frailty measures as screening tools to identify those patients who might benefit from a full CGA.⁵¹ Others have modified the CGA to address these issues. For example, the Cancer-Specific Geriatric

TABLE 4. Phenotypic Frailty^a

Shrinking (weight loss)	≥10-lb weight loss in past y
Weakness	Grip strength in lowest 20% based on sex and body mass index
Exhaustion	Self-reported exhaustion, fatigue, and/or loss of motivation
Slow gait speed	Time it takes to walk 15 ft at normal speed
Low activity	Kilocalories of expenditure based on self-reported physical activities

^aScoring and cutoff points vary, based on the study: 0-1 indicates robust; 1-3, prefrail; 1 to ≥4, frail (see Kristjansson 2010,⁵ Makary 2010,¹⁰ Tan 2012,¹¹ Fried 2004,¹⁶ Bylow 2011,²¹ Courtney-Brooks 2012,²² Li 2016,⁴⁵ and Degesys 2011.⁴⁶

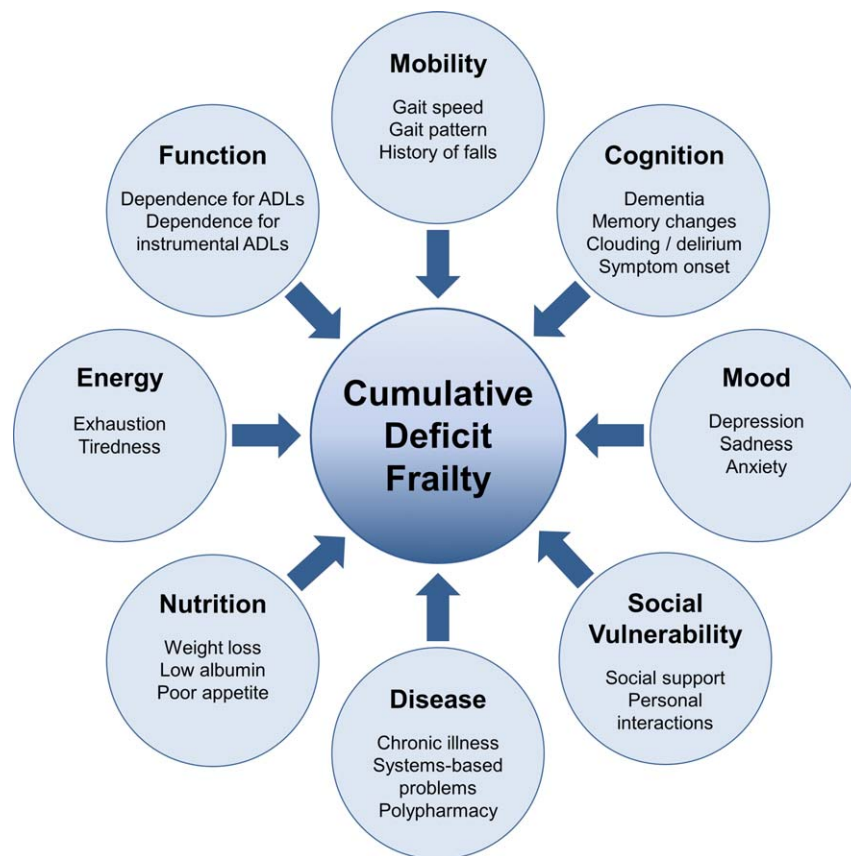


FIGURE 3. The Cumulative Deficit Model of Frailty, Which Proposes That the Accumulation of Medical, Social, and Functional Deficits Over a Person’s Lifetime Leads to a Nonspecific, Age-Associated Vulnerability, or Frailty. ADLs indicates activities of daily living. Figure adapted from: Robinson TN, Walston JD, Brummel NE, et al. Frailty for surgeons: review of a National Institute on Aging conference on frailty for specialists. *J Am Coll Surg.* 2015;221:1083-1092.¹³

Assessment (CSGA) is a brief and more focused tool that combines both self-administered and in-office assisted assessments.⁵² It includes 6 of the 9 domains from the full CGA, and the tools to measure those domains were specifically chosen for their reliability, validity, brevity, and prognostic ability in patients with cancer (Table 6).^{34,53-60}

Although it has been shown to be independently predictive of treatment-related toxicities, how the CSGA relates to frailty and other cancer-specific outcomes is currently unknown.⁶¹

Frailty Measures Beyond Age

Although frailty is typically associated with advanced age, it is important to understand that younger patients outside the geriatric population can have frailty as well. This is particularly true for patients with cancer, in whom the disease itself, and not necessarily age, may be responsible for the most significant or the only declines in physiologic reserve. This underscores the importance of assessing the extrinsic factors, such as the social context in which a patient lives, that contribute to frailty.

Social vulnerability is a measure of a patient’s social status and has been both associated with frailty and identified as an independent predictor of mortality.⁶²⁻⁶⁴ The Social Vulnerability Index was constructed based on a compilation of social-related factors from the Frailty Index and the National Population Health Survey and includes 5 domains: communication, living situation, social support, social engagement and leisure, empowerment and life control, and socioeconomic status.⁶² Although social vulnerability has been studied most in elderly patients, its applicability to patients with

TABLE 5. Modified Frailty Index^a

Nonindependent functional status
History of diabetes mellitus
History of either chronic obstructive pulmonary disease or pneumonia
History of congestive heart failure
History of myocardial infarction
History of percutaneous coronary intervention, cardiac surgery, or angina
Hypertension requiring the use of medications
Peripheral vascular disease or rest pain
Impaired sensorium
Transient ischemic attack or cerebrovascular accident without residual deficit
Cerebrovascular accident with deficit

^aModified Frailty Index indicates (total number of variables present)/(total number of variables assessed). Proposed cutoff score: > 0.36 indicates frail.

TABLE 6. Cancer-Specific Geriatric Assessment

ASSESSMENT	INSTRUMENT	REFERENCE
Functional Status	Activities of Daily Living (from MOS Physical Health Scale)	Stewart 1992 ⁵³
	Instrumental Activities of Daily Living (from OARS questionnaire)	Fillenbaum & Smyer 1981 ⁵⁴
	Karnofsky physician-rated performance rating scale	Yates 1980 ⁵⁵
	Karnofsky self-reported performance rating scale	Loprinzi 1994 ⁵⁶
	Timed Up-and-Go	Podsadlo & Richardson 1991 ³⁴
	No. of falls in last 6 mo	
Comorbidity	Physical Health Section (from OARS questionnaire)	Fillenbaum & Smyer 1981 ⁵⁴
Cognition	Blessed Orientation-Memory-Concentration test	Kawas 1995 ⁵⁷
Mental health	Hospital Anxiety and Depression Scale	Zigmond & Snaith 1983 ⁵⁸
Social functioning	MOS Social Activity Limitations Measure	Stewart 1992 ⁵³
Social support	MOS Social Support Survey (Emotional/Information and Tangible)	Stewart 1992 ⁵³
	Seeman and Berkman Social Ties	Seeman 1993 ⁵⁹
Nutrition	Body mass index	
	Percentage unintentional weight loss in the last 6 mo	White 2012 ⁶⁰
	Loss of muscle mass and/or body fat	White 2012 ⁶⁰

Abbreviations: MOS, Medical Outcomes Study; OARS, Older American Resources and Services.

cancer is age-independent. Thus, social status should be taken into consideration when evaluating any patient with malignancy. In addition, consultation with a social worker and access to a financial expert to discuss cost and coverage options for cancer treatment is strongly encouraged.

Frailty and Oncology Surgery

Surgery is an essential component of multimodality therapy, and often the only curative option, for many solid tumors. The decision regarding a patient's "fitness" for surgery, however, has traditionally been based on fairly subjective and overly simplistic measures, which can be limited in their ability to predict postoperative morbidity and mortality.^{32,65-69} The heterogeneity of patients with cancer, as well as the multisystem and multidimensional effects of both malignancy and surgery, underscore the importance of incorporating more comprehensive preoperative assessments into oncology surgery.

Because it moves beyond age or any single organ-system, it has been demonstrated that frailty is a stronger predictor of postoperative outcomes compared with several previous surgical risk-assessment tools, and it is increasingly recognized as a valuable measure in nononcologic surgical patients.^{10,70,71} For example, the mFI has been validated in several studies as a reliable measure of postoperative complications, discharge destination, and mortality in vascular, orthopedic, gynecologic, thoracic, and general surgeries.^{48,71-78} Similarly, it has been demonstrated that

phenotypic frailty is predictive of postoperative outcomes in patients presenting for elective surgery, including major abdominal and transplantation surgeries.^{10,45,70,79,80} In a study by Revenig et al, frailty was even predictive of postoperative complications among patients undergoing minimally invasive abdominal surgery.⁸¹

Although less well studied, there is a growing body of literature investigating the value of frailty specifically in oncologic surgery (Table 7).^{7,8,11,12,22,23,29,82-87}

Frailty and Survival

Frailty has been associated with worse long-term and short-term survival in patients undergoing surgery for a wide variety of malignancies. In a study of 176 patients undergoing colectomy for colorectal cancer, Kristjansson et al reported that frailty was associated with worse overall survival (OS), even when controlling for patient age and disease stage, using both phenotypic frailty (hazard ratio [HR], 2.67; 95% confidence interval [95% CI], 1.11-6.83 [$P = .029$]) and CGA-based frailty measures (HR, 3.39; 95% CI, 1.82-6.29 [$P < .001$]).²⁴ By using a CSGA-based frailty tool, Clough-Gorr et al observed worse 5-year and 10-year OS and disease-specific survival in patients undergoing resection for breast cancer.⁷ Lu et al used a frailty measure based on preoperative laboratory values (albumin < 3.4 g/dL, hematocrit $< 35\%$, and creatinine > 2 mg/dL) and similarly observed worse OS (HR, 1.613; 95% CI, 1.052-2.473 [$P = .028$]), disease-specific survival (HR, 1.606; 95% CI, 1.027-2.512 [$P = .038$]), and recurrence-free survival (HR,

TABLE 7. Summary of Studies Examining the Association of Frailty With Surgery-Related Outcomes

STUDY	CANCER TYPE	NO. OF PATIENTS	FRAILITY TOOL	OUTCOME DATA	SUMMARY OF RESULTS
Clough-Gorrr 2010 ⁸	Breast	660	CGA	Mortality	<ul style="list-style-type: none"> GA domains were associated with mortality, independent of age and stage of disease
Robinson 2011 ⁸²	Colorectal	60	CGA	Hospital cost, nonhome discharge, 30-d readmission	<ul style="list-style-type: none"> Increasing no. of GA measures was associated with increased hospital cost and with more frequent nonhome discharges and 30-d readmissions
Tan 2012 ¹¹	Colorectal	83	Phenotypic	Major complications	<ul style="list-style-type: none"> Frailty was associated with increased risk for major postop complications
Courtney-Brooks 2012 ²²	Gynecologic	40	Phenotypic	Postop complications, nonhome discharge, 30-d readmission	<ul style="list-style-type: none"> Frailty was associated with more frequent 30-d complications, but not with nonhome discharge or 30-d readmission
Kristjansson 2012 ²³	Colorectal cancer	176	Phenotypic, CGA	OS, postop complications	<ul style="list-style-type: none"> Both phenotypic frailty and CGA were associated with OS Only CGA was predictive of any and major postop complications
Clough-Gorrr 2012 ⁷	Breast	660	C-SGA	OS, DSS	<ul style="list-style-type: none"> Lower survival among patients with C-SGA ≥ 3 and decreased survival as the no. of deficits increased After adjusting for confounding factors, 2-fold higher death rate in women with ≥ 3 C-SGA deficits
Adams 2013 ⁸³	Head and neck	6727	mFI	Postop complications, mortality	<ul style="list-style-type: none"> Increasing mFI score was associated with higher risks of all complications, serious complications, and mortality
Lascano 2015 ⁸⁴	Urologic	41,681	mFI (15 variables) + ASA class	Major complications, 30-d mortality	<ul style="list-style-type: none"> Proposed 15-point mFI combined with ASA class was most predictive of major complications and 30-d mortality
Abt 2016 ⁸⁵	Head and neck	1193	mFI	Major complications, 30-d mortality	<ul style="list-style-type: none"> mFI was associated with major complications, but not 30-d mortality
Chappidi 2016 ⁸⁶	Bladder	2679	mFI	Major complications, 30-d mortality	<ul style="list-style-type: none"> Higher mFI was associated with major complications and overall mortality
Buettner 2016 ²⁹	GI malignancies	1326	mFI, sarcopenia	1-y mortality	<ul style="list-style-type: none"> Sarcopenia combined with other clinical factors was a stronger predictor of frail patients at highest risk of 1-y mortality after surgery compared with the mFI
Mogal 2017 ⁸⁷	Pancreas	9986	mFI	Postop morbidity, 30-d mortality	<ul style="list-style-type: none"> High mFI was associated with postop morbidity and mortality
Lu 2017 ¹²	Gastric	165	Preop frailty, inflammation-based prognostic scores	Postop complications, survival	<ul style="list-style-type: none"> Frailty was associated with increased risk of postop complications Frailty was associated with decreased OS, RFS, and DSS, while inflammation-based prognostic scores were not

Abbreviations: ASA, American Society of Anesthesiologists; CGA, Comprehensive Geriatric Assessment; C-SGA, Cancer-Specific Geriatric Assessment; DSS, disease-specific survival; GA, geriatric assessment; GI, gastrointestinal; mFI, modified Frailty Index; OS, overall survival; preop, preoperative; postop, postoperative; RFS, recurrence-free survival.

1.532; 95% CI, 1.030–2.252 [$P = .035$]) in frail patients undergoing resection for gastric cancer, even when taking into account other adverse clinicopathologic factors.¹² Several studies have demonstrated worse long-term survival in frail patients undergoing resection or transplantation for hepatocellular carcinoma using sarcopenia alone as a measure of frailty.^{88–91} In patients undergoing resection for

gastrointestinal malignancies, Buettner et al found the strongest association between frailty and 1-year mortality when sarcopenia was combined with age, preoperative hemoglobin, and Eastern Cooperative Oncology Group (ECOG) score.³⁰

By using the NSQIP mFI, frail patients demonstrated higher 30-day mortality rates compared with nonfrail patients

undergoing surgery for pancreas (6.3% vs 2.7%; $P < .001$), head and neck (11.9% vs 0.2%; $P < .001$), and bladder cancers (3.5% vs 1.8%; $P = .01$).^{83,86,87} Expanding the mFI to include 15 variables, Lascano et al observed that, in patients undergoing resection for urologic malignancies, there was a 2 to 6 times increased risk of death within 30 days for every 0.05 increase in calculated mFI compared with nonfrail patients (mFI < 0.05). Those authors also reported that combining their expanded mFI with American Society of Anesthesiologists (ASA) class yielded the highest sensitivity and specificity for mortality (C-statistic, 0.71) compared with either measure alone (C-statistic, 0.66 and 0.67, respectively).⁸⁴

Frailty and Postoperative Complications

Although it has been demonstrated using certain measures, the overall association between frailty and postoperative complications in patients with cancer is unclear. Although both are associated with worse survival, Kristjansson et al found that only CGA-based frailty was associated with higher rates of any complication ($P = .001$) and major complications (Clavien-Dindo grade \geq II; $P = .002$) after surgery for colorectal cancer, whereas phenotypic frailty is not associated with either ($P = .18$ and $P = .23$, respectively).^{6,24,92} Conversely, in their study of 83 patients undergoing resection for colorectal cancer, Tan et al reported that phenotypic frailty, in fact, was associated with major complications (Clavien-Dindo grade \geq II; odds ratio [OR], 4.083; 95% CI, 1.433-11.638 [$P = .006$]).¹¹ In patients who were undergoing resection for gastric cancer, Lu et al observed that frail patients were at significantly higher risk of systemic complications (OR, 6.063; 95% CI, 1.758-20.911 [$P = .004$]) but of not local, surgery-specific complications (OR, 1.650; 95% CI, 0.649-4.196 [$P = .293$]).¹² In a study by Abt et al of 1193 major head and neck cancer surgeries from the NSQIP database, although the mFI was not associated with composite “morbidity” (any complication, unplanned reoperation, and unplanned readmission), it was associated with major complications (Clavien-Dindo grade IV; OR, 1.65; 95% CI, 1.15-2.37 [$P = .007$]).⁸⁵ Lascano et al similarly reported that patients undergoing surgery for urologic malignancies with high frailty (mFI > 0.20) had a significantly increased risk of major complications (Clavien-Dindo grade IV) compared with nonfrail patients (OR, 3.70; 95% CI, 2.87-7.79 [$P < .0005$]). Frailty has also been associated with higher rates of complications in esophageal, pancreas, and gynecologic cancers, as well as in patients undergoing liver resection for primary liver tumors and colorectal liver metastases.^{23,31,87,93-96}

Frailty and Other Postoperative Outcomes

Very few studies have assessed the utility of frailty in patients with cancer as a predictor of postoperative

outcomes beyond mortality and specific in-hospital complications, and those that did have reported mixed results. By using a simplified CGA-type measure of frailty, Robinson et al found that frailty was associated with increased hospital cost (\$76,363 vs 27,731; $P < .001$), more frequent nonhome discharge (59% vs 0%; $P < .001$), and higher rates of 30-day readmission (32% vs 4%; $P = .044$) after surgery for colorectal cancer.⁸³ However, a study by Courtney-Brooks et al of 37 patients undergoing resection for gynecologic cancers demonstrated no significant association between frailty based on a phenotypic model and either nonhome discharge (0% vs 0%; $P = .25$) or 30-day hospital readmission (17% vs 5%; $P = .35$).²² Although there was no association between VES-13 frailty and any of the outcomes, Dale et al reported that, in patients undergoing pancreaticoduodenectomy, self-reported exhaustion, which is a component of phenotypic frailty, was associated with increased surgical intensive care admission (OR, 4.30; $P = .01$) and longer hospital length of stay ($\beta = 0.27$; $P = .02$), whereas the Short Physical Performance Battery test, which is a component of CGA-based frailty, was associated with increased nonhome discharge (OR, 1.49; $P = .04$). In that study, only age, but none of the frailty measures, was associated with 30-day readmissions.⁹⁷ In a study by Abt et al of patients undergoing major surgeries for head and neck cancer, there was no association between the mFI and unplanned readmissions (OR, 1.15; 95% CI, 0.52-2.55).⁸⁵

Using Frailty to Change Surgical Practice

Beyond a preoperative risk-assessment tool, frailty can be used potentially to improve and change practice in surgery. In recent study, Hall et al assessed 9153 patients who underwent surgery and participated in a preoperative Frailty Screening Initiative (FSI). On the basis of that initiative, if patients were identified as frail, then clinicians from surgery, anesthesia, critical care, and palliative care were notified; and perioperative plans were modified based on team input, if indicated. The authors reported reductions in 30-day, 6-month, and 1-year mortality after FSI implementation, which were particularly pronounced in frail patients (30-day mortality, 3.8% vs 12.2%; 6-month mortality, 7.7% vs 23.9%; 1-year mortality, 11.7% vs 34.5% [all $P < .001$]). Although no specific intervention was identified, nor causality assigned, that study emphasizes the potential efficacy of system-wide initiatives aimed at improving surgical outcomes in frail patients.⁹⁸

Prehabilitation

Using frailty to guide prehabilitation interventions, such as exercise and nutrition, before an operation may improve a frail patient’s physiologic reserve and outcomes after surgery. For example, it has been demonstrated that enrolling patients in preoperative physical therapy programs improves

pulmonary complications and shortens hospital lengths of stay after elective cardiac surgery.⁹⁹ Prehabilitation studies in patients undergoing surgery for malignancy, however, have been less promising. Although measurable improvements have been documented in certain physiologic variables with prehabilitation programs, including improved functional capacity and cardiopulmonary fitness, no studies have demonstrated decreased postoperative complications in patients undergoing surgery for malignancy.¹⁰⁰

Anesthesia considerations

Because the ability of frail patients to tolerate psychoactive medications is often impaired, the goals of anesthesia for frail patients should be to minimize sedation and optimize regional and nonnarcotic anesthetics. In a randomized controlled trial by Watkins et al, application of ice packs to abdominal wounds after major abdominal surgery, including for malignant indications, was associated with improved postoperative pain and decreased narcotics use.¹⁰¹ It has been demonstrated in several other studies that regional anesthetics reduce postoperative delirium and are recommended by the American Geriatrics Society whenever possible.¹⁰² Thus, knowledge of a patient's frailty status can help guide the choice of anesthetic and pain-control regimen used by anesthesiologists in the perioperative period. This point further underscores the importance of multidisciplinary communication that involves the entire management team when caring for frail patients.

Palliative care

Although it has long been associated with hospice and the care of terminal patients with cancer, over the last 2 decades, there has been increased recognition among the surgical community of the benefits of palliative care for surgical patients.^{103,104} It has been demonstrated that palliative care improves the quality of life for patients and their caregivers, particularly if sought out early in the disease process.¹⁰³ In 2005, the ACS released a statement acknowledging the critical role that palliative care plays in the management of a broad range of surgical patients, not just those at the end of life.¹⁰⁵ Thus, frailty assessments may help identify patients who would benefit most from early palliative care involvement, particularly for patients with cancer who are undergoing surgery.

In a study by Ernst et al examining the effects of the preoperative FSI mentioned above, the authors reported that, after initiation of the program, there was an increase in the rate of palliative care consultations (56 per year vs 32 per year) as well as an increase in the proportion of consultations that were requested by surgeons (56.7% vs 24.4%; $P < .05$) and occurred before surgery (52% vs 26.3%; $P < .05$). These findings coincided with an observed significant decrease in 30-day (21.3% vs 31.9%), 6-month (44% vs

70.6%), and 1-year mortality (66% vs 78.8%; all $P < .05$) among patients who were referred for palliative care, although no direct causal relationship was demonstrated. It is important to note that the authors also reported an increase in the proportion of patients who did not undergo surgery after implementation of the FSI (19.3% vs 5.6%; $P < .05$), suggesting that frailty screening may have prevented unnecessary operations in patients who might not have benefitted from surgery, may have been too high-risk, or perhaps did not really want surgery at all.¹⁰⁶ However, further studies to identify direct relationships between frailty screening, palliative care, and outcomes in surgical patients with cancer are needed.

The Future of Frailty in Oncology Surgery

In 2012, the ACS, along with the American Geriatrics Society, published guidelines recommending that frailty be assessed and documented preoperatively in all patients.⁴⁴ Still, surgeons have a long way to go. In a prospective study by Revenig et al comparing patients' self-assessments with their surgeons' subjective assessments of frailty, the authors found that, although surgeons' assessments were more strongly correlated with objective frailty measures compared with assessments by patients, surgeons tended to rely too heavily on a patient's chronologic age rather than objective measures of physiologic reserve.⁴³

More recently, the International Society of Geriatric Oncology conducted an international survey of oncology surgeons from the United States and Europe and found that, although age was not perceived as a direct prohibiting factor for surgery, screening for frailty was limited. Although 90% of respondents routinely used some sort of preoperative tool to assess surgical fitness (most commonly, ASA classification, performance status, and nutritional status), only 48% considered frailty screening a mandatory practice, and less than one-quarter used formal frailty measures to assess patients, such as the VES-13, the Frailty Index, and the CGA. Furthermore, only 19% of surgeons collaborated with geriatricians greater than 50% of the time to manage their oncogeriatric patients, whereas 36% never did.¹⁰⁷

Moving forward, continued efforts by oncology surgeons to recognize frailty as an important concept, incorporate screening measures as part of routine practice, and engage in multidisciplinary initiatives are required to help ensure that optimal management strategies and outcomes of patients with cancer undergoing surgery are achieved.

Frailty and Chemotherapy

Chemotherapy is widely used in the treatment of many cancers, particularly hematologic malignancies, and is commonly used as an adjunct to surgery and radiation in solid tumors. In addition to treatment with curative intent,

chemotherapy is used in the treatment of metastatic disease with the goal to slow disease progression and extend survival.¹⁰⁸ ECOG performance status (ECOG-PS) is commonly used for the clinical assessment of a patient's ability to tolerate treatment; however, ECOG-PS is an assessment of daily living activities and does not consider age, comorbidities, or other aspects of frailty.¹⁰⁹ Because the main sources of stress in these patients are the cancer itself and the agents used to treat the cancer, including chemotherapy, it is important to continually evolve care in patients with cancer, particularly in older populations. It is in this context that an assessment of frailty can inform the choice and dosage of chemotherapy, particularly for older patients who are underrepresented in standard clinical trials and typically have worse outcomes than younger patients.¹¹⁰⁻¹¹² To date, several studies from different parts of the world (the United States, Europe, Asia), in different care settings (inpatient or outpatient), and across many tumor types have recognized the role of frailty assessment for patient selection and "risk-stratification" for chemotherapy.^{5,50} Many of the previous studies reported the prevalence of frailty among patients with cancer, and few of those included outcome data.⁵ However, the most important limitations in the existing literature regarding chemotherapy and fragility are the retrospective nature of these studies, small sample size, and lack of power to determine clinically relevant changes.^{50,113} Table 8 summarizes the characteristics of some of the important frailty studies that have reported outcome data other than surgery.^{7,8,114-125}

Frailty and Chemotherapy Tolerance

Frailty as well as certain components of frailty assessment have been associated in several studies with a higher risk of chemotherapy-related toxicities and poor treatment tolerance. Hurria et al reported the results of a large prospective study from the Cancer and Aging Research Group that included 500 patients from 7 different institutions in the United States. The authors reported a significant association between grade 3, 4, and 5 toxicity and geriatric assessment variables.¹¹⁴ Another prospective study (Chemotherapy Risk Assessment Scale for High-Age Patients [CRASH]) similarly demonstrated that the CRASH score distinguished several risk levels of severe toxicity.¹¹⁹ Both of those studies included multiple different tumor types. In a study of elderly patients with metastatic breast cancer, Hamaker et al reported an association of frailty with both toxicity and survival. The study enrolled 78 patients with median age of 76 years, and frailty was defined as a CGA score ≥ 1 . Grade 3 and 4 chemotherapy-related toxicity was experienced by 19% of patients without geriatric conditions versus 56% of patients who had 2 geriatric conditions and 80% of those who had 3 or more geriatric conditions ($P = .002$).¹²²

Clough-Gorr et al evaluated geriatric assessment domains in relation to self-reported treatment tolerance and all-cause mortality in older survivors of breast cancer and found that some of the geriatric assessment domains were associated with poor treatment tolerance and mortality.⁸ Falandry et al investigated the impact of geriatric risk factors in a homogeneous group of patients with metastatic breast cancer who received treatment with pegylated liposomal doxorubicin and found that geriatric covariates were associated with severe hematological toxicities.¹²¹ Aparicio et al reported the association of geriatric factors and outcomes in patients with metastatic colorectal cancer who were about to start first-line chemotherapy. The authors concluded that geriatric factors, such as Mini-Mental Status Examination scores and Instrumental Activities of Daily Living, are predictive of severe toxicity or unexpected hospitalization.¹²⁰ In a small study of 112 newly diagnosed patients with cancer who were older than 65 years, the authors used 7 frailty markers and 4 functional status measures and found that the majority of the study population had one or more frailty marker(s), yet only low grip strength predicted toxicity.¹¹⁶ Shin et al evaluated the association between chemotherapy-related toxicity and CGA in 64 elderly Korean patients with cancer. Significant declines were seen after chemotherapy in ECOG-PS, activities of daily living, Instrumental Activities of Daily Living, Mini-Mental Status Examination scores, and short-form Geriatric Depression Scale assessments. Baseline ECOG-PS was an independent predictive factor of significant toxicity, and a mininutritional assessment was marginally associated with significant toxicity in univariate analysis.¹¹⁸ Biesma et al reported a phase 3 study in 181 chemotherapy-naive patients with advanced non-small cell lung cancer. In that study, pretreatment CGA and minigeriatric assessments during and after treatment were collected, and the CGA items were only related to neuropsychiatric toxicity.¹¹⁷ However, the authors performed further principal component analysis and found that CGA and QoL items measured one underlying dimension, which was highly prognostic.

Using Frailty to Guide Cancer Treatment

Current treatment planning in cancer care is based on physician discretion and clinical judgment. According to the existing literature, frailty and prefrailty are very common in patients with cancer, and those patients are at risk for treatment-related mortality and morbidity.^{5,50} Thus, routine assessment of older patients with cancer may help clinicians for both patient and treatment selection. The Elderly Selection on Geriatric Index Assessment (ESOGIA) is a landmark study published recently using the CGA to guide therapy decisions for elderly patients with advanced non-small cell lung cancer.¹²⁴ This was a prospective, open-label, randomized trial in patients ages 70 years or older who were

TABLE 8. Summary of Studies Examining the Association of Frailty With Chemotherapy-Related Outcomes

STUDY	CANCER TYPE	NO. OF PATIENTS	FRAILTY TOOL	OUTCOME DATA	SUMMARY OF RESULTS
Clough-Gorr 2010 ⁸	Breast	660	CGA	Treatment tolerance and all-cause mortality	<ul style="list-style-type: none"> GA domains were independently associated with poor treatment tolerance (clinical, psychosocial) and predicted mortality (sociodemographic, clinical, functional status, psychosocial), independent of age and stage of disease
Hurria 2011 ¹¹⁴	Multiple	500	CGA	Chemotherapy-related toxicity	<ul style="list-style-type: none"> GA variables were associated with grade 3-5 toxicity
Caillet 2011 ¹¹⁵	Multiple	375	CGA	Cancer treatment outcome	<ul style="list-style-type: none"> Functional status assessed by ADL score and malnutrition were independently associated with changes in cancer treatment
Puts 2011 ¹¹⁶	Multiple solid tumors	112	CIFA frailty markers/functional status	Treatment toxicity and 6-mo mortality	<ul style="list-style-type: none"> Toxicity predicted by low grip strength, but none of the functional measures
Biesma 2011 ¹¹⁷	Lung	181	CGA	QOL	<ul style="list-style-type: none"> ECOG performance status and ADL disability, but none of the CIFA frailty markers, predicted time to death CGA items were only associated with neuropsychiatric toxicity CGA and QOL items measure one underlying dimension, which is highly prognostic
Clough-Gorr 2012 ⁷	Breast	660	C-SGA	All-cause and breast-cancer-specific mortality	<ul style="list-style-type: none"> Lower survival among patients with C-SGA ≥ 3 and decreased survival as the number of deficits increased After adjusting for confounding factors, 2-fold higher death rate in women with ≥ 3 C-SGA deficits
Shin 2012 ¹¹⁸	Multiple	64	CGA	Chemotherapy-related outcome	<ul style="list-style-type: none"> Baseline ECOG PS was an independent predictive factor of significant chemotherapy-related toxicity
Extermann 2012 ¹¹⁹	Multiple	518	CGA/CRASH score	Chemotherapy-related toxicity	<ul style="list-style-type: none"> GA variables comprising the CRASH score were associated with hematologic and nonhematologic toxicities
Aparicio 2013 ¹²⁰	Colon	123	CGA	Chemotherapy-related outcome	<ul style="list-style-type: none"> GA factors were predictive for: <ul style="list-style-type: none"> Grade 3-4 toxicity: MMSE $\leq 27/30$, and impaired IADL Dose-intensity reduction: alkaline phosphates $> 2 \times$ ULN Unexpected hospitalization: MMSE $\leq 27/30$ and GDS ≤ 2
Falandryr 2013 ¹²¹	Breast	60	CGA	Chemotherapy-related outcome	<ul style="list-style-type: none"> Age ≥ 80 y and living in residential homes were associated with nonhematologic toxicities Age, deficiency in IADL, cardiac dysfunction, and living in residential homes were associated with decreased PFS Living in residential homes was associated with decreased OS
Hamaker 2014 ¹²²	Breast	78	CGA	Chemotherapy-related toxicity	<ul style="list-style-type: none"> Grade 3-4 chemotherapy-related toxicity observed in 19% of patients without deficits, 56% of those with 2 deficits, and 80% of those with ≥ 3 deficits
Sastrer 2015 ¹²³	Colorectal	33	CGA	Chemotherapy-related outcomes	<ul style="list-style-type: none"> No deaths or grade 4-5 adverse events were related to panitumumab in frail patients
Correr 2016 ¹²⁴	Lung	494	CGA	Treatment failure, OS, PFS, toxicity	<ul style="list-style-type: none"> No association between CGA arm and TFFS or OS Fewer treatment failures and toxicities observed in CGA arm
Meresse 2017 ¹²⁵	Breast	223	Age	Chemotherapy-related toxicity	<ul style="list-style-type: none"> Patients ages 75-80 y received chemotherapy treatment less often than younger patients No differences in toxicity

Abbreviations: ADL, activities of daily living; CGA, Comprehensive Geriatric Assessment; CIFA, Canadian Institute on Frailty and Aging; CRASH, Chemotherapy Risk Assessment for High-Age Patients; C-SGA, Cancer-Specific Geriatric Assessment; ECOG, Eastern Cooperative Oncology Group; GA, geriatric assessment; GDS, Geriatric Depression Scale; IADL, independent activities of daily living; MMSE, Mini-Mental Status Examination; OS, overall survival; PFS, progression-free survival; QOL, quality of life; TFFS, treatment failure-free survival; ULN, upper limit of normal.

randomly assigned to the CGA to assess fitness versus “standard care” (PS and age). In the CGA arm, “fit” patients received carboplatin-based doublet, vulnerable patients received docetaxel, and frail patients received supportive care. In the standard care arm, carboplatin was given to patients ages 75 years and younger who had a PS ≤ 1 , and docetaxel was given to patients ages 75 years and older who had a PS > 2 . Although there was no statistical difference in OS or treatment failure-free survival between the CGA and standard care groups, patients in the CGA group experienced less toxicity (all grades) and had less treatment failure because of toxicity. Despite the lack of difference in OS, the ESOGIA study indicates that the CGA (as a frailty assessment) is useful in increasing access to chemotherapy for “fit” patients and is not associated with increased toxicity during treatment.¹²⁴

Sastre et al reported the results of a prospective clinical trial of first-line, single-agent panitumumab in frail elderly patients (ages ≥ 70 years, intermediate-risk or high-risk according to the Kohne prognostic classification, and frailty and/or ineligibility for chemotherapy) with metastatic colorectal cancer. Those authors reported a median progression-free survival of 4.3 months and a median OS of 7.1 months. There were no deaths or grade 4 or 5 adverse events related to panitumumab, leading the authors to suggest that single-agent panitumumab may be a therapeutic option for high-risk, frail elderly patients who are not considered candidates for chemotherapy.¹²³

For multiple myeloma, a specific CGA has been developed by the International Myeloma Working Group to categorize a patient’s level of fitness as fit, intermediate, or frail.¹²⁶ There are recommended treatment regimens for each group (particularly dosing and schedule). For fit patients, first-line treatments are recommended (bone marrow transplantation, if eligible, or lenalidomide). For patients of intermediate fitness, decreased doses of first-line agents are recommended. For frail patients, steroids for supportive/palliative care are recommended. The aim of these recommendations is to minimize treatment interruption because of toxicities. However, to date, no study has shown an increase in OS or progression-free survival after treatment stratification according to frailty level, and further investigation is required to establish international standardization of cutoff points for frailty and optimal geriatric parameters to guide clinical practice.¹²⁶

Frailty and Radiotherapy

As with surgery and chemotherapy, there is an increasing clinical need to use frailty to guide patients’ treatment

decisions and to understand the outcomes of patients who receive radiotherapy. Many times patients, and potentially physicians, may have a bias that radiotherapy may be quite acceptable for frail patients. Nonetheless, this important point has remained understudied. Although it has been found that frailty generally influences decision making in a few select disease sites in which radiotherapy is administered (eg, radical radiotherapy vs surgery for early-stage lung cancer and active surveillance vs treatment in prostate cancer), the literature in the link between frailty and radiotherapy decision making is underdeveloped.^{127,128} Some progress has been made, however, in analyzing frailty and radiotherapy outcomes. In a recent effort evaluating several factors that influence radiotherapy completion and toxicity, Spyropoulou et al found that age was not a predictor of radiation-induced toxicity, which has motivated others to consider the role of frailty in predicting radiotherapy toxicity.¹²⁹ One recent report by Keenan et al used the Edmonton Frail Scale, which was identified as predictive of all-cause mortality in general medical patients, to determine correlations with radiotherapy side effects across all disease sites.¹³⁰⁻¹³² An analysis of 63 recruited patients revealed that 29% had grade 3 or higher toxicity, but no statistical correlation was observed between the Edmonton Frail Scale score and toxicity.¹³⁰ Clearly, efforts to examine the role of frailty in the setting of radiotherapy are very preliminary, and much additional research is needed to determine the role that frailty should play in radiotherapy treatment decisions and the impact of frailty on radiotherapy cancer control and toxicity outcomes.

Conclusions

Frailty is emerging as one of the most important determinants of health and health outcomes. Despite the wide, and often overwhelming, variety of frailty measures, the concept of frailty is increasingly being recognized specifically in patients with cancer and has been identified as a predictor of postoperative complications, chemotherapy intolerance, disease progression, and death. Still, further research, specifically in the context of clinical trials, is needed to develop a standardized definition of and cutoff points for frailty and, critically, to better understand the value of frailty to patient care. Continued efforts by oncology physicians and surgeons to identify frailty, incorporate frailty concepts into training curricula, and promote multidisciplinary decision making will help to develop more individualized management strategies and optimize care for patients with cancer. ■

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