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REVIEW

Frailty and Cancer: Current Perspectives on Assessment and Monitoring

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Abstract: Frailty, an age-related condition of increased vulnerability to acute endogenous or exogenous stressors, is a key barrier to successful treatment of cancer in older people. In this group of patients, assessment of frailty is required before starting a new treatment. According to guidelines, the gold standard to assess frailty in older adults with cancer is geriatric screening followed by geriatric assessment (GA) across essential GA-domains (social status, physical function, nutrition, cognition, emotion, co-morbidity, polypharmacy). GA enables tailoring of both oncological therapy and non-oncological interventions to the patient's vulnerabilities. Large clinical trials recently have demonstrated that the feasibility and tolerability of systemic cancer treatment in older patients are significantly improved by such GA-guided management. Indications and optimal tools for frailty monitoring during the course of cancer treatment have not yet been defined in greater detail. New technologies such as wearable sensors or apps offer promising new opportunities to further develop frailty monitoring. This review describes the current standards and perspectives for the assessment and monitoring of frailty in elderly patients with cancer.

Keywords: cancer, frailty, geriatric screening, geriatric assessment

Introduction

Every year, 20 million new cancer cases occur worldwide.[1] Incidence rates are low in younger people, but show a steep increase in older adults.[2] In the United States, for example,[3] the incidence in people up to the age of 50 years is less than 500 per 100,000 inhabitants a year. For those over 70 years, however, it is four times higher. Approximately 30% of US patients newly diagnosed with cancer are 65 to 74 years old. Another 25% are 75 years or older. Comparable incidence rates across age groups have been reported for other regions and countries.[2]

Unlike younger patients with cancer, vulnerable older subjects are more susceptible to unfavorable health events and medical complications during the clinical course. "Frailty" is an established term to describe aging-associated vulnerability,[4–7] and it has been recognized as a main obstacle of cancer therapy in patients of advanced age.[8,9] With frailty, longer lasting therapeutic success is more difficult to achieve. For example, frailty increases the risk of chemotherapy intolerance and of poorer treatment response.[10,11] Patients with frailty undergoing cancer surgery have an increased likelihood of post-operative complications.[5,12] Advanced frailty may also pose competing risks of morbidity and mortality independent of cancer and its treatment. The prevalence of frailty in older adults with cancer is around 40–50% with a wide range from 5% to 90% depending on the patient population and the method used to assess frailty.[8,13]

Over the past two decades, huge efforts have been made in order to optimize the detection and quantification of frailty in such patients. The basic underlying idea was to determine a patient's individual degree of frailty at baseline (ie, before the start of cancer therapy) and to use this information to adjust the oncological treatment.[14] This includes the decision whether the patient should receive tumor therapy or not as well as the choice of the most adequate treatment modality and regimen (eg, standard versus gentler therapy).[15] The principle of using information from a frailty evaluation to therapeutically target this condition with suitable interventions has been established in geriatric medicine for a long time but just recently adopted to the oncological context.[16]

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International and national medical societies (eg, International Society of Geriatric Oncology [SIOG], American Society of Clinical Oncology [ASCO]) have developed detailed recommendations for the assessment of frailty in older adults prior to the initiation of cancer therapy.[17–19] There is a growing understanding that frailty in older patients with cancer is not a static biomarker that just needs to be recorded at a single point in time to make final treatment decisions.[20,21] Instead, frailty in such individuals is subject to dynamic changes throughout a patient's remaining lifespan. This raises the question whether and for what specific purposes frailty should be recorded repeatedly during cancer therapy. Compared to the amount of guidance that is available for the initial frailty assessment in older adults with cancer, there is surprisingly little advice on frailty monitoring so far.

This narrative review makes the effort to summarize the latest advances in the conceptualization of frailty in the context of cancer. The focus is on the increasingly important link between frailty evaluation and frailty interventions as well as the re-evaluation of frailty during cancer treatment. A PubMed search was performed by using variations of the following global search term: [cancer OR tumor] AND [frailty OR geriatric] AND [screening OR assessment OR management OR evaluation OR intervention]. Articles published from January 2005 to January 2023 considered relevant to the topic were examined in greater detail. Additionally, we examined guidelines and consensus recommendations that have been published by SIOG and ASCO or other medical societies (eg, National Comprehensive Cancer Network [NCCN])[17–19,22] on the assessment and management of frailty in older adults with cancer. This literature served as the basis for preparing this review.

General Definition and Identification of Frailty

Frailty is generally defined as an age-related clinical condition of increased vulnerability to acute endogenous or exogenous stressors.[4–7] Older adults with frailty are at increased risk to experience worsening of their overall health status due to adverse health events emerging from interactions between existing frailty features and new stressor events (Figure 1). Frailty arises primarily from normal aging and age-related diseases.[7,23,24] Ordinary aging processes at the

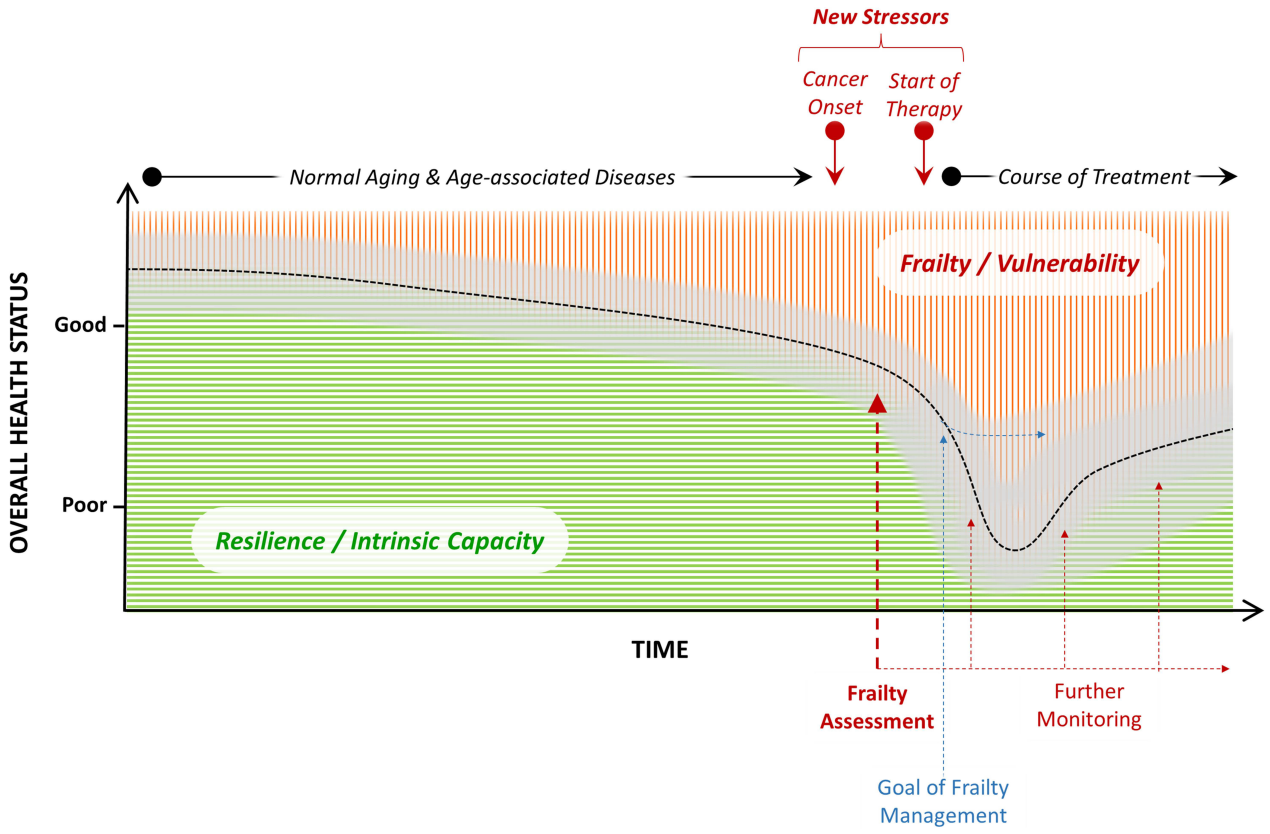

Figure 1 Illustration of the general concept, impact, assessment, management, and monitoring of frailty in older adults with cancer (red area represents the magnitude of a patient's frailty and green area represents his/her intrinsic capacity at a given point in time, respectively; the black dotted curve reflects the overall health status at specific time points, with the gray band indicating inter-individual variance).

molecular and cellular level including senescence and stem cell exhaustion cause a physiological decrease of the reserve capacity of organs and organ systems.[25,26] Coincidently, these processes may promote the creation of an environment that fosters the development of pathological tissue degeneration (eg, vascular, musculoskeletal) and subclinical inflammation which lead to common aging-associated diseases (eg, coronary heart disease, osteoarthritis)[27] followed by a possible decline in physical and mental function and disability. Later, the cancer disease and damage caused by its treatment may contribute to frailty.[28,29] In older patients with cancer, comorbidity (ie, the burden of chronic illness), disability (ie, the loss of function and autonomy), and frailty often co-exist.[9] They are considered as overlapping although not identical phenomena. There is also significant overlap between the concepts of frailty and "intrinsic capacity".[30] From a simplified view, intrinsic capacity and resiliency can be understood as the opposite to vulnerability and frailty (Figure 1).

Two methods are generally recognized as the gold standard to identify frailty in older people.[6,7] The "Fried frailty criteria" are based on a phenotype model. In this model, presence of at least 3 of the following 5 criteria in a patient indicate frailty: low physical activity, poor endurance (self-reported exhaustion), weakness (reduced grip strength), slowness (decreased walking speed), and unintentional weight loss.[31] However, the use of this approach to identify frailty in routine clinical care has remained uncommon, because there is no generally accepted and clinically easily applicable operationalization of the individual criteria. The "Rockwood frailty index" is based on a deficit-accumulation model.[32] The index is calculated by dividing the number of deficits diagnosed by the total number of 70 pre-defined deficits. Deficit items include various diseases, signs from clinical examinations, and impairments of activities of daily living. In contrast to the phenotype model, deficit-accumulation models not just allow to determine whether frailty is present or not (categorical variable), but also to quantify the extent of frailty in a patient (continuous variable). With the 70-item model, an index of 0.25 and above may indicate frailty. In routine care, however, an index calculation with 70 or even with fewer deficit items (eg, 50 or 20) has proven to be too cumbersome to capture frailty. This approach has therefore not become more widely established in clinical practice. In the oncology context, a minority of studies have used Fried criteria or the Rockwood index to identify and measure frailty in older cancer patients.[8,9]

Techniques other than Fried criteria or the Rockwood index have been accepted as appropriate for detecting frailty in older people.[33] These include frailty screenings and geriatric assessment (GA). Both methods are easier to implement in everyday clinical care.

Among numerous frailty screening tools (eg, Identification of Seniors at Risk [ISAR], Groningen Frailty Indicator [GFI], Vulnerable Elders Survey-13 [VES-13], Triage Risk Screening Tool [TRST]),[34–37] the Clinical Frailty Scale (CFS) has recently received greater attention and increasingly been used in clinical settings during the Covid pandemic.[38–40] This pictogram-driven screening tool summarizes the overall level of frailty of an older person and is easy for clinicians to use as part of their medical history taking and physical examination. Due to its simple structure, CFS is also suitable in situations with acute or new illness to record the previous level of frailty before the new stressor disease has occurred (eg, a symptomatic Covid-19 infection).[39] Such information is highly relevant and helps to avoid under-treatment or over-treatment of older patients when it comes to far-reaching treatment decisions (eg, for or against ventilation therapy in the example of Covid-19). Independent of the pandemic, this principle can also be applied to the oncological context. In old patients with newly diagnosed cancer who present in poor general condition, knowledge of frailty before the onset of the tumor disease is very important when anticipating the prospect of tumor-specific therapy of re-improving the condition. The number of studies examining CFS in the oncology setting has increased over the past 1–2 years. A majority was conducted in the context of tumor surgery. Results were promising regarding the usefulness of this tool to predict outcomes (Table 1).

GA is a core methodology in geriatric medicine.[41,42] Its use for a systematic and comprehensive recording of vulnerabilities in older patients across geriatric domains (social support - activities of daily living - mobility and falls - nutrition - cognition - emotion - sleep - vision and hearing - pain and wounds - co-morbidity - polypharmacy) is firmly anchored in routine geriatric care. GA makes use of traditional assessment tools that have been tried and tested over many years. Among these are scores and scales (eg, Lawton scale for instrumental activities of daily living, Katz scale for basal activities of daily living, Charlson score for comorbidities) as well as performance tests (eg, Timed-Up&Go test for mobility, Mini Mental State Exam for cognition).[43–47] Notably, new approaches are

Table 1 Key Findings from Recently Published Studies Investigating the Clinical Frailty Scale (CFS)[38] in Older Adults with Cancer

Author (Year)	N	Median Age	Setting	Key Results
Pearce et al (2022)[86]	514	76 years	Gastro-esophageal cancer, 1L palliative chemotherapy (multi center)	Higher CFS scores were associated with poor overall treatment utility, progression, and death
Philip et al (2022)[87]	820	≥ 65 years	Various cancers, surgical resection (single center)	Higher CFS scores were associated with longer stay, post-op mortality, morbidity, and readmission rate
Stamatakos et al (2022)[88]	52	76 years	Bladder cancer, with radical cystectomy (single center)	Higher CFS scores were associated with 1-year-mortality, longer hospital stays, and respiratory complications
Osatnik et al (2022)[89]	269	69 years	Critically ill patients with cancer on ICU (single center)	CFS scores predicted hospital mortality
Niemeläinen et al (2021)[90]	161	85 years	Colorectal cancer, elective surgery (multi center)	CFS scores ≥ 3 were correlated with more postoperative complications
Mima et al (2021)[91]	142	≥ 60 years	Pancreatic cancer, surgical resection (single center)	Higher CFS scores predicted poor survival

Abbreviations: CFS, clinical frailty scale; 1L, first line; ICU, intensive care unit.

currently emerging to perhaps replace parts of a GA using modern sensor-based diagnostics (eg, wearable sensors, apps).

Over recent years, medical disciplines other than geriatrics, such as cardiology or trauma surgery, have begun to discover GA as a potentially useful technique specific to their field.[48,49] Oncology is at the forefront of this development.

Frailty Evaluation and Interventions in Older Cancer Patients

A fundamental goal of frailty assessment and management in older adults with cancer is to protect them from adverse health outcomes as well as possible (Figure 1). Unfavorable outcomes to be prevented in general must be distinguished from those that are specific to the oncological context (Table 2). Practical recommendations on frailty evaluation and interventions in older patients with cancer are based on clinical studies examining whether an assessment was able to predict the occurrence or reduced the incidence of such outcomes.[17–19] Approaches that

Table 2 Potential Adverse Outcomes Related to Frailty in Older Adults with Cancer

General Frailty Outcomes	Oncology-Specific Frailty Outcomes (by Setting)
Early death Care dependency Nursing home admission Hospital admission Permanent bedrest Falls Delirium Exacerbation / Progression of chronic diseases Onset of acute illnesses Adverse drug interactions	Systemic drug treatment (incl. chemotherapy) • Increased drug toxicity • (incl. cytopenias, infections, organ toxicities) • Unplanned treatment interruption • Premature treatment discontinuation • Drug-drug interactions • Unplanned hospitalization Radiotherapy • Increased toxicity • (incl. late-onset radiation damage) • Unplanned treatment interruption • Premature treatment discontinuation • Unplanned hospitalization Surgical treatment • Prolonged immobilization • Postoperative nutritional problems

(*Continued*)

Table 2 (Continued).

General Frailty Outcomes	Oncology-Specific Frailty Outcomes (by Setting)
	• Postoperative delirium or depression • Postoperative wound healing disorders • Postoperative bleeding disorders • Delayed recovery • Other postoperative complications (incl. infections) Cancer survivor • Long-term toxicity

were subject to these studies included performance scores, frailty screening, and geriatric assessment. The validity of these approaches can be summarized as follows.

Validity of Performance Scores

In routine care, oncologists often use Eastern Cooperative Oncology Group or Karnofsky performance score (ECOG PS, KPS) to roughly estimate the general condition of their patients.[50,51] ECOG PS and KPS are tools to describe the overall health status and global activity level of cancer patients. However, poor ECOG PS or KPS numbers may be observed in already chronically ill patients with severe pre-existing diseases (eg, terminal COPD, progressive Parkinson disease) as well as in otherwise healthy patients but with acute symptomatic cancer illness (eg, cancer fatigue, cancer pain, acute infection). However, good ECOG PS or KPS numbers do not rule out the existence of chronic and clinically relevant vulnerabilities in older patients (eg, tendency to fall, mild cognitive impairment, inappropriate polypharmacy).[52] The capacity of ECOG PS to predict chemotherapy toxicity in older cancer patients is low.[53] Performance scores such as ECOG PS or KPS are therefore insufficient to comprehensively surrogate frailty in older adults with cancer. Neither do these tools allow for differentiated oncological treatment decisions nor for the selection of meaningful frailty interventions.

Validity of Frailty Screenings

Most recommendations of international and national medical societies have in common that frailty assessment in older adults with cancer should start with a quick screening in order to identify those patients who are presumably vulnerable and could benefit from a comprehensive GA. Table 3 lists the screening tools proposed by SIOG and ASCO.[17–19] The advice is based on study results. The available evidence has been compiled in several systematic reviews (Table 4). The most frequently applied tool is the so-called G8 (Geriatrics 8) screening.[54] Numerous studies in older patients with cancer demonstrated

Table 3 SIOG Recommendations and ASCO Guidelines for the Assessment of Frailty in Older Adults with Cancer

SIOG Recommendations[17,18] (for All Cancer Patients ≥ 70 Years)	ASCO Guidelines[19] (for Cancer Patients ≥ 65 Years with Chemotherapy)
Frailty Screening • G8 • TRST • VES-13	 • G8 • VES-13
Geriatric Assessment 0. Social Status • No tool recommended 1a. Functional Status - Autonomy • IADL (Lawton) • ADL (Katz)	 • No tool recommended • IADL • (ADL)

(*Continued*)

Table 3 (Continued).

SIOG Recommendations[17,18] (for All Cancer Patients ≥ 70 Years)	ASCO Guidelines[19] (for Cancer Patients ≥ 65 Years with Chemotherapy)
1b. Functional Status - Mobility	
• TUG	• No. of falls over 6 months • (SPPB) • (TUG) • (Gait speed)
2. Nutritional Status	
• MNA	• BMI + weight loss from baseline in % • - (MNA)
3. Cognitive Status	
• MMSE • MOCA	• MINI-COG • BOMC • (MMSE) • (MOCA)
4. Emotional Status	
• GDS	• GDS
5. Comorbidity	
• CIRS • ACE-27	• Review of chronic conditions • (CIRS-G) • (CCS)
6. Polypharmacy	
• (BEERS) • (STOP/START)	• No tool recommended
7. Other Domains / Tools	
• QLQ-C30 • WHO ICOPE APP	• CARG • CRASH • ePROGNOSIS

Note: () = To be considered, ePROGNOSIS, www.eprognosis.ucsf.edu (calculators for remaining life expectancy).
Abbreviations: SIOG, International Society of Geriatric Oncology; ASCO, American Society of Clinical Oncology; G8, Geriatrics 8; TRST, Triage Risk Screening Tool; VES-13, Vulnerable Elders Survey 13; IADL, Instrumental Activities of Daily Living; ADL, (Basal) Activities of Daily Living; TUG, Timed-Up-And-Go; SPPB, Short Physical Performance Battery; MNA, Mini Nutritional Assessment; BMI, Body Mass Index; MMSE, Mini Mental State Exam; MOCA, Montreal Cognitive Assessment; BOMC, Blessed Orientation Memory Concentration; GDS, Geriatric Depression Scale; CIRS(-G), Cumulative Illness Rating Scale (Geriatric); ACE-27, Adult Comorbidity Evaluation 27; CCS, Charlson Comorbidity Score; BEERS, Beers criteria; START/STOP, Start/Stop criteria; CARG, Cancer Aging Research Group Chemotoxicity Calculator; CRASH, Chemotherapy Risk Assessment Scale for High-Age Patients; QLQ-C30, Quality of Life Questionnaire C30; WHO ICOPE, World Health Organization Integrated Care for Older People.

Table 4 Systematic Reviews* of Studies Examining Frailty Screening and Geriatric Assessment in Older Adults with Cancer

Author	Year	No. of Included Studies	Major Findings
Shaw et al[12]	2022	71	Review included studies of cancer surgery. Frailty was associated with 30-day and long-term mortality, postoperative complications, length of stay, and adverse discharge disposition.
Chuang et al[92]	2022	6	Review included 6 RCTs exploring GA plus geriatric interventions. GA was associated with lower incidence of grade 3–5 treatment-related toxicity and dose reduction compared with standard of care.
Hamaker et al[61]	2022	61	GA led to changes of oncologic treatment plans in one third of patients, recommendations of non-oncologic frailty interventions in more than two thirds of patients, improved communication about treatment goals, lower treatment toxicity, more frequent treatment completion, improved physical function, and better quality of life.

(*Continued*)

Table 4 (Continued).

Author	Year	No. of Included Studies	Major Findings
Garcia et al[58]	2021	17	G8 and VES-13 were the most frequently evaluated screening tools. G8 had higher sensitivity, VES-13 had higher specificity.
Scheepers et al[93]	2020	44	Review included only studies in hematologic malignancies. Frailty as assessed by screening or GA was predictive for poor overall survival and, with more variation between studies, treatment complications, treatment non-completion, and hospitalization.
Van Walree et al[56]	2019	46	Sensitivity for G8 screening was high, but specificity was low. Abnormal G8 results were associated with shorter overall survival and more treatment-related complications.
Bruijnen et al[94]	2019	46	Physical function and nutritional status were the GA domains most often associated with adverse outcomes.
Hamaker et al[95]	2018	35	After GA, oncologic treatment plans were altered in about one third of patients, and non-oncologic frailty interventions were recommended in more than two thirds of patients.
Handforth et al[8]	2015	20	Presence of frailty was associated with increased all-cause mortality, postoperative mortality, and treatment complications.
Hamaker et al[96]	2014	15	Review included only studies in hematologic malignancies. Impairments assessed by GA were associated with poor overall survival and (in 2 studies) chemotherapy-related toxicity.
Puts et al[97]	2014	34	Abnormal GA results were associated with adverse outcomes.
Ramjaun et al[98]	2013	9	Results of GA predicted mortality, chemotherapy-related toxicity, and (in 1 study) complications post-surgery.
Puts et al[99]	2012	73	GA time was 10–45 minutes. Some GA domains were associated with adverse outcomes.
Hamaker et al[59]	2012	14	G8 and TRST screenings had the highest sensitivity (but poor specificity) for frailty as assessed by GA. Frailty screenings appear to have insufficient discriminative power to select patients for GA.

Note: *Table excludes systematic reviews of studies examining frailty assessment in single cancer entities (eg, lung cancer, colorectal cancer etc.).

associations between abnormal G8 scores and poor frailty outcomes such as shortened survival, increased treatment toxicity and complications after tumor surgery (Table 4).[55,56] The G8 tool queries key vulnerabilities (mobility issues, nutritional issues, cognitive issues and mood problems, and polypharmacy) together with age and subjective health perception. During routine oncological work-ups, such frailty features are usually not checked systematically. Meanwhile, a self-reported version of the G8 has been made available to facilitate its implementation in busy clinics.[57] A G8 screening score of ≤14 identifies patients with possibly increased vulnerability and should prompt for a comprehensive GA. Importantly, abnormal results of G8 or other frailty screenings such as VES-13 should not be used alone to mark a patient as being "frail", because false positive screening may occur. G8 has a high sensitivity albeit lower specificity. In contrast, VES-13 has lower sensitivity but higher specificity than G8.[58] Of note, frailty must not be considered as an absolute measure, but always judged in relation to the level of stress burdened on the patient by an offered cancer treatment. The level of stress may vary depending on the type of the tumor therapy (eg, major surgery, high-dose chemotherapy, hematopoietic stem cell transplantation vs mild chemotherapy, immunotherapy, oral hormone therapy etc.). Therefore, G8 or VES-13 are well suited in distinguishing between presumably robust and vulnerable patients. However, these tools have not been sufficiently validated regarding their utility to tailor final oncological treatment or frailty intervention plans.[59] For these purposes, greater knowledge about single vulnerabilities is required including information on their severeness, underlying causes, possible consequences in the course of the cancer disease and treatment, and intervenability.

Utility of Geriatric Assessment

SIOG and ASCO strongly recommend to perform comprehensive GA in cancer patients ≥ 65–70 years who were identified as presumably vulnerable by prior frailty screening.[17–19] The SIOG recommendations are not targeted to a specific subset of older cancer patients.[17,18] The ASCO guideline refers to the subset of older adults receiving chemotherapy.[19] Both guidelines uniformly recommend that the GA should cover essential geriatric domains. The minimum is physical function including instrumental and basic activities of daily living (IADL, ADL), mobility, nutrition, cognition, mood, co-morbidity, and co-medications. For each geriatric domain, the guidelines propose a set of GA instruments (Table 3).

To date, a plethora of retrospective and prospective, non-comparative and comparative GA studies in older patients with cancer has been published. The accumulated study evidence has been summarized in several systematic reviews (Table 4) and is the basis for the current recommendations made by SIOG and ASCO (Table 3) or for other country-specific guidelines (eg, NCCN). In general, studies of GA in older adults with cancer were highly heterogenous regarding oncological settings, patient populations, sizes, and endpoints (Table 4). Many of these studies examined one of the following aspects:

- Feasibility of GA in older cancer patients.
- Prevalence of geriatric impairments (as assessed by GA) in older cancer patients.
- Association of geriatric impairments with treatment complications such as toxicity, dose modifications, treatment discontinuation, length of hospital stay, or unplanned hospitalization.
- Association of geriatric impairments with cancer treatment efficacy endpoints such as response rates or progression-free survival.
- Association of geriatric impairments with overall survival (mostly all-cause mortality).
- Impact of performing a GA (vs not performing GA) on communication with patients and their caregivers.
- Impact of performing a GA (vs not performing GA) on oncological or non-oncological treatment decisions.
- Impact of performing GA (vs not performing GA) on outcomes such as treatment complications or survival.
- Impact of performing GA with vs without geriatric management (frailty interventions) on outcomes.

Overall, it can be concluded from these studies that GA uncovers geriatric impairments, predicts treatment tolerability and feasibility, predicts (all-cause) mortality, facilitates communication about treatment goals and preferences, results in changes of oncological treatment plans, and enables targeted non-oncological treatment of geriatric impairments in older cancer patients (Table 4).

The ability of GA to predict treatment complications was exploited by developing chemotoxicity risk calculators. These tools incorporated GA elements and allow to calculate the likelihood of grade 3–5 toxicity during chemotherapy of older patients with cancer. Use of such calculators is strongly recommended by the ASCO guideline addressing the subset of chemotherapy-treated older patients.[19] The CARG (Cancer Aging Research Group) and the CRASH (Chemotherapy Risk Assessment Score for High Age Patients) tool are easily accessible online.[53,60] Both tools take functional impairments of the patient into account and thus require careful geriatric examination of the patient. Results of selected studies investigating CARG or CRASH in older patients with cancer are outlined in Table 5. It should be noted that neither the CARG nor the CRASH score have been validated in greater detail for their capacity to predict toxicity of non-chemotherapeutic agents (eg, kinase inhibitors, immune checkpoint inhibitors).

Recent pivotal randomized-controlled trials (RCTs) investigating the impact of GA with and without subsequent geriatric management added very compelling evidence that GA is a powerful frailty assessment for older patients with cancer.[61,62] These RCTs demonstrated that GA-directed management of vulnerabilities is able to reduce the risk of these patients to experience toxicity or premature discontinuation of systemic cancer treatment. In the two largest RCTs (GAP70+ and GAIN study) with more than 600 patients each, rates of grade 3–5 toxicity were reduced by 20% and 10%, respectively.[63,64] The smaller INTEGERATE trial reported lower chemotherapy discontinuation rates with integrated GA-guided oncogeriatric care compared with usual care (33% vs 53%).[65] In a RCT in colorectal cancer patients with

Table 5 Key Findings from Studies Investigating the CARG and CRASH Chemotherapy Toxicity Risk Calculators in Older Adults with Cancer

Author (Year)	N	Median Age	Setting	Key Results
Suto et al (2022)[100]	76	71 years	Solid tumors treated with new anticancer regimen	Incidence of grade 3–5 AE during first treatment course correlated with risk predicted by the CARG tool
Cavdar et al (2022)[101]	208	70 years	Solid tumors treated with chemotherapy	CARG tool predicted incidence of grade 3–5 toxicity
Mittal et al (2021)[102]	100	68 years	Tumors treated with new chemotherapy	CRASH tool predicted severe chemotherapy toxicity
Ostwal et al (2021)[103]	270	69 years	Solid tumors treated with curative intent with chemotherapy	CARG tool predicted incidence of grade 3–5 toxicity
Alibhai et al (2021)[104]	175	73 years	Metastatic cancer of the prostate treated with chemotherapy or androgen-receptor targeted therapy	CARG tool predicted incidence of grade 3–5 toxicity in patients receiving chemotherapy as well as patients treated with antihormone drugs
Chan et al (2021)[105]	259	73 years	Solid tumors treated with chemotherapy or targeted tumor drugs	CARG tool did not predict severe treatment-related AE
Ortland et al (2020)[106]	120	77 years	Patients with systemic cancer therapy	CARG and CRASH tools showed similar performance in predicting grade 3–5 AE
Zhang et al (2019)[107]	106	Years	Solid tumors treated with chemotherapy	CARG and CRASH scores were correlated and predicted grade 3–5 toxicity
Kotzerke et al (2019)[108]	104	73 years	Solid tumors treated with chemotherapy	CARG tool (but not G8) predicted severe (grade 4) chemotherapy-related toxicity
Alibhai et al (2017)[109]	46	75 years	Patients with prostate cancer treated with chemotherapy	Observed incidence of grade 3–5 AE was lower than predicted by CARG tool
Hurria et al (2016)[110]	250	73 years	Tumors treated with new chemotherapy	Rate of grade 3–5 toxicity increased with increasing CARG score
Extermann et al (2012)[60]	518	76 years	Cancers treated with chemotherapy	Development and initial validation of the CRASH tool
Hurria et al (2011)[53]	500	73 years	Cancers treated with chemotherapy	Development and initial validation of the CARG tool

Abbreviations: CARG, Cancer Aging Research Group; CRASH, Chemotherapy Risk Assessment Scale for High-Age Patients; AE, adverse events.

tumor surgery followed by chemotherapy (GERICO),[66] more patients in the oncogeriatric intervention arm completed scheduled chemotherapy compared with patients of the control arm (45% vs 28%). More details for RCTs examining GA with or without geriatric management are shown in Table 6. Of note, there have also been trials which did not meet their primary endpoint.[67–69]

Comprehensive delivery of GA-guided frailty interventions ideally happens within a multidisciplinary approach involving social workers, nurses/nurse practitioners, physiotherapists, occupational therapists, dieticians, psychologists, pharmacists, and geriatricians in addition to oncologists, radiotherapists, and surgeons.[70,71] Table 7 shows a list of interventions used in GAP70+, GAIN, INTEGERATE, and GERICO with the intention to improve single vulnerabilities and hence to modify the overall frailty level of older cancer patients over time.[63–66] Next to the measurement of oncological outcome improvements (eg, decreased treatment toxicity), successful frailty intervention may also be validated by measuring whether vulnerabilities captured at baseline improve during further follow-up. However, except for the GAP70+ trial,[63] none of the randomized frailty intervention trials shown in Table 6 included a geriatric re-assessment during or after the cancer treatment.

Table 6 Selection of Randomized-Controlled Trials (RCTs) Examining Geriatric Assessment (GA) with Frailty Interventions in Older Adults with Cancer

RCT (Author, Year)	N	Med. Age	Setting	Intervention vs. Control	Key Results
GAP70+ (Mohile et al 2021)[63]	718	77 y	40 oncology practices (USA), patients with solid tumors or lymphomas starting a new systemic therapy	Oncologists provided with tailored geriatric assessment summary plus recommendations for management of geriatric issues vs usual care	51% vs 71% grade 3–5 AE, similar OS; fewer falls and more medications discontinued with intervention
GAIN (Li et al 2021)[64]	605	71 y	Single cancer center (USA), patients with solid tumors starting a new chemotherapy	GA at baseline (in both arms) ± geriatric intervention provided or organized by an MDT	51% vs 61% grade 3–5 AE, 28% vs 13% completion of advance directive
INTEGERATE (Soo et al 2022)[65]	154	76 y	Three cancer centers (AUS), patients with solid tumors or aggressive lymphoma	GA at baseline with geriatric consultation, creation of a personal management plan and according interventions vs usual care	Better HRQOL and lower rate of hospital admissions (unplanned) with the intervention, 33% vs 53% treatment discontinuations
GERICO (Lund et al 2020)[66]	142	75 y	Two oncology clinics (DK), patients with colorectal cancer post-surgery treated with adjuvant or palliative chemotherapy	GA with GA-directed interventions vs usual care	45% vs 28% completion of the chemotherapy as scheduled, better HRQOL and better mobility in the intervention arm
5C (Puts et al 2021)[67]	351	76 y	Eight hospitals (CAN), patients with solid or hematological cancer referred for new chemotherapy	GA by nurse and geriatrician with monthly follow-up by nurse vs usual care	No difference in HRQOL scores

Abbreviations: RCT, randomized-controlled trial; y, years; AE, adverse events; OS, overall survival; GA, geriatric assessment; MDT, multidisciplinary team; HRQOL, health-related quality of life.

Table 7 Proposal for the Monitoring of Frailty Interventions as Used to Target Single Vulnerabilities in Older Adults with Cancer in Pivotal Randomized-Controlled Trials (GAP70+, GAIN, INTEGERATE, GERICO)[63–66]

Domain	Vulnerabilities	Used Interventions in Trials	Proposal for Monitoring
Social status	Loneliness Poverty	Referral to social worker, implementation of visiting nurse service or transportation service, assistance for economic and social needs, involvement of health care proxy	Re-assessments of HRQOL using questionnaires
Functional status Autonomy	Impairment of IADL Impairment of ADL	Referral to aide service, referral to occupational therapist, implementation of nurse service, implementation of home service	Re-assessments using IADL or ADL questionnaires
Functional status Mobility	Walking slowness Frequent falls Weakness / Sarcopenia	Referral to aide service, referral to physical therapist, prescription of exercise, deprescription of orthostatic or psychoactive drugs, education on fall risk evaluation of home safety	Re-assessments using TUG or SPPB etc.; use of activity tracker (eg, footstep count etc.)
Nutritional status	Low body mass index / Cachexia Low food or fluid intake Swallowing or teeth problems	Referral to dietician, referral to specialist for swallowing, referral to dentist, use of anti-emetics, recommendation of diet, education on diet and nutrition	Re-assessments of body mass index; use of a calorie-counting apps

(*Continued*)

Table 7 (Continued).

Domain	Vulnerabilities	Used Interventions in Trials	Proposal for Monitoring
Cognitive status	Mild cognitive impairment (MCI) Dementia	Referral to memory clinic, referral to psychiatry, optimization of pharmacological treatment with psychoactive drugs, shared information with health care proxy, written instructions for appointments and medications, prevention of delirium, use of simple cancer treatment regimens	Re-assessments using MMSE etc.; use of wearable activity tracker, recording of activity using an electronic diary
Emotional status	Depression Anxiety	Referral to psychologist, referral to spiritual services, optimization of pharmacological treatment with antidepressants, appointment with local support groups	Re-assessments using GDS; use of activity tracker, recording of mood using an electronic diary
Comorbidity	Co-existing chronic disease	Communication with primary care physician, review of medication, initiation of investigations, modification of cancer treatment regimen	Disease-specific re-assessment (physical exam, laboratory etc.)
Polypharmacy	High number of drugs Potentially inadequate drugs	Referral to pharmacist, recommendation of pill box and medication calendar, communication with primary care physician, deprescribing, education on polypharmacy	Re-assessments of medication risks using BEERS list or electronic prescription tools

Abbreviations: SIOG, International Society of Geriatric Oncology; ASCO, American Society of Clinical Oncology; G8, Geriatrics 8; TRST, Triage Risk Screening Tool; VES-13, Vulnerable Elders Survey 13; IADL, Instrumental Activities of Daily Living; ADL, (Basal) Activities of Daily Living; TUG, Timed-Up-And-Go; SPPB, Short Physical Performance Battery; MNA, Mini Nutritional Assessment; BMI, Body Mass Index; MMSE, Mini Mental State Exam; MOCA, Montreal Cognitive Assessment; BOMC, Blessed Orientation Memory Concentration; GDS, Geriatric Depression Scale; CIRS(-G), Cumulative Illness Rating Scale (Geriatric); ACE-27, Adult Comorbidity Evaluation 27; CCS, Charlson Comorbidity Score; BEERS, Beers criteria; START/STOP, Start/Stop criteria; CARG, Cancer Aging Research Group Chemotoxicity Calculator; CRASH, Chemotherapy Risk Assessment Scale for High-Age Patients; QLQ-C30, Quality of Life Questionnaire C30; WHO ICOPE, World Health Organization Integrated Care for Older People; RCT, randomized-controlled trial; y, years; AE, adverse events; OS, overall survival; GA, geriatric assessment; MDT, multidisciplinary team; HRQOL, health-related quality of life.

Frailty Monitoring in Older Cancer Patients

Following the initial frailty assessment at the start of a cancer therapy, the overall frailty level as well as single vulnerabilities may undergo significant changes during treatment and throughout a patient's further life (Figure 1). Over time, alterations of the social situation, the physical and mental functionality, and co-morbidities may occur. Observations from studies suggest that both deterioration and improvements are possible. For example, in a study of 144 over 50 years old breast cancer patients examined for frailty by using modified Fried criteria before and after chemotherapy, the proportion of subjects with a Fried score of 3 or 4 increased from 13% to 46%.[72] Another study with 439 older adults with cancer (≥70 years) found functional declines in IADL and ADL in about one third of the patients during chemotherapy.[21] The large GOSAFE study, which included more than 1000 participants, explored functional recovery after cancer surgery.[73] In individual patients of this study, both loss and gain of function were observed at 3 and 6 months follow-up. There have also been some studies suggesting loss of cognitive capacity (memory function) in patients after chemotherapy.[74] Other analyses demonstrated that cancer survivors develop frailty earlier and more frequently compared to non-cancer survivors.[29] In the GAP70+ trial, delivery of targeted frailty interventions to older patients receiving chemotherapy resulted in lower numbers of falls and lower numbers of prescribed drugs while physical functioning (IADL, mobility) and mood remained unchanged.[63]

However, the total number of studies exploring frailty over time in older cancer patients have remained rather low and the available data are of descriptive nature. Therefore, underlying mechanisms of worsening or improvement of frailty must be inferred from clinical observations rather than from systematic study evidence. Clinical experience suggests that progressive tumor disease, toxicity by the tumor treatment, and exacerbation or progression of chronic conditions or acute intercurrent diseases independent of the cancer could drive deterioration of frailty, whereas improvements may occur in response to the remission of a tumor or targeted frailty interventions. Although frailty is subject to dynamic

changes and actively modifiable the currently available recommendations by SIOG and ASCO on frailty assessment in older cancer patients are lacking further advice on how to monitor this condition during or after the tumor treatment.[17–19] At present, this topic must be discussed in the absence of broader evidence or guidance.

Potential Indications for Frailty Monitoring

Frailty monitoring may play a role in clinical research as well as in clinical practice:

In RCTs investigating cancer treatments, oncology-specific outcomes such as response rates, progression-free and overall survival, adverse events, and quality of life are typical study endpoints. In contrast, re-evaluation of geriatric domains such as physical or cognitive functioning or nutritional status post-treatment have remained uncommon in such trials, even when studying a population of older patients.[75] Nevertheless, the inclusion of these endpoints in future RCTs is essential to better understand the risks and benefits of oncological therapies in vulnerable older patients.[76]

In routine care, re-performing frailty assessments after the start of an oncological treatment together with non-oncological frailty interventions (Table 7) would allow an evaluation of whether and to what degree a patient is responsive to such management. This would enable a multidisciplinary team to decide whether frailty interventions should be continued, escalated, de-escalated, or stopped, or whether the focus of frailty interventions must be shifted towards other vulnerabilities than those considered crucial at the beginning of the tumor treatment. Furthermore, frailty monitoring over time may guide oncologists to increase or decrease the intensity (eg, dosing) of the cancer treatment. To date, however, there has been no study exploring the utility of repeated frailty assessments to guide continuous adaptation of cancer treatment after its initiation.

In routine practice, re-doing a frailty assessment also appears useful if the overall health status of an old patient suddenly deteriorates during systemic cancer treatment and the patient gets hospitalized in an unplanned manner (Figure 1). In addition to the standard investigations of the primary cause of the hospitalization (eg, an infection), a careful holistic view on vulnerabilities at this time point could support decision-making about the need of early rehabilitation measures in the hospital, for example on an acute geriatric ward. Finally, re-assessment of frailty after the end of cancer treatment could inform rehabilitation measures as well as reasonable rehabilitation goals.[77,78] This approach seems particularly useful after tumor surgery, radiotherapy, or adjuvant systemic therapy.

Traditional Tools for Frailty Monitoring

Various tools may be used to monitor a patient's general frailty level as well as his or her individual vulnerabilities (Table 7). Performance scores (ECOG PS, KPS) are commonly used in oncology to follow the general condition and activity level of patients.[50,51] However, these tools do not provide deeper insight into the course of single vulnerabilities. The same applies to frailty screenings such as G8 that was not designed to monitor frailty.[36,54] However, some screening tools (eg, CFS) may be usable and easy to implement in workflows. Repeated GA using standard assessments (Table 7) are another option for frailty monitoring in older cancer patients. There is no consensus whether the entire GA should be repeated or monitoring of selected GA domains (eg, those that showed abnormal results on initial assessment) is sufficient. Of note, neither the CARG nor the CRASH tool have been studied with regards to monitoring the risk of chemotherapy toxicity over time (eg, between treatment cycles or prior and after rehabilitation).

Smart Digital Tools for Frailty Monitoring

Frailty monitoring in older adults with cancer could be an application for wearable sensors and other digital assessment technology (Table 7). Meanwhile, the technological progress allows for the collection of a multitude of data by portable devices such as wristwatches, foot pods, breast belts, and smartphones worn on the body and equipped with apps. Numerous manufacturers offer such devices fully configured and ready to use for end users. Using commercial activity trackers, physical activity and movement behavior including number of steps, falls, etc. can be tracked in real time. Moreover, these devices are increasingly capable of recording sleeping behavior as well as circulatory and respiratory parameters as for example heart rate, oxygen saturation, and body temperature. Surrogates of cardiopulmonary capacity (eg, VO2max) can be calculated and monitored over time. Downloadable apps for smart phones and tablets offer new opportunities to follow frailty domains other than physical activity and cardiopulmonary reserve. For example, users can

repeatedly enter information about their drinking and eating habits, calorie intake or body weight into apps offered commercially in app stores. In the future, apps might also allow us to remotely query mood and drive, or to follow cognitive function through repeated app-embedded cognitive testing.

A growing number of studies examine whether these features of new smart technologies can help to measure frailty in patients at least as well or even better than standard GA instruments or than the Fried criteria or the Rockwood index.[79,80] The majority of these studies is aimed to develop digital biomarkers for physical frailty,[81] but there have also been some studies exploring the role of digital sensors to assess other aspects of frailty (eg, cognitive frailty).[82] Unfortunately, the feasibility and usefulness of such approaches have only been little investigated in oncological settings. So far, there is only rudimentary data available. For example, in a study with 84 older cancer patients (median age 71 years), gait and balance parameters assessed by wearables were degraded when compared with age-matched non-cancer patients as well as in patients with chemotherapy-induced peripheral neuropathy (CIPN) versus without CIPN.[83] Another trial explored a wearable activity tracker in somewhat younger patients with cancer undergoing chemotherapy. This study reported a correlation between unplanned health encounters and tracker-recorded activity data, but not ECOG PS.[84]

Advantages and disadvantages must be weighed against each other when using wearable sensors and apps to assess and monitor frailty in older patients with cancer. Although many products might be available off-the-shelf and consumer-ready (eg, smart watches, app stores), there is no broader accepted standard device and no consented protocol regarding the processing, safe storage and transmission of these digital data. For the moment, the lack of technical standards as well as data protection rules may limit a broader application of these tools for assessing and monitoring frailty. However, if such hurdles are overcome, many new possibilities open up. For example, the data might be transmitted to oncological practitioners or a multiprofessional team responsible for frailty interventions. These caregivers could be alerted in real-time if a patient's frailty level deteriorates or improves, and may enable them to immediately adjust therapeutic approaches to the new frailty situation.

Conclusions

The evidence for benefits of a frailty assessment in older adults with cancer has significantly increased in recent years. Most importantly, recent prospective, randomized-controlled studies have demonstrated that frailty assessment improves the outcome of such patients.[63–66] Frailty assessment followed by frailty interventions significantly enhances the treatment tolerability and feasibility, particularly in elderly patients receiving systemic cancer therapy. The number needed to treat is relatively low at around 5–10.[63,64] These new data underscore that frailty assessment is not meant to exclude patients with pre-identified vulnerabilities from cancer therapy, but to make oncological treatments in these patients as safe as possible through additional supportive measures. Based on these new data, performing a comprehensive GA (ie, GA with GA-guided interventions) is at the edge of becoming mandatory in older adults with cancer. However, despite the high level of evidence, only a minority of cancer centers worldwide have integrated GA and GA-led interventions into the routine care of elderly cancer patients so far.[85] The implementation barriers are diverse and include lack of knowledge, limited human, temporal and spatial resources, and billing and reimbursement problems.

In addition to a broad implementation of frailty assessments before starting cancer therapy, there is also a growing need to follow-up frailty in older cancer patients in the course of their disease and treatment. Modern digital technologies such as wearable sensors and apps may offer new ways to simplify and advance frailty assessment and monitoring in this patient population. However, evidence in the oncology context remains low. In the future, such approaches could perhaps replace or supplement parts of a GA, thereby reducing the need of resources.

This review is the first to address the issue of continuous frailty assessment in elderly patients with cancer in more detail. Further studies are needed to expand the evidence base. In such studies, the following key questions should be examined as a matter of priority:

- Which frailty trajectories are particularly common and typical in older cancer patients receiving a particular treatment?

- How do frailty interventions modify such trajectories and how can the success or failure of these interventions be predicted in individual patients?
- What tools should be used as a standard to determine changes in frailty in individual patients during cancer treatment and frailty interventions?
- How can frailty assessment and monitoring be improved by new smart technologies in older patients with cancer?

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