Characteristics Associated With Functional Changes During Systemic Cancer Treatments: A Systematic Review Focused on Older Adults

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ABSTRACT

Background: Maintaining functional status is important to older adults with cancer, but data are limited on how systemic treatments affect functional status. We systematically reviewed changes in functional status during systemic cancer treatments and identified characteristics associated with functional decline and improvement. **Methods:** We searched PubMed, Embase, Web of Science, and Cochrane Register of Controlled Trials for articles examining characteristics associated with functional changes in older adults during systemic cancer treatment published in English between database inception and January 11, 2019 (PROSPERO CRD42019123125). Findings were summarized with descriptive statistics. Study characteristics between older adult-specific and non-older adult-specific studies were compared using the Fisher exact test. **Results:** We screened 15,244 titles/abstracts and 519 full texts. The final analysis included 44 studies, which enrolled >8,400 patients; 39% of studies focused on older adults (1 study enrolled adults aged ≥60 years, 10 enrolled adults aged ≥65 years, and 6 enrolled adults aged ≥70 years). Almost all studies (98%) used patient-reported outcomes to measure functional status; only 20% used physical performance tests. Reporting of functional change was heterogeneous, with 48% reporting change scores. Older adult-specific studies were more likely to analyze functional change dichotomously (29% vs 4%; $P=.008$). Functional decline ranged widely, from 6% to 90%. The most common patient characteristics associated with functional decline were older age ($n=7$ studies), worse performance status ($n=4$), progressive disease status ($n=4$), pain ($n=4$), anemia ($n=4$), and worse nutritional status ($n=4$). Twelve studies examined functional improvement and identified 11 unique associated characteristics. **Conclusions:** Functional decline is increasingly recognized as an important outcome in older adults with cancer, but definitions and analyses are heterogeneous, leading to a wide range of prevalence. To identify patients at highest risk of functional decline during systemic cancer treatments, trials need to routinely analyze functional outcomes and measure characteristics associated with decline (eg, nutrition).

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Background

Older adults with cancer are at increased risk for treatment toxicity and functional impairment,^{1–4} resulting in increased healthcare use and mortality.^{5–10} Maintaining functional status (FS) during cancer treatment is critically important to patients. More than 70% of older patients with cancer report that they would not choose a treatment that results in functional impairment, even if it improves survival.¹¹ Despite the importance of functional outcomes to older adults, cancer clinical trials rarely capture the full impact of treatment on FS. Instead, trials focus on narrow definitions of treatment toxicity using provider-reported adverse effects,¹² which do not capture FS or changes over time. As a result, limited data are available on how cancer treatments affect FS in older adults, hindering delivery of goal-concordant care.

Understanding how FS may change during systemic cancer treatment (eg, chemotherapy, immunotherapy, targeted therapy) and which patient characteristics are associated with these changes can inform shared decision-making to individualize cancer care. Identifying which patients are at highest risk of functional decline is

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necessary to weigh the potential benefits and harms of treatment options, to better inform patient and caregiver anticipatory guidance, and to enable early introduction of tailored interventions, such as exercise and rehabilitation programs, to prevent functional impairment.^{13–15}

Given the increasing recognition of the importance of FS in older adults with cancer¹⁶ and the explosion of new cancer treatments, an increasing number of studies have examined characteristics associated with FS change during treatment. Although a prior systematic review examined the prognostic and predictive value of FS at baseline,¹⁰ no review has systematically synthesized the literature on changes in FS during systemic cancer treatment. Therefore, we aimed to examine changes in FS during systemic cancer treatments with a focus on older adults and to identify patient characteristics associated with functional decline and improvement.

Methods

Search Strategy and Selection Criteria

This systematic review was conducted in accordance with the 2009 PRISMA guidelines.¹⁷ With a medical librarian (D.A. Castillo), we searched PubMed, Embase, Web of Science, and Cochrane Central Register of Controlled Trials for articles examining changes in FS during systemic cancer treatment among adults aged ≥ 65 years published in English between database inception and January 11, 2019. Full search terms are shown in supplemental eTable 1 (available with this article at JNCCN.org) and included the following: “neoplasms,” “cancer,” “malignancy,” or “tumor,” AND “chemotherapy,” “immunotherapy,” or “antineoplastic,” AND “functional status,” “functional decline,” “physical function,” “mobility,” “daily living activity,” or “activities of daily living.” This systematic review is registered with PROSPERO (CRD42019123125).

Studies were evaluated using these inclusion criteria: (1) the study included patients aged ≥ 65 years with any cancer type; (2) participants received systemic cancer therapy; (3) FS was quantitatively measured using physical performance tests, patient-reported outcomes (PROs; eg, instrumental activities of daily living [IADLs]), physical well-being as part of a quality-of-life measure, physical activity (eg, step count), and/or clinician-reported performance status (PS); (4) FS was measured at ≥ 2 time points (one before or during treatment such that change in FS during treatment could be ascertained); (5) FS was analyzed as an outcome; (6) the study reported an analysis of associations between patient characteristics and change in FS; and (7) the study was published in English. Studies of systemic

therapy and other treatment modalities (eg, surgery) were included only if they reported results separately for patients who received systemic therapy. Notably, studies of concurrent chemoradiation were allowed because chemoradiation is the standard of care for some cancer types (eg, head and neck). In addition, studies of FS interventions (eg, exercise) were required to have control arms to allow evaluation of the effect of systemic cancer treatment on FS. Exclusion criteria included the following: (1) studies of hormone therapy, radiation, or surgery alone; (2) articles that did not report original data; and (3) full text was unavailable.

All identified articles were imported into Covidence (Veritas Health Innovation) and duplicates were removed. At each step described, discrepancies were resolved by consensus. Two investigators independently screened each title and abstract for eligibility. This evaluation was then repeated for full-text review. The final list of included full texts was used for data extraction.

Data Extraction and Quality Appraisal

A standardized template for data extraction was pilot tested. Two investigators independently extracted data for each study. Extracted data included first author, publication year, journal, geographic region, study design, intervention and control arms (if applicable), key inclusion criteria, sample size, age distribution, cancer treatment(s), measure(s) of FS, time points assessed, definition of change in FS, key findings, and characteristics associated with functional change.

Two investigators independently performed each appraisal of study quality using the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, which consists of 14 criteria.¹⁸ Example criteria included clearly defined research question, study population, inclusion criteria, and exposure and outcome measures. Participation rate and loss to follow-up were also considered. Meeting each criterion earned 1 point, and a summary score was calculated.

Data Analysis

Descriptive statistics were used to summarize study characteristics, including cancer type, measures of FS used (PROs, clinician-reported PS, physical performance test), assessment time points, and analytic approach. Fisher exact test was used to compare study characteristics between older adult-specific and non-older adult-specific studies. Characteristics associated with functional decline and improvement were summarized. No meta-analysis was planned a

priori, given the heterogeneity in measures used to assess FS, cancer populations studied, and analytic methods.

Results

Study Characteristics

We screened 15,244 titles/abstracts and 519 full texts (supplemental eFigure 1). The final analysis included 44 studies,^{1,2,19–60} which were published from 1991 to 2019 (Figure 1) and enrolled >8,400 patients with cancer. Seventeen studies (39%) focused on older adults (supplemental eTable 2), whereas 27 (61%) included adults of all ages (supplemental eTable 3). Among the older adult–specific studies, which increased in number in recent years (Figure 1), one study enrolled only adults aged ≥ 60 years,¹⁹ 10 enrolled only adults aged ≥ 65 years,^{1,2,20–27} and 6 enrolled only adults aged ≥ 70 years.^{28–33} One-fourth of studies enrolled a heterogeneous population of patients with a solid or hematologic malignancy, and one-fourth enrolled patients with lung cancer. The next most common cancer types were breast cancer (16%) and hematologic malignancies (16%). Most studies (84%) evaluated FS during chemotherapy, with only 5^{32,33,36,59,60} including targeted therapy and 2^{54,59} including immunotherapy.

Quality Assessment

Using the NHLBI Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, we found that the mean quality assessment score was 9.86 (range, 7–13; supplemental eTables 2 and 3). The most common reasons for lower study quality were lack of participation rate reporting, lack of sample size justification, loss to follow-up $\geq 20\%$, and lack of adjustment for confounders. Outcome assessors were often not blinded to the patient's exposure status (eg, demographics). Only 59% of studies adjusted for key potential confounders in their analyses between patient characteristics and FS change.

Measures of FS

Almost all studies (98%) used PROs to measure FS (Table 1). The most commonly used PRO was the EORTC Quality of Life Questionnaire-Core 30 (QLQ-C30) physical functioning scale⁶¹ (34% of studies). Patient-reported activities of daily living (ADLs) (20%) and IADLs (16%) were also commonly used. Physical performance was tested in 20% of studies, with grip strength, chair stands, and walk tests being the most common. Traditional oncology measures of PS (eg, ECOG PS) were uncommon among included studies. There were no statistically significant differences in

Figure 1. Included studies, by publication year.

FS measures used in older adult–specific versus non–older adult–specific studies.

Assessment Time Points and Analytic Approach to FS

Most studies assessed FS before starting systemic therapy and at 1 (20% of studies), 2 (14%), or ≥ 3 (50%) follow-up time points, whereas 16% of studies performed the first assessment after therapy had started (Table 1). Analyses of FS change were heterogeneous, with many reporting change scores between 2 assessments (48% of studies). Only 32% of studies used longitudinal methods to examine trajectories of FS over ≥ 2 time points. The remaining studies analyzed FS change dichotomously by defining cutoff scores for decline and/or improvement (14% of studies), time to deterioration (5%), or association with patient-reported change (2%). Older adult–specific studies were more likely to analyze FS change dichotomously (29% of older adult–specific studies vs 4% of non–older adult–specific studies; $P=.008$).

Changes in FS and Associated Characteristics

Among studies that reported the percentage of patients who developed functional decline, results ranged widely, from 6%²¹ to 90%,³³ depending on the cancer type, treatment, measure of FS, and timing of assessments (supplemental eTables 2 and 3). Functional improvement occurred in between 9%⁵⁵ and 57%²¹ of patients. The most common patient characteristics associated with functional decline during systemic cancer therapy (Table 2) were older age (7 studies^{1,2,38,39,42,47,51}), worse PS (4 studies^{35,39,52,60}), progressive disease status (4 studies^{2,31,35,60}), pain (4 studies^{24,35,39,45}), anemia (4 studies^{1,20,24,47}), and worse nutritional status (4 studies^{2,31–33}). Definitions of these characteristics are listed in Table 2.

Only 12 studies^{19,22,27,29,34,40–43,46,51,56} examined characteristics associated with functional improvement. Three articles^{34,51,56} reporting results of a study of acute myeloid

Table 1. Measures of Functional Status, Assessment Time Points, and Analytic Approach

Characteristic	Overall n (%)	Older Adult-Specific Studies n (%)	Non-Older Adult-Specific Studies n (%)	P Value ^a
Total, N	44	17	27	
Measures of functional status				
Patient-reported outcomes ^b	43 (98)	17 (100)	26 (96)	1.00
EORTC QLQ-C30	15 (34)	5 (11)	10 (37)	
ADLs	9 (20)	7 (16)	2 (7)	
IADLs	7 (16)	5 (11)	2 (7)	
Physical performance test ^b	9 (20)	3 (18)	6 (22)	1.00
Grip strength	8 (18)	3 (18)	5 (19)	
Walk tests	6 (14)	3 (19)	3 (11)	
Chair stands	5 (11)	1 (12)	4 (15)	
Clinician reported	4 (9)	1 (6)	3 (11)	1.00
ECOG PS	3 (7)	1 (6)	2 (7)	
KPS	1 (2)	0 (0)	1 (4)	
Assessment time points				.91
Pretreatment and 1 follow-up	9 (20)	3 (18)	6 (22)	
Pretreatment and 2 follow-ups	6 (14)	3 (18)	3 (11)	
Pretreatment and ≥3 follow-ups	22 (50)	8 (47)	14 (52)	
Other assessment schedule ^c	7 (16)	3 (18)	4 (15)	
Analytic approach				.008
Change score between 2 assessments	21 (48)	6 (35)	15 (56)	
Longitudinal analysis	14 (32)	3 (18)	11 (41)	
Dichotomous functional decline	6 (14)	5 (29)	1 (4)	
Time to deterioration	2 (5)	2 (12)	0 (0)	
Other analysis ^d	1 (2)	1 (6)	0 (0)	

Abbreviations: ADLs, activities of daily living; EORTC QLQ-C30, EORTC Quality of Life Questionnaire-Core 30; IADLs, instrumental activities of daily living; KPS, Karnofsky performance status; PS, performance status.

^aFisher exact test comparing older adult-specific studies and non-older adult-specific studies.

^bOnly the 3 most common measures of functional status within each subgroup are shown.

^cOther assessment schedule: initial assessment occurred after initiation of systemic therapy.

^dOther analysis: association with patient-reported change in physical condition.

leukemia found that younger age was associated with greater improvement in timed chair stands during intensive chemotherapy. Lower symptom burden was associated with greater improvement in FS in 3 studies.^{22,40,41} Additional characteristics associated with greater functional improvement included female sex,⁵⁶ married status,²² baseline functional dependence,²⁷ better cognition,¹⁹ lack of depression,⁴¹ higher hemoglobin,⁴² cancer type,^{43,46} and <4 positive nodes (in a breast cancer study).²² In a randomized controlled trial of a cognitive behavioral therapy intervention, worse comorbidity was associated with greater improvement in FS in the intervention arm.⁴¹

Discussion

Over almost 3 decades of research from 1991 to 2019, we identified only 44 studies that included older adults and rigorously examined patient characteristics associated

with FS change during systemic cancer treatment. Although the increasing number of studies in more recent years is promising, especially the increasing number of older adult-specific studies, the relative lack of studies examining FS as a longitudinal outcome highlights the importance of synthesizing the existing data and the ongoing need to add this patient-centered outcome to cancer clinical trials and observational cohort studies.

This systematic review identified a substantial amount of heterogeneity between studies in how FS is measured, when it is assessed during systemic cancer treatment, and how it is analyzed, limiting direct comparisons between studies. For example, functional decline was identified in 6% of women aged ≥65 years with breast cancer in a trial of adjuvant therapy using patient-reported worsening physical condition.²¹ In contrast, with use of ADLs, functional

Table 2. Common Characteristics Associated With Functional Decline During Systemic Treatment^a

Characteristic	Total Studies Examining Characteristic and Functional Decline, n	Studies Reporting an Association With Functional Decline, n	Studies Reporting No Association, n	Studies Including Characteristic as a Covariate Without Reporting Association, n	Characteristic Variable Details ^b
Age	25	Older age: 7 ^{1,2,38,39,42,47,51} Younger age: 1 ⁵⁸	12 ^{22,24,26,28-31,35,45,49,52,59}	5 ^{19,20,44,55,57}	<ul style="list-style-type: none"> • Categorical age (y): 65–69 vs 70–74 vs 75–84¹ 25–45 vs 46–70³⁸ <60 vs ≥60⁵¹ <65 vs ≥65⁵⁸ • Continuous age⁴² • Age details not specified^{2,39,47}
Worse PS	11	4 ^{35,39,52,60}	6 ^{20,26,29-31,49}	1 ¹⁹	<ul style="list-style-type: none"> • ECOG PS: 0–1 vs 2–4⁶⁰ • Continuous KPS score³⁹ • Change in ECOG/WHO PS^{35,52}
Progressive disease status	8	4 ^{2,31,35,60}	4 ^{19,42,49,60}		<ul style="list-style-type: none"> • Refractory/progressive disease at treatment completion vs complete remission² • Disease progression/relapse vs new diagnosis⁵¹ • Tumor response: partial/complete response vs progressive/stable disease³⁵ • Disease progression: yes vs no⁶⁰
Pain	7	4 ^{24,35,39,45}	3 ^{26,31,47}		<ul style="list-style-type: none"> • Back pain: yes vs no²⁴ • EORTC QLQ-C30 pain: quite a bit/very much vs not at all/a little³⁵ • Quality of Life–Cancer pain score³⁹ • Pain-O-Meter worst pain intensity score⁴⁵
Anemia	7	4 ^{1,20,24,47}	3 ^{26,30,38}		<ul style="list-style-type: none"> • Categorical hemoglobin level: 7.3–10.9, 11.0–12.9, 13.0–13.9, 14.0–15.6¹ • Continuous hemoglobin level²⁴ • Hemoglobin change ≥1 g/dL²⁰ • Anemia CTCAE grade 0–2 vs 3–4⁴⁷
Worse nutritional status	6	4 ^{2,31-33}	2 ^{30,49}		<ul style="list-style-type: none"> • Sarcopenia: severe (low muscle mass, slow gait speed, and low handgrip strength) vs none² • Mini Nutritional Assessment–Short Form score: ≤11 vs >11³¹ • Cancer cachexia: unintentional weight loss >5% in last 6 mo (or >2% if BMI <20 kg/m²) or presence of muscle depletion vs no cachexia^{32,33}

Abbreviations: BMI, body mass index; EORTC QLQ-C30, EORTC Quality of Life Questionnaire–Core 30; KPS, Karnofsky performance status; PS, performance status.

^aStudies that examined functional decline (N=36).

^bCharacteristic variable details are shown for studies that reported an association with functional decline.

decline was identified in 90% of adults aged ≥70 years with advanced non–small cell lung cancer receiving chemotherapy.³³ Study populations also differed widely in cancer types and specific treatments evaluated. However, most studies included only chemotherapy, revealing a gap in understanding of the functional impact of immunotherapy and targeted therapy, which are key components of modern cancer care.

FS was most commonly assessed using PROs (98% of studies), such as the EORTC QLQ-C30.⁶¹ The widespread use of PRO measures to assess FS among patients with cancer mirrors the broader surge of PROs used to assess symptoms and adverse effects during

routine cancer care and in trials.^{62–65} Advantages of PRO FS measures in clinical care include the ability to assess FS outside of busy clinic visits (eg, previsit questionnaire), remotely without an in-person component (which is increasingly important during the COVID-19 pandemic), and with potentially fewer resources than available when conducting a physical performance test. PROs also allow FS to be more easily studied longitudinally in clinical trials or observational cohort studies in which FS is not the primary outcome. Compared with physical performance tests, PROs are more representative of the patient perspective about their FS. Furthermore, patient-reported functional

decline in ADLs is a strong predictor of overall survival among older adults with cancer.³¹

Several challenges existed in the analysis of FS changes during systemic treatment. There were no uniform definitions of clinically meaningful functional decline or improvement. Despite half of the included studies measuring FS at ≥ 3 follow-up assessments, $>60\%$ only analyzed data from 2 time points, effectively ignoring informative patient-centered information. To illustrate, 48% of studies analyzed longitudinal FS as a change score between 2 assessments, and 14% used a threshold definition of a dichotomous functional decline outcome. Although these types of analytic approaches may assist in clinical interpretation (eg, percentage of patients who experience functional decline after one cycle of chemotherapy³⁰), they do not capture FS trajectories that may include both declines and improvements. In contrast, Hurria et al²² combined more nuanced changes in FS over time and clinically applicable results by conducting 4 analyses using dichotomous outcomes to examine functional decline at the end of adjuvant breast cancer chemotherapy, functional decline at 12 months, improvement of FS among those with decline, and resistance to decline. This study exemplifies an alternative analytic approach that examines several time points and several definitions of FS change.

Older age, which was defined differently across studies, was the most common characteristic associated with functional decline. However, because many studies did not adjust for comorbidity, which is more common among older adults⁶⁶ and associated with functional decline,^{5,24,29,49} there may have been residual confounding. We also found that worse PS, comorbidity, worse nutrition, presence of pain, and anemia were associated with functional decline, highlighting the importance of assessing and addressing these concerns. Evaluation of these characteristics and other domains important to older adults (eg, cognition) through geriatric assessment⁶⁷ is necessary to comprehensively risk-stratify patients. Geriatric assessment results can guide recommendations to address modifiable risk factors via supportive care interventions (eg, physical therapy for worse PS) and comanagement with a multidisciplinary team (eg, palliative medicine for pain, dietitian for malnutrition).⁶⁸

Some older adults with cancer do not experience functional decline during systemic treatment, some experience decline but later improve, and some never improve. “Resilience” refers to the process of adapting well in the face of a stressor⁶⁹ or simply the ability to recover to baseline.^{22,70} Understanding characteristics associated with functional improvement can guide conversations regarding cancer

treatment, because patients may be more willing to undergo treatment if they are likely to recover. Future studies should evaluate the underlying mechanisms by which these characteristics lead to functional improvement, which can guide development of interventions.

This systematic review had several limitations. First, our review focused on the effects of systemic cancer therapy on FS changes and did not examine surgery or radiation. Second, we included only studies that reported results separately for patients who received systemic therapy. Therefore, studies were excluded that examined FS changes in a heterogeneous sample of patients with cancer receiving a variety of treatments. In addition, we focused on studies examining patient characteristics associated with functional decline and improvement rather than performing a comprehensive review of the prevalence of functional change. Finally, because of heterogeneity of patient populations, FS measures, time points, and analytic approaches, a meta-analysis was not possible.

Future studies of cancer treatments in older adults, particularly beyond chemotherapy, must include serial FS measures and analyze these data to determine which older patients are at highest risk of functional decline and which may be more resilient. Measurement of characteristics associated with functional decline, such as nutritional status, which is absent from many trials, is equally important. This is especially critical given the rapidly evolving treatment landscape and the need to understand how newer therapies impact older adults. Many cancer trials already contain a collection of valuable, unanalyzed FS information as part of broader quality-of-life questionnaires. These data have the potential to greatly expand the knowledge base on FS changes during cancer treatment and to inform shared decision-making with information on this important patient-centered outcome.

Furthermore, the development of risk prediction tools, such as risk scores or nomograms, would make information about characteristics associated with FS change more clinically accessible for patient care and shared decision-making. Examples of successful translations of research data into clinical practice include the Cancer and Aging Research Group chemotherapy toxicity calculator^{71,72} and the ePrognosis.org collection of prognostic indices (<https://eprognosis.ucsf.edu/>).⁷³ Studies of FS changes among older adults with the same cancer type are also needed to make results less heterogeneous and more clinically applicable.

Conclusions

There is increasing recognition that change in FS is an important outcome among older patients with cancer

receiving systemic treatment. However, definitions and analyses of functional decline and improvement are heterogeneous, leading to a wide range of prevalence. To better understand functional decline and improve outcomes in this vulnerable population, measures of FS outcomes need to be incorporated with traditional oncology outcomes.

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Characteristics Associated With Functional Changes During Systemic Cancer Treatments: A Systematic Review Focused on Older Adults

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eFigure 1: Study Selection Flowchart

eTable 1: Search Strategies

eTable 2: Older Adult–Specific Studies Meeting Inclusion Criteria and Primary Functional Status Results

eTable 3: Non–Older Adult–Specific Studies Meeting Inclusion Criteria and Primary Functional Status Results

eFigure 1. Study selection flowchart.

eTable 1. Search Strategies

Database	Search Strategy
PubMed	<p>("Neoplasms"[MeSH] OR Neoplas*[tiab] OR Cancer*[tiab] OR Malignan*[tiab] OR Carcin*[tiab] OR Oncolog*[tiab] OR Tumor*[tiab] OR Tumor*[tiab])</p> <p>AND</p> <p>("Consolidation Chemotherapy"[MeSH] OR "Antineoplastic Combined Chemotherapy Protocols"[MeSH] OR "Induction Chemotherapy"[MeSH] OR "Maintenance Chemotherapy"[MeSH] OR "Chemoradiotherapy"[MeSH] OR "Chemotherapy, Adjuvant"[MeSH] OR "Antineoplastic Protocols"[MeSH] OR "Radioimmunotherapy"[MeSH] OR "Antineoplastic Agents"[MeSH] OR Chemotherap* OR Antineoplastic* OR Anticancer OR Antitumor OR Antitumour OR Chemoradiotherap* OR Radiochemotherap* OR Radioimmunotherap* OR "Immunotherapy"[MeSH] OR Immunotherap* OR "Molecular Targeted Therapy"[MeSH] OR "Targeted Therapies"[tiab] OR "Targeted Therapy"[tiab])</p> <p>AND</p> <p>("Physical Functional Performance"[MeSH] OR "Functional Decline"[tiab] OR "Functional Status"[tiab] OR "Physical Function"[tiab] OR "Mobility"[tiab] OR "Activities of Daily Living"[MeSH] OR "Activity of Daily Living"[tiab] OR "Activities of Daily Living"[tiab] OR ADL[tiab] OR "Daily Living Activity"[tiab] OR "Daily Living Activities"[tiab])</p>
Embase	<p>('neoplasm'/exp OR neoplas* OR cancer OR malignan* OR carcin* OR oncolog* OR tumor* OR tumor*)</p> <p>AND</p> <p>('chemotherapy'/exp OR 'consolidation chemotherapy'/exp OR 'induction chemotherapy'/exp OR 'maintenance chemotherapy'/exp OR 'chemoradiotherapy'/exp OR 'adjuvant chemotherapy'/exp OR 'radioimmunotherapy'/exp OR 'antineoplastic agent'/exp OR chemotherap* OR antineoplastic* OR anticancer OR antitumor OR antitumour OR chemoradiotherap* OR radiochemotherap* OR radioimmunotherap* OR 'immunotherapy'/exp OR immunotherap* OR 'molecularly targeted therapy'/exp OR 'targeted therap*')</p> <p>AND</p> <p>('functional decline'/exp OR 'functional decline' OR 'functional status'/exp OR 'functional status' OR 'functional performance'/exp OR 'functional performance' OR 'physical function'/exp OR 'physical function' OR 'patient mobility'/exp OR mobility OR 'daily life activity'/exp OR 'activit* of daily living' OR adl OR 'daily living activit*')</p>
Web of Science: all databases	<p>(Neoplas* OR Cancer* OR Malignan* OR Carcin* OR Oncolog* OR Tumor* OR Tumor*)</p> <p>AND</p> <p>(Chemotherap* OR Antineoplastic* OR Anticancer OR Antitumor OR Antitumour OR Chemoradiotherap* OR Radiochemotherap* OR Radioimmunotherap* OR Immunotherap* OR "Targeted Therapies" OR "Targeted Therapy")</p> <p>AND</p> <p>("Functional Decline" OR "Functional Status" OR "Physical Function" OR Mobility OR "Activity of Daily Living" OR "Activities of Daily Living" OR ADL OR "Daily Living Activity" OR "Daily Living Activities")</p>
Cochrane Register of Controlled Trials	<p>(Neoplas* OR Cancer* OR Malignan* OR Carcin* OR Oncolog* OR Tumor* OR Tumor*)</p> <p>AND</p> <p>(Chemotherap* OR Antineoplastic* OR Anticancer OR Antitumor OR Antitumour OR Chemoradiotherap* OR Radiochemotherap* OR Radioimmunotherap* OR Immunotherap* OR "Targeted Therapies" OR "Targeted Therapy")</p> <p>AND</p> <p>("Functional Decline" OR "Functional Status" OR "Physical Function" OR Mobility OR "Activity of Daily Living" OR "Activities of Daily Living" OR ADL OR "Daily Living Activity" OR "Daily Living Activities")</p>

eTable 2. Older Adult-Specific Studies Meeting Inclusion Criteria and Primary Functional Status Results (N=17)

Age Inclusion Criteria	Study/Quality Assessment Score ^a	Sample (Cancer Stage)	N	Age Distribution	Systemic Cancer Treatment(s)	Primary Measure(s) of Function Status	Assessment Time Points	Definition of Functional Status During Treatment	Change in Functional Status During Treatment	Association of Patient Characteristics ^b With Functional Status Change
Age ≥60 y	Klepin et al ¹ Score: 8	AML Single-center observational cohort (United States)	49	Mean age, 70 y (SD, 2); 57.1% aged 60–69 y; 34.7% aged 70–79 y; 8.2% aged ≥80 y	Chemo	Paper Assessment Tool for Disability (ADL, IADL, mobility), SPPB, grip strength	Pretx (hospitalization for induction chemo); 8 wk after discharge	Decline using standard cutoffs	<ul style="list-style-type: none"> IADL dependence worsened (1.4 baseline vs 2.1 follow-up; $P<.001$) SPPB worsened (7.5 vs 5.9; $P=.02$) Grip strength declined (mean, 38.9 vs 34.2; $P<.001$; women, 24.5 vs 21.8; $P=.007$) 	<ul style="list-style-type: none"> Unfavorable cytogenetic risk score ($P=.05$) and receipt of the most intensive chemotherapy (granulocyte colony-stimulating factor) were associated with ADL decline Higher BMI ($P=.03$) and unfavorable cytogenetic risk score ($P=.01$) were associated with IADL decline Depressive symptoms at baseline and follow-up were associated with decline in SPPB ($P=.03$) Receipt of the most intensive chemotherapy was associated with decline in SPPB ($P=.02$) Higher baseline cognition score was associated with improvement in SPPB baseline ($P=.05$) Resistance status was not associated with functional decline
Age ≥65 y	Dont et al ² Score: 9	Multicenter observational cohort (Italy)	578	Mean age, 72.6 y (SD, 5.0); median, 71.9 y (range, 64.9–100 y)	Chemo	ADL, ECOG PS	Pretx; before each cycle (for ≥12 wk)	Longitudinal modeling	<ul style="list-style-type: none"> Mean ADL score worsened up to wk 20 Progressive worsening of ECOG PS starting from wk 11–13 (pretx, 49% ECOG 0, 41% ECOG 1, 9.8% ECOG ≥2; at follow-up, 46.6% ECOG 0, 42.2% ECOG 1, 11.1% ECOG ≥2) 	<ul style="list-style-type: none"> At wk 12, hemoglobin change of ≥1 g/dL was associated with ADL decline ($P<.05$) Stage and PS were not associated
Age ≥65 y	Gajra et al ³ Score: 10	Breast; stages I–III Multicenter RCT (United States)	145	Median age 71 y; 40% aged 65–69 y; 54% aged 70–80 y; 6% aged >80 y	Adjuvant chemo (AC, CMF) vs capecitabine	Subjective Significance Questionnaire (self-reported change in physical condition), EORTC QLQ-C30 PF	Midtx, 1, 12, 18, and 24 mo after EOT	Self-reported worsening physical condition	<ul style="list-style-type: none"> At midtx, 25% reported worse, 49% same, and 26% improved physical condition At 1 y, 6% reported worse, 37% same, and 57% improved physical condition 	<ul style="list-style-type: none"> Low preference for chemo was associated with worse physical condition at midtx ($P=.005$) but not at the other time points No association between chemo preference and EORTC QLQ-C30 PF
Age ≥65 y	Goodwin et al ⁴ Score: 10	Solid tumor; all stages Multicenter observational cohort (United States)	26	Mean age, 71 y (SD, 5; range, 65–82 y)	Chemo	Short Functional Dependence Scale ADL and IADL	Pretx; chemo visits 1–9	Longitudinal modeling	<ul style="list-style-type: none"> Not reported 	<ul style="list-style-type: none"> Older age, cancer type, surgery, radiation, and lower hemoglobin were associated with higher functional dependence across visits
Age ≥65 y	Hurria et al ⁵ Score: 10	Breast; stages I–III Multicenter RCT (United States)	256	Mean age, 71.9 y (SD, 4.7; range, 65–85 y)	Chemo	EORTC QLQ-C30 PF	Pretx, posttx; 12 mo after chemo initiation	Decline from pretx to posttx: ≥10-point decrease from pretx to posttx Resilience (only those declined): returned to within 10 points of pretx PF Decline at 12 mo: ≥10-point decrease from pretx to 12 mo after Resistance to decline: <10-point decrease from pretx to posttx and 12 mo after	<ul style="list-style-type: none"> Decline from pretx to posttx: 42% (median decline, 20 points; range, 11.7–73.3) Resilience at 12 mo: 47% recovered Decline at 12 mo: 30% (median decline, 20 points; range, 13.1–53.3) Resistance to decline: 49.6% 	<ul style="list-style-type: none"> Decline from pretx to posttx was associated with baseline fatigue (OR, 2.37; $P=.02$). Comorbidity was not associated at posttx Resilience at 12 mo was associated with being married (OR, 2.52; $P=.04$), having <4 positive nodes (OR, 3.57; $P=.048$), and no pretx appetite loss (OR, 3.65; $P=.02$) Decline at 12 mo was associated with being unmarried (OR, 1.98; $P=.01$) and pretx dyspnea (OR, 2.37; $P=.007$). Fatigue, having <4 positive nodes, and older age were not associated with decline at 12 mo Resistance to decline was associated with no pretx fatigue (OR, 2.49; $P=.01$) and no dyspnea (OR, 1.94; $P=.03$). Comorbidity was not associated

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eTable 2. Older Adult-Specific Studies Meeting Inclusion Criteria and Primary Functional Status Results (N=17) (cont.)

Age Inclusion Criteria	Study/Quality Assessment Score ^a	Sample (Cancer Type(s); Stage)	N	Age Distribution	Systemic Cancer Treatment(s)	Primary Measure(s) of Function Status	Assessment Time Points	Definition of Functional Change	Change in Functional Status During Treatment	Association of Patient Characteristics ^b With Functional Status Change
Age ≥65 y	Manokumar et al ^b Score: 9	Single-center observational cohort (Canada)	36	First line: mean age, 77.3 y (SD, 4.5) Second line: mean age, 71.4 y (SD, 6.2)	Docetaxel	OARS-IADL, TUG, timed chair stands, handgrip strength, falls (≥1)	Pretx; every 3 mo until posttx	Change score	<ul style="list-style-type: none"> First-line chemo: IADL: 21% improved, 52% stable, 28% declined TUG: 22% improved, 39% stable, 35% declined Timed chair stands: 17% improved, 42% stable, 42% declined Handgrip strength: 11% improved, 61% stable, 29% declined Falls: 38% experienced one fall 	<ul style="list-style-type: none"> VES-13 score ≥3 was associated with greater increase in timed chair stand score
Age ≥65 y	Miaikowski et al ^c Score: 9	Multicenter observational cohort (United States)	363	Mean age between 70.7 y (SD, 72.7 y (SD, 5.4–6.0))	Chemo	SF-12 PCS	Baseline (chemo within prior 4 wk); 1 and 2 wk after chemo; then repeat for subsequent cycle	Change score	<ul style="list-style-type: none"> 3 classes based on latent class analysis (above, below, and well below the normative norm of individuals aged 65–74 y) PCS score remained relatively stable over 2 cycles of chemo 	<ul style="list-style-type: none"> Unemployment ($P<.001$), lower income ($P=.002$), and a history of heart disease ($P=.001$) were associated with being in the below and well below classes Exercise on a regular basis ($P<.001$), self-reported back pain ($P<.001$), lower hemoglobin ($P=.002$), and self-reported depression ($P=.028$) were associated with being in the well below class Age, sex, cancer diagnosis, time since cancer diagnosis, number of metastatic sites, number and types of prior cancer tx, and chemo cycle length were not associated with latent class membership
Age ≥65 y	Rier et al ^d Score: 11	Single-center observational cohort study (Netherlands)	142	Median age, 72 y (range, 69–78)	Chemo	IADL	Pretx; midtx; posttx	IADL independence: ≥8 points; IADL decline: ≥3-point decline at posttx or ≥2-point decline at 1 y posttx	<ul style="list-style-type: none"> IADL independence: pretx (63.9%), posttx (56.3%) IADL decline: 11.5% 	<ul style="list-style-type: none"> Age ($P=.05$), impaired cognition ($P=.05$), refractory or progressive disease at posttx (vs complete remission: $P=.003$), and severe sarcopenia (vs normal: $P=.05$) were associated with IADL decline (all univariable analyses) None were associated with decline in multivariable analysis
Age ≥65 y	Verelst et al ^e Score: 11	Multicenter RCT (Netherlands)	284	Median age, 72 y (range, 65–84)	Melphalan/ prednisone/ melphalan/ prednisone/ thalidomide	EORTC QLQ-C30 PF	Pretx; cycle 3 (3 mo); cycle 8 (9 mo); 12 mo, 18 mo	Change score	<ul style="list-style-type: none"> EORTC QLQ-C30 improved in both arms over time, though this was in favor of the 2-drug regimen early during induction phase 	<ul style="list-style-type: none"> Female sex was associated with lower scores on EORTC QLQ-C30 PF ($P=.003$)
Age ≥65 y	Wong et al ^f Score: 10	Multicenter observational cohort (United States)	363	Mean age, 71.4 y (SD, 5.5)	Chemo	SF-12 PCS	Baseline (chemo within prior 4 wk); 1 and 2 wk after chemo; then repeat for subsequent cycle	Longitudinal modeling	<ul style="list-style-type: none"> PCS scores decreased slightly (0.21 points; $P<.01$) at each subsequent assessment 	<ul style="list-style-type: none"> Higher morning fatigue (PCS score = .04) and lower enrollment PCS scores ($P=.01$) were associated with decrease in PCS score over time Age, sex, ethnicity, education, marital status, living alone, employment status, child care responsibilities, BMI, smoking status, hemoglobin, KPS, comorbidity, regular exercise, cancer type, time since cancer diagnosis, prior cancer treatments, metastatic disease, chemo toxicity index, cycle length, evening fatigue, morning energy, evening energy, pain, anxiety, and attentional function were not associated

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eTable 2. Older Adult-Specific Studies Meeting Inclusion Criteria and Primary Functional Status Results (N=17) (cont.)

Age Inclusion Criteria	Study/Quality Assessment Score ^a	Study Design	Sample (Cancer Type(s); Stage)	N	Age Distribution	Systemic Cancer Treatment(s)	Primary Measure(s) of Function Status	Assessment Time Points	Definition of Functional Change	Change in Functional Status During Treatment	Association of Patient Characteristics ^b With Functional Status Change
Age ≥65 y	Xue et al ¹¹ Score: 7	Single-center RCT (China)	NSCLC; stages IIIb-IV	24	Mean age, 73 y (SD, 5.3; range, 65-83 y)	Chemo	EORTC QLQ-C30 PF	Pretx; day 1 before chemo; 7, 21, 42, 63 after chemo	Change score	<ul style="list-style-type: none"> No change in functioning scale among function-independent and mildly function-impaired patients For function-dependent patients, PF improved 	<ul style="list-style-type: none"> Worse baseline functional status was associated with improvement in PF
Age ≥70 y	Chakiba et al ¹² Score: 11	Multicenter observational cohort (France)	Colon, pancreatic, stomach, ovarian, bladder, prostate, lung, NHL, cancer of unknown primary; all stages	292	Median age, 77 y (range, 70-93 y); 36% aged 70-75 y; 35% aged 76-80 y; 22% aged 81-85 y; 7% aged >85 y	Chemo	ADL	Pretx; before cycle 2	Decline; 0.5-point decrease	<ul style="list-style-type: none"> 16% declined; 10% improved; 73% stable ADL score 	<ul style="list-style-type: none"> Abnormal G8 (≤14) was associated with functional decline (OR 4.3; 95% CI, 1.28-14.92; P=.018) in multivariable model Age, sex, tumor type, stage, neutrophil count, platelet count, creatinine clearance, albumin, and CRP were not associated
Age ≥70 y	Fiteni et al ¹³ Score: 10	Multicenter RCT (France)	NSCLC; stages III-IV	361	Mean age, 77.1 y (range, 70-88 y); 49.9% aged <77 y; 50.1% aged ≥77 y	Carboplatin/paclitaxel vs gemcitabine vs vinorelbine	EORTC QLQ-C30 PF	Pretx; 6 and 18 wk	PF MCID; 5 points; time to deterioration	<ul style="list-style-type: none"> Median time to deterioration: doublet chemo 2.04 mo (95% CI, 1.87-3.88) vs monotherapy 1.71 (95% CI, 1.58-1.91); P=.01 	<ul style="list-style-type: none"> Doublet chemo was associated with longer time to PF deterioration (HR, 0.57; 95% CI, 0.42-0.78; P=.008) Female sex (HR, 1.53; 95% CI, 1.09-2.15; P=.01) and CD score >2 (HR, 1.50; 95% CI, 1.08-1.12; P=.002) were associated with shorter time to PF deterioration Age, P5, smoking status, BMI, MMSE, ADL stage, and histology were not associated with time to PF deterioration
Age ≥70 y	Hoppe et al ¹⁴ Score: 12	Multicenter observational cohort (France)	Colon, pancreatic, stomach, ovarian, bladder, prostate, lung, NHL, unknown primary origin; all stages	364	Median age, 77.3 y (range, 70-93 y)	Chemo	Katz ADL	Pretx; before cycle 2	ADL decline: decrease of ≥0.5 in total score	<ul style="list-style-type: none"> Decline: 16.7% (median, 0.5 points; range, 0.5-3) Improvement: 10.7% (median, 0.5 points; range, 0.5-2.5) 	<ul style="list-style-type: none"> High GDS-15 (OR, 2.16; P=.03) and low IADL (OR, 2.87; P=.04) were associated with decline Age, sex, P5, weight loss, BMI, leukocytes, platelet count, creatinine, CRP, hemoglobin, albumin, tumor type, disease extension, CRF-G, MAX2 index, ADL, MNA, MMSE, and GUG were not associated with decline
Age ≥70 y	Kenis et al ¹⁵ Score: 11	Multicenter observational cohort (Belgium)	Breast, CRC, ovarian, lung, prostate, hematologic malignancy; all stages	439	Mean age, 75 y (range, 70-95 y)	Chemo	Katz ADL, Lawton IADL	Pretx; 2-4 mo after chemo	ADL decline: change of ≥2 in total score IADL decline: change of ≤1 in total score	<ul style="list-style-type: none"> ADL decline: 19.9% IADL decline: 41.3% 	<ul style="list-style-type: none"> Abnormal nutritional status (OR, 2.02; P=.007) and baseline IADL dependency (OR, 1.76; P=.037) were associated with ADL decline Disease status (progression/relapsed vs new diagnosis; OR, 0.59; P=.014) was associated with IADL decline Age, geriatric screening tools, ECOG P5, fall, pain, polypharmacy, living situation, comorbidity, fatigue, baseline ADL, cognition, depression, cancer type, and tx were not associated with both ADL and IADL decline
Age ≥70 y	Morikawa et al ¹⁶ Score: 8	Single-center observational cohort (Japan)	NSCLC; stages III-IV	18	Median age, 74.5 y (range, 70-82 y)	Chemo, targeted therapy	Physical activity (accelerometer)	Pretx (before hospitalization); during hospitalization; 1, 2, and 3 wk after discharge	Hospitalization-associated physical inactivity: decreased mean daily steps both during hospitalization and during the first week compared with mean daily steps at baseline	<ul style="list-style-type: none"> 50% walked fewer daily steps during hospitalization and did not recover to baseline level at 1 wk after discharge 	<ul style="list-style-type: none"> Cachexia and longer hospitalization (≥8 vs <8 d) were associated with hospitalization-associated physical inactivity

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eTable 2. Older Adult-Specific Studies Meeting Inclusion Criteria and Primary Functional Status Results (N=17) (cont.)

Age Inclusion Criteria	Study/Quality Assessment Score ^a	Sample (Cancer Type(s); Stage)	N	Age Distribution	Systemic Cancer Treatment(s)	Primary Measure(s) of Function Status	Assessment Time Points	Definition of Functional Change	Change in Functional Status During Treatment	Association of Patient Characteristics ^b With Functional Status Change
Age ≥70 y	Naïto et al ¹⁷ Score: 18	NSCLC; stages III–IV	30	Median age, 74 y (range, 70–82 y)	Chemo- targeted therapy	Barthel ADL	Pretx; each hospital visit	Disabling event defined as decrease in Barthel ADL >10 points; disability-free survival	<ul style="list-style-type: none"> 90% were disabled at the cutoff date Disabling events: stair climbing (100%), morbidity (98%), bathing (89%), toilet use (53%), and transferring (41%) 	<ul style="list-style-type: none"> Cachexia was associated with shorter disability-free survival (7.5 vs 17.1 mo; $P<.05$) and longer postdisability survival (2.3 vs 0.7 mo; $P<.05$)

Abbreviations: AC, cyclophosphamide/doxorubicin; ADL, activities of daily living; AML, acute myeloid leukemia; BMI, body mass index; CCI, Charlson comorbidity index; chemo, chemotherapy; CIRS-G, Cumulative Illness Rating Scale–Geriatrics; CMF, cyclophosphamide/methotrexate/fluorouracil; CRC, colorectal cancer; CRP, C-reactive protein; EORTC QLQ-C30, EORTC Quality of Life Questionnaire-Core 30; EOT, end of treatment; G8, Geriatric 8; GDS-15, Geriatric Depression Scale–15; GI, gastrointestinal; GUG, Timed Get Up and Go; GYN, gynecologic; HR, hazard ratio; IADL, instrumental activities of daily living; KPS, Karnofsky performance status; MCID, minimal clinically important difference; midtx, midtreatment; MMSE, Mini Mental State Examination; MNA, Mini Nutritional Assessment; NHL, non-Hodgkin lymphoma; NSCLC, non-small cell lung cancer; OARS, Older Americans Resources and Services; OR, odds ratio; PCS, physical component summary; PF, physical functioning; posttx, posttreatment; PS, performance status; pretx, pretreatment; RCT, randomized controlled trial; SF-12, 12-item Short Form Health Survey; SPPB, Short Physical Performance Battery; TUG, Timed Up and Go; tx, treatment; VES-13, Vulnerable Elders Survey.

^aQuality assessment was performed using the National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, which consists of 14 criteria.

^bWe list patient characteristics that are associated with functional change and those that are not associated. We did not list patient characteristics if they were only included as covariates without a reported result.

eTable 3. Non–Older Adult–Specific Studies Meeting Inclusion Criteria and Primary Functional Status Results (N=27)

Study/Quality Assessment Score ^a	Study Design	Sample (Cancer Type(s), Stage)	N	Age Distribution	Systemic Cancer Tx(s)	Primary Measure(s) of Functional Status	Assessment Time Points	Definition of Functional Status Change	Change in Functional Status During Tx	Association of Patient Characteristics ^b With Functional Status Change
Alibhai et al ¹⁰ Score: 10	Multicenter observational cohort (Canada)	AML	237	59% aged <60 y (median age, 52.9 y); 41% aged ≥60 y (median age, 68.7 y; range, 21–81 y)	Induction: daunorubicin/cytarabine	2MWT, chair stands, grip strength, IADL	Pretx: 4–6, 9–12, 13–16 wk; 6, 8, 10, 12 mo	2MWT MCD: 59 ft; grip strength MCD: 4.5 kg (MCD not reported for chair stands and IADL)	<ul style="list-style-type: none"> • 2MWT (P<.001), chair stands (P<.001), and IADLs (P=.003) improved • No change in grip strength 	<ul style="list-style-type: none"> • Younger age was associated with greater recovery in chair stands (P=.048) • Sex, smoking status, baseline PS, and hemoglobin were not associated with change in physical function
Bergman et al ¹⁹ Score: 9	Single-center observational cohort (Sweden)	SCLC; all stages	62	Mean age, 66 y (range, 36–80 y); 35% aged ≥70 y	Chemo	Sickness Impact Profile physical index (ambulation, body care/movement, mobility)	Pretx; 3, 6, 9, 12 mo	Correlation with physical index change score	<ul style="list-style-type: none"> • Body care/movement subscale worsened 5 points at 3 mo and 6.1 points at 6 mo (P<.05); no difference at 12 mo • No change in ambulation or mobility 	<ul style="list-style-type: none"> • Characteristics associated with worsening physical index: worsening ECOG/WHO PS, pain, appetite (P<.01); tumor response, cisplatin-containing regimen, neutropenia (P<.05) • Age, sex, depression, hair loss, and nausea were not associated
Bezjak et al ²⁰ Score: 13	Multicenter RCT (global)	NSCLC; stages IIIB–IV	425	Median age, 61 y	Erlotinib vs placebo	EORTC QO-C30 PF	Pretx; every 4 wk during tx; 4 wk posttx; every 12 wk until EOT	PF decline: ≥10-point decrease, improvement: ≥10-point increase, stable: <10-point change	<ul style="list-style-type: none"> • Erlotinib: 51% declined, 31% improved, 18% stable PF 	<ul style="list-style-type: none"> • Only tx with erlotinib was associated with improvement in PF (P=.006). • Age, sex, ethnicity, PS prior tx, histology, and smoking history were not associated
Chen et al ²¹ Score: 9	Single-center observational cohort (USA)	Solid tumor; nonleukemic hematologic malignancy; all stages	37	Mean age, 75.6 y (range, 70–87 y); 38% aged 70–74 y; 54% aged 75–80 y; 8% aged 81–87 y	Chemo	IADL, ECOG PS	Pretx; EOT (or at 6 mo)	Change score	<ul style="list-style-type: none"> • Mean 1.44-point decline in IADL score (P=.04) • No change in ECOG PS 	<ul style="list-style-type: none"> • Severe chemo toxicities were associated with decline in IADL (change score, −293 vs −0.17; P=.03) and ECOG PS (change score, 0.56 vs −0.11; P=.03)
de Jong et al ²² Score: 12	Multicenter observational cohort (Netherlands)	Breast; stages I–III	157	Mean age, 47.3 y (SD, 8.8; range, 25–70 y)	Adjuvant CMF or doxorubicin-containing regimen	Multidimensional Fatigue Inventory reduced activity subscale	Cycles 1, 3, 5; 4 and 12 wk after last cycle	Longitudinal modeling	<ul style="list-style-type: none"> • Activity level stable during study period 	<ul style="list-style-type: none"> • Older age and not having children were associated with lower activity level over time • Mastectomy (vs lumpectomy), longer duration of radiation, and fewer total chemo treatments were associated with lower activity level • Chemo type, marital status, education, having a job, hemoglobin, and time between surgery and chemo were not associated with change in activity level
Dodd et al ²³ Score: 10	Multicenter RCT (USA)	All types; all stages	93	Mean age, 55.4 y (SD, 14.6)	Chemo (RCT of 2 mouthwashes for mucositis)	Patient-reported KPS	Pretx; end of cycle 3	Longitudinal modeling	<ul style="list-style-type: none"> • Pretx mean KPS 84.8 • End of cycle 3, mean KPS, 82.7 	<ul style="list-style-type: none"> • Pretx KPS, older age, worse pain, and worse fatigue were associated with worse KPS at the end of cycle 3 • Sleep insufficiency was not associated
Dodd et al ²⁴ Score: 8	Multicenter RCT (USA)	Breast; stages I–III	112	Mean age, 50 y (SD, 9.3)	Chemo (RCT of exercise intervention during chemo, after chemo, vs usual care)	Patient-reported KPS	Before cycle 2; EOT; 1 y	Association with symptom clusters (pain, fatigue, sleep disturbance, depression) at each assessment	<ul style="list-style-type: none"> • Not reported 	<ul style="list-style-type: none"> • Before cycle 2, all low symptom cluster was associated with better KPS than moderate cluster (P=.002) • At EOT, all low cluster was associated with better KPS than all other clusters (P<.0001) • At 1 y, mild cluster was associated with better KPS than moderate and all high clusters (P<.005)
Doorenbos et al ²⁵ Score: 10	Multicenter RCT (USA)	Solid tumor; all stages	237	Mean age, 60 y (SD, 10; range, 31–87 y)	Chemo (RCT of cognitive behavioral theory-guided intervention vs usual care)	SF-36 PF	Baseline; 10, 20, 32 wk	Longitudinal modeling	<ul style="list-style-type: none"> • Baseline mean PF 64.2 (SD, 29.5), wk 20 mean PF 70.6 (SD, 28.1) 	<ul style="list-style-type: none"> • At wk 20, patients with a higher number of chronic health conditions (vs low number) benefited more from the effect of the intervention on PF (P=.02) • Lower depressive symptoms and lower symptom limitations were associated with increased intervention effect on PF (P=.001); men with lung cancer had higher PF than women with lung cancer (P=.02)

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eTable 3. Non-Older Adult-Specific Studies Meeting Inclusion Criteria and Primary Functional Status Results (N=27) (cont.)

Study/Quality Assessment Score ^a	Study Design	Sample (Cancer Type(s); Stage)	N	Age Distribution	Systemic Cancer Tx(s)	Primary Measure(s) of Functional Status	Assessment Time Points	Definition of Functional Status Change	Change in Functional Status During Tx	Association of Patient Characteristics ^b With Functional Status Change
Fallowfield et al ²⁶ Score: 12	Multicenter RCT (global)	Solid tumor or nonmyeloid hematologic malignancies; all stages	375	Epoetin arm: mean age, 58.1 y (SD, 14.2; range, 18–84 y) Placebo arm: mean age, 59.2 y (SD, 14.3; range, 21–88 y)	Nonplatinum chemo (RCT of epoetin alfa vs placebo)	CLAS daily activities; SF-36 PCS	Randomization; 4, 16, 28 wk	Change score at last available assessment	<ul style="list-style-type: none"> Mean CLAS daily activities change score: epoetin arm 7.78 vs placebo arm -1.96 ($P<.04$) No difference in mean SF-36 PCS change score by arm: epoetin arm 1.27 vs placebo arm 0.05 ($P=.33$) 	<ul style="list-style-type: none"> Higher hemoglobin level was associated with higher CLAS daily activities and SF-36 PCS over time ($P<.01$) Higher baseline endogenous erythropoietin was associated with lower CLAS daily activities over time ($P<.05$) Lower reticulocyte count and prestudy transfusion dependency were associated with higher SF-36 PCS over time ($P<.05$) Older age was associated with lower SF-36 PCS score over time ($P<.01$) Age, race, and disease progression were not associated with change in CLAS daily activities Sex and disease progression were not associated with change in SF-36 PCS
Frödin et al ²⁷ Score: 9	Single-center observational cohort (Sweden)	Myeloma, lymphoma, testicular, sarcoma, AML; all stages	96	Mean age, 54 y (SD, 12)	Auto-SCT	EORTC QLO-C30 PF	Pretx; weekly during wk 1–4; monthly during months 2 and 3; 6 mo; every 6 mo up to year 3	Longitudinal modeling	<ul style="list-style-type: none"> At wk 2, 42% declined in PF PF improved back to baseline by month 2 	<ul style="list-style-type: none"> At wk 2, a diagnosis of myeloma (vs lymphoma) was associated with better PF ($P=.001$)
Frödin et al ²⁸ Score: 10	Single-center observational cohort (Sweden)	Any hematologic malignancy; all stages	94	Mean age, 48 y	Allogeneic SCT, reduced-intensity conditioning	EORTC QLO-C30 PF	Pretx; weekly during wk 1–4; monthly during months 2 and 3; 6 mo; every 6 mo up to year 3	Change score	<ul style="list-style-type: none"> Pretx PF mean: 81 At 3 wk, change score -36 ($P<.05$ vs pretx) At 3 mo, change score -20 ($P<.05$) At 1 y, change score -8 At 3 y, change score -5 	<ul style="list-style-type: none"> Extensive chronic GVHD was associated with worse PF than limited chronic GVHD and no chronic GVHD at 1.5, 2, and 2.5 y (all $P<.01$)
Gaton-Johansson et al ²⁹ Score: 11	Single-center observational cohort (USA)	Breast; all stages	30	Mean age, 52.7 y (SD, 10.2; range, 32–72 y)	Chemo	FACT-Breast physical and functional well-being	Pretx; midpoint; EOT	Longitudinal modeling	<ul style="list-style-type: none"> Physical and functional well-being decreased at midpoint and EOT compared with pretx (all $P<.001$) 	<ul style="list-style-type: none"> Worst pain intensity was associated with worse functional well-being at EOT No association with age or stage
Given et al ³⁰ Score: 10	Multicenter RCT (USA)	Solid tumor and NHL; all stages	113	Mean age, 58 y (SD, 10.5)	Chemo (RCT of nursing symptom management intervention vs usual care)	SF-36 physical role functioning	Baseline (within 8 wk of chemo initiation); 10, 20 wk	Longitudinal modeling	<ul style="list-style-type: none"> Intervention arm: mean physical role functioning score 11 (SD, 22) at baseline, 50 (SD, 41) at 20 wk Control arm: mean physical role functioning score 11 (SD, 22) at baseline, 31 (SD, 36) at 20 wk 	<ul style="list-style-type: none"> Intervention was associated with improved physical role functioning at 20 wk (mean score, 50 vs 31) Diagnosis of breast cancer (vs nonbreast cancer) was associated with improved physical role functioning at 20 wk
Greimel et al ³¹ Score: 10	Multicenter RCT (Germany, Austria)	Ovarian; stages IIB–IV	416	Mean age, 56.6 y (SD, 10.1)	Cisplatin/paclitaxel vs carboplatin/paclitaxel	EORTC QLO-C30 PF	Pretx; cycles 2, 4; EOT, every 6 mo	Longitudinal modeling	<ul style="list-style-type: none"> Mean PF change score, 9.4 (carboplatin/paclitaxel) vs 1.7 (cisplatin/paclitaxel) 	<ul style="list-style-type: none"> Carboplatin/paclitaxel arm had better EOT PF Characteristics associated with worse PF over time: anemia, neurotoxicity, toxicity, older age Hematologic toxicity, pain, and tx change in PF over time
Kim et al ³² Score: 8	Single-center observational cohort (Korea)	DLBCL or FL; all stages	32	Mean age, 55.9 y (range, 21–79 y)	Chemo	SF-36 PCS	Pretx; second visit during chemo; last visit after cycle 6	PCS score <40	<ul style="list-style-type: none"> Pretx: 12 patients had a PCS score <40 Second visit: 12 patients had a score <40 Last visit: 5 patients had a score <40 	<ul style="list-style-type: none"> Neuropathy at second visit was associated with lower PCS score at the last visit (PCS score, 44.5 for neuropathy vs 49.9 for nonneuropathy; $P=.02$)
Kinsey et al ³³ Score: 12	Multicenter RCT (global)	NSCLC; stages IIB–IV	236	37.5% aged ≥ 65 y	Chemo	Sair climb power	Pretx; day 84	Percentage loss	<ul style="list-style-type: none"> $\geq 10\%$ loss: 31% 0 to <10% loss: 18% ≥ 0 to <10% gain: 10% $\geq 10\%$ gain: 31% 	<ul style="list-style-type: none"> Taxane (vs nontaxane therapy; $P=.023$) and prior smoking (vs current use; $P=.027$) were associated with functional decline Prior weight loss, disease response, lean body mass, ECOG PS, disease stage, age, sex, and comorbidities were not associated with functional decline

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eTable 3. Non–Older Adult–Specific Studies Meeting Inclusion Criteria and Primary Functional Status Results (N=27) (cont.)

Study/Quality Assessment Score ^a	Study Design	Sample (Cancer Type(s); Stage)	N	Age Distribution	Systemic Cancer Tx(s)	Primary Measure(s) of Functional Status	Assessment Time Points	Definition of Functional Status Change	Change in Functional Status During Tx	Association of Patient Characteristics ^b With Functional Status Change
Land et al, ²⁰⁰⁴ /12	Multicenter RCT (USA, Canada)	Breast; stages I–II	160	50.6% aged ≤49 y; 32.5% aged 50–59 y; 16.9% aged ≥60 y	Chemo	SF-36 return to normal activity	Pretx; start of each chemo cycle (several time points from wk 3 to 52)	Change score	<ul style="list-style-type: none"> Return to normal activity score did not change during chemo 	<ul style="list-style-type: none"> Lumpectomy and radiation (vs mastectomy) were associated with lower return to normal activity score (1.11 points lower; $P=.02$) Chemo (CMF vs AC) tamoxifen, surgery, tumor size, and age were not associated with return to normal activity score
Mohamedali et al ²⁵ Score: 10	Single-center observational cohort (Canada)	AML	103	Younger; median age, 52.0 y (range, 21–59 y) Older; median age, 69.7 y (range, 60–80 y)	Induction: daunorubicin, cytarabine	EORTC QLO-C30 PF handgrip strength, timed chair stands, 2MWT	Time of diagnosis: 4–5 wk; 8–10 wk; 12–16 wk (after each cycle of chemo)	Change scores; MCID, 10 points	<ul style="list-style-type: none"> No statistically significant change in EORTC PF Handgrip strength decreased 	<ul style="list-style-type: none"> Older patients had greater magnitude of decline in handgrip strength (younger, 30.7 to 28.0; older, 31.1 to 25.0) Younger patients had improved chair stands over time (22.3 to 29.0; $P<.001$), but older adults did not (20.3 to 19.8; $P=.36$) Both groups improved on the 2MWT ($P<.001$) Younger patients had less decline or greater improvement in all 3 PF tests over time compared with older patients
Morita et al ²⁶ Score: 10	Multicenter RCT (Japan)	NSCLC; stages IIIB–IV	377	Median age, 61 y (range, 35–75 y)	Chemo	QOL-ACD physical well-being, ECOG PS	Pretx; days 8, 15, 22	Change scores	<ul style="list-style-type: none"> Maximum decrease in score for each domain was observed at wk 1 More severe deterioration of PS was observed in wk 1 and 2, whereas a noticeable number of patients experienced improved PS in wk 4 	<ul style="list-style-type: none"> Nausea/vomiting ($P<.001$), anorexia ($P<.001$), diarrhea ($P<.001$), and PS deterioration ($P=.001$) were associated with decline of physical well-being Age, sex, and tx arm were not associated
Oechsle et al ²⁷ Score: 9	Single-center observational cohort (Germany)	All types; stage II	53	Median age, 58 y (range, 29–76 y)	Chemo	Questionnaire for Measurement of Habitual Physical Activity (work, sports, leisure indices), EORTC QLO-C30 PF International Physical Activity Questionnaire	Baseline; 4 wk	Change score	<ul style="list-style-type: none"> Work index: decreased from 2.25 to 0.56 ($P<.001$) Sports index: decreased from 2.91 to 2.47 ($P<.001$) Leisure time index: increased from 2.81 to 3.01 ($P<.01$) Median time of sport activities decreased (1.6 h to 0.8 h; $P<.01$) No change in EORTC QLO-C30 PF 	<ul style="list-style-type: none"> Sports index before cancer diagnosis was higher among men ($P<.05$) but no difference in sports index during chemo by sex No sex differences in EORTC QLO-C30 PF
Revicki et al ²⁸ Score: 9	Multicenter RCT (global)	Melanoma; stages IIIA–IV	676	Mean age, 56.2 y (SD, 57)	Iplimumab/gp100 vs iplimumab alone vs gp100 alone	EORTC QLO-C30 PF	Pretx; 12 wk	No change, 0–5 points; a little change, 5–10 points; moderate change, 10–20 points; very much, >20 points	<ul style="list-style-type: none"> Change scores: <ul style="list-style-type: none"> Iplimumab + gp100: –6.2 Iplimumab alone: –5.1 Gp100 alone: –10.1 	<ul style="list-style-type: none"> Older and younger patients (aged <65 vs ≥65 y) had similar PF decline in the iplimumab + gp100 and iplimumab alone groups
Shallwani et al ²⁹ Score: 8	Single-center observational cohort (Canada)	NSCLC; stages IIIA–IV	47	Mean age, 63.3 y (SD, 12.2)	Chemo	SF-36 PCS, 6MWT, 1-min chair rise test, grip strength	Pretx; post cycle 2	SF-36 MCID: 5 units 6MWT MCID: 54 min Longitudinal modeling	<ul style="list-style-type: none"> SF-36 PCS worsened overall: pretx 40.8, posttx 38; $P=.02$; 20% had clinically significant improvements; 33% deteriorated 6MWT worsened overall: pretx (454.5), posttx (414.3); $P<.01$; 9% had clinically significant improvements; 14% deteriorated Chair rise test stable: pretx (21.4), posttx (20.7); $P<.25$ Grip strength worsened: pretx (27.4), posttx (26.5); $P=.03$ 	<ul style="list-style-type: none"> Nutritional status, fatigue, and 6MWT were not associated with SF-36 PCS

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eTable 3. Non–Older Adult–Specific Studies Meeting Inclusion Criteria and Primary Functional Status Results (N=27) (cont.)

Study/Quality Assessment Score ^a	Sample (Cancer Type(s); Stage)	N	Age Distribution	Systemic Cancer Tx(s)	Primary Measure(s) of Functional Status	Assessment Time Points	Definition of Functional Status Change	Change in Functional Status During Tx	Association of Patient Characteristics ^b With Functional Status Change
Timishina et al ¹⁰ Score: 9	AML Multicenter observational cohort (Canada)	71	Median age, 52 y (IQR, 41–58 y)	Intensive chemo	EORTC QLQ-C30 PF; grip strength, 10 timed chair stands	Pretx; 11 time points over 3 y	Recovery defined as reaching 1 MCID unit for each outcome (EORTC QLQ-C30 MCID: 10, FACT-F MCID: 4, grip strength MCID: 4.5 kg, 6MWT MCID: 54 min, timed chair stand MCID: 3.4 s)	<ul style="list-style-type: none"> EORTC QLQ-C30 PF unchanged: baseline (80.6), 12 mo (85.2), 24 mo (82.5), 36 mo (90.0) EORTC QLQ-C30 PF: 72% returned to normal at 1 y and 77% at 3 y Grip strength unchanged: baseline (30.3), 12 mo (31.2), 24 mo (31.8), 36 mo (32.0) Grip strength: 50% returned to normal at 1 y and 54% at 3 y Chair stands/min improved: baseline (25.6), 12 mo (35.0), 24 mo (39.0), 36 mo (40.7); P=.002 Chair stands: 44% returned to normal at 1 y and 64% at 3 y 	<ul style="list-style-type: none"> Older age (time × age interaction; P=.01) and male sex (time × sex interaction; P=.002) were associated with slower recovery in timed chair stands Age and sex were not associated with recovery for other functional status measures
Verdonck-de Leeuw et al ¹¹ Score: 10	HNSCC; all stages (curative only)	164	Median age, 59 y (range, 40–84 y)	Chemoradiation (generally cisplatin)	EORTC QLQ-C30 PF	Pretx (1 wk before tx); 6 wk; 6, 12, 18, 24 mo; post RT	Change score	<ul style="list-style-type: none"> EORTC QLQ-C30 worsened in the first 6 wk, then improved in survivors EORTC QLQ-C30 worsened in nonsurvivors 	<ul style="list-style-type: none"> Comorbidity (P=.03) and nonsurvivors were associated with lower EORTC QLQ-C30 PF over time
Watters et al ¹² Score: 10	Breast; all stages	65 (45 young, 25 old)	Old (age ≥ 65 y): mean age, 70 y (SD, 5; range, 65–80 y) Young (age < 65 y): mean age, 55 y (SD, 6; range, 31–64 y)	5-FU, doxorubicin, cyclophosphamide	EORTC QLQ-C30 PF; SF-36 PF; KPS, handgrip strength	Pretx; before cycle 3; 3 wk post cycle 6; 6 mo; 12 mo	Change score	<ul style="list-style-type: none"> EORTC QLQ-C30 and SF-36 PF were lower at completion of chemo (P<.01 and P<.05, respectively) EORTC QLQ-C30 and SF-36 PF were similar from baseline to follow-up KPS declined significantly by completion of chemo (92 ± 6 vs 85 ± 1; P<.001) KPS did not differ from baseline to follow-up No change in handgrip strength 	<ul style="list-style-type: none"> Younger age was associated with greater decline in EORTC QLQ-C30 PF (P<.05) Age was not associated with changes in SF-36 PF
Williamson et al ¹³ Score: 10	Lung; all stages	101	Mean age, 64.5 y (SD, 11.6)	Chemo, immunotherapy, targeted therapy, combination	FACT-L TOI (physical/functional well-being)	Baseline (study entry); 6 wk; 12 wk	Change score	<ul style="list-style-type: none"> Baseline: 51.37 6 wk: 33.17 12 wk: 44.55 	<ul style="list-style-type: none"> Lower baseline physical/functional well-being (P<.001), being unmarried (P=.017), non-Hispanic White race (P=.004), and higher internalized stigma (P=.045) were associated with lower physical/functional well-being at 6 wk Lower baseline physical/functional well-being (P<.001) was associated with lower physical/functional well-being at 12 wk Age, sex, education, smoking history, months since diagnosis, cancer stage/type, prior surgery, prior chemo, and constrained disclosure (avoidance of or discomfort about disclosing one's cancer status to others) were not associated with physical/functional well-being at 6 and 12 wk

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eTable 3. Non–Older Adult–Specific Studies Meeting Inclusion Criteria and Primary Functional Status Results (N=27) (cont.)

Study/Quality Assessment Score ^a	Study Design	Sample (Cancer Type(s); Stage)	N	Age Distribution	Systemic Cancer Tx(s)	Primary Measure(s) of Functional Status	Assessment Time Points	Definition of Functional Status Change	Change in Functional Status During Tx	Association of Patient Characteristics ^b With Functional Status Change
Yang et al ⁴⁴ Score: 10	Single-center observational cohort (Taiwan)	NSCLC; stages IIIB–IV	344	Gefitinib: mean age, 63.7 y (SD, 11.2) Erlotinib: mean age, 61.9 y (SD, 12.8) Afatinib: mean age, 60.8 y (SD, 10.2)	Gefitinib, erlotinib, afatinib	WHOQOL-BREF physical, mobility, daily activities	Baseline; every 2–4 wk during tx up to 25 mo (no specific time point)	Change score	Physical, mobility, and daily activity scores were lower in the afatinib arm	<ul style="list-style-type: none"> • ECOG PS 2–4 (vs 0–1) was associated with worse scores on physical, mobility, and daily activities ($P<.001$) • EGFR exon 19 deletion was associated with worse scores on physical ($P<.05$), mobility ($P<.05$), and daily activities ($P<.01$) • Brain metastasis was associated with worse scores on mobility ($P<.05$) • Disease progression was associated with worse scores on physical, mobility, and daily activities ($P<.001$) • Afatinib (vs gefitinib) was associated with worse scores on physical ($P<.05$), mobility ($P<.01$), and daily activities ($P<.01$) • Sex, education, employment, marital status, comorbidities, and recurrence were not associated with any decline

Abbreviations: 2MWT, 2-minute walk test; 6MWT, 6-minute walk test; AC, cyclophosphamide/doxorubicin; AML, acute myeloid leukemia; chemo, chemotherapy; auto-SCT, autologous stem cell transplant; CLAS, Cancer Linear Analog Scale; CMF, cyclophosphamide/methotrexate/fluorouracil; DLBCL, diffuse large B-cell lymphoma; EORTC QLQ-C30, EORTC Quality of Life Questionnaire-Core 30; EOT, end of treatment; FACT-Breast, Functional Assessment of Cancer Therapy–Breast; FACT-F, Functional Assessment of Cancer Therapy–Fatigue; FACT-L, Functional Assessment of Cancer Therapy–Lung Trial Outcome Index; FL, follicular lymphoma; GI, gastrointestinal; GVHD, graft-versus-host disease; HNSCC, head and neck squamous cell carcinoma; IADL, instrumental activities of daily living; IQR, interquartile range; KPS, Karnofsky performance status; MCI, minimal clinically important difference; NHL, non-Hodgkin lymphoma; NSCLC, non-small cell lung cancer; PCS, physical component summary; PF, physical functioning; posttx, posttreatment; pretx, pretreatment; PS, performance status; QOL-ACD, Quality of Life Questionnaire for Cancer Patients Treated with Anti-Cancer Drugs; RCT, randomized controlled trial; RT, radiotherapy; SCLC, small cell lung cancer; SCT, stem cell transplant; SF-36, 36-item Short Form Health Survey; tx, treatment; WHOQOL-BREF, WHO Quality of Life Brief Questionnaire.

^aQuality assessment was performed using the National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, which consists of 14 criteria.

^bWe listed patient characteristics that are associated with functional change and those that are not associated. We did not list patient characteristics if they were only included as covariates without a reported result.

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