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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 change in older adults

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during systemic cancer treatment published in English from database inception to January 11, 2019 (PROSPERO CRD42019123125). Findings were summarized with descriptive statistics. We used Fisher's exact tests to compare study characteristics between older adult- and non-older adult-specific studies.

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 age ≥60, 10 studies ≥65, 6 studies ≥70). Almost all studies (98%) utilized patient-reported outcomes to measure functional status; only 20% utilized 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% versus 4%, P=0.008). 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 (e.g., nutrition).

Keywords

geriatric oncology; functional status; functional decline; systemic therapy; chemotherapy

INTRODUCTION

Older adults with cancer are at increased risk for treatment toxicity and functional impairment,[1–4] resulting in increased healthcare utilization 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 events,[12] which do not capture FS or changes over time. As a result, there are limited data on how cancer treatments affect FS in older adults, hindering delivery of goal-concordant care.

Understanding how FS may change during systemic cancer treatment (e.g., 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 necessary to weigh the potential benefits and harms of treatment options, better inform patient and caregiver anticipatory guidance, and allow for early introduction of tailored interventions to prevent functional impairment such as exercise and rehabilitation programs.[13–15]

Given the rising recognition of the importance of FS in older adults with cancer[16] and explosion of new cancer treatments, an increasing number of studies have examined characteristics associated with FS change during treatment. While 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 identify patient characteristics associated with functional decline and improvement.

Methods

Search strategy and selection criteria

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 guidelines.[17] With a medical librarian (DC), 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 age ≥65 published in English between database inception and January 11, 2019. Full search terms are shown in the Supplemental Table and included: "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) study included patients age ≥65 with any cancer type; 2) participants received systemic cancer therapy; 3) FS quantitatively measured using physical performance tests, patient-reported outcomes (PROs; e.g., instrumental activities of daily living [IADL]), physical well-being as part of a quality of life (QOL) measure, physical activity (e.g., step count), and/or clinician-reported performance status (PS); 4) FS measured at ≥2 time points (one before or during treatment such that change in FS during treatment could be ascertained); 5) FS analyzed as an outcome; 6) study reported an analysis of associations between patient characteristics and change in FS; and 7) study published in English. Studies of systemic therapy and other treatment modalities (e.g., surgery) were only included if they reported results separately for patients who received systemic therapy. Of note, studies of concurrent chemoradiation were allowed since chemoradiation is the standard of care for some cancer types (e.g., head and neck). Additionally, studies of FS interventions (e.g., exercise) were required to have control arms to allow evaluation of the effect of systemic cancer treatment on FS. Exclusion criteria included: 1) studies of hormonal therapy, radiation, or surgery alone; 2) articles that did not report original data; and 3) full text unavailable.

All identified articles were imported into Covidence (Veritas Health Innovation) and duplicates were removed. At each step below, discrepancies were resolved by consensus (KPL, MLW). Two investigators independently screened titles and abstracts 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 (KPL, MLW). Two independent investigators extracted data for each study. Extracted data included first author, publication year, journal, geographic region, study design, intervention and control arm (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 independent investigators performed 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 criteria earned one point and a summary score was calculated.

Data analysis

Descriptive statistics were used to summarize study characteristics including cancer type, measures of FS used (patient-reported outcome, clinician-reported, physical performance test), assessment time points, and analytic approach. Fisher's exact tests were 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 Figure). The final analysis included 44 studies,[1, 2, 19–60] which were published from 1991-2019 (Figure 1) and enrolled more than 8,400 patients with cancer. Seventeen studies (39%) focused on older adults (Table 1) while 27 (61%) included adults of all ages (Table 2). Among the older adult-specific studies, which increased in number in recent years (Figure 1), one study enrolled only adults age ≥60,[19] ten enrolled only adults age ≥65,[1, 2, 20–27] and six enrolled only adults age ≥70.[28–33] A quarter of studies enrolled a heterogeneous population of patients with a solid or hematologic malignancy and a quarter enrolled patients with lung cancer. The next most common cancer types were breast cancer (16%) and hematologic malignancies (16%). The majority of studies evaluated FS during chemotherapy (84%) with only five studies[32, 33, 36, 59, 60] including targeted therapy and two studies[54, 59] including immunotherapy.

Quality assessment

Using the NHLBI Quality Assessment Tool, the mean quality assessment score was 9.86 (range 7 to 13; Tables 1 and 2). The most common reasons for lower study quality were lack of participation rate reporting, lack of sample size justification, loss to follow-up ≥20%, and lack of adjustment for confounders. Outcome assessors were often not blinded

to the patient's exposure status (e.g., 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 3). The most commonly used PRO was the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) physical functioning scale[61] (34% of studies). Patient-reported ADL (20%) and IADL (16%) were commonly used as well. Physical performance was tested in 20% of studies with grip strength, chair stands, and walking tests as the most common. Traditional oncology measures of PS (e.g., Eastern Cooperative Oncology Group PS) were uncommon among included studies. There were no statistically significant differences in 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 prior to starting systemic therapy and at 1 (20% of studies), 2 (14%), or ≥3 (50%) follow-up time points, while 16% of studies performed the first assessment after therapy had started (Table 3). Analyses of FS change were heterogeneous with many reporting change scores between two assessments (48% of studies). Only 32% of studies utilized 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 versus 4% of non-older adult-specific studies, P=0.008).

Changes in FS and its 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 (Tables 1 and 2). Functional improvement occurred between 9%[55] and 57%[21] of patients. The most common patient characteristics associated with functional decline during systemic cancer therapy (Table 4) were older age (n=7 studies[1, 2, 38, 39, 42, 47, 51]), worse PS (n=4[35, 39, 52, 60]), progressive disease status (n=4[2, 31, 35, 60]), pain (n=4[24, 35, 39, 45]), anemia (n=4[1, 20, 24, 47]), and worse nutritional status (n=4[2, 31–33]). Definitions for these characteristics are listed in Table 4.

Only twelve studies[19, 22, 27, 29, 34, 40–43, 46, 51, 56] examined characteristics associated with functional improvement. Three articles[34, 51, 56] reporting results from a study of acute myeloid 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 three studies.[22, 40, 41] Additional characteristics associated with greater functional improvement included female sex,[56] being married,[22] baseline functional dependence,[27] better cognition,[19] lack of depression,[41] higher hemoglobin,[42] cancer type,[43, 46] and less than four 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 improvements in FS in the intervention arm.[41]

DISCUSSION

Over almost three decades of research from 1991-2019, we identified only 44 studies that included older adults that rigorously examined patient characteristics associated with FS change during systemic cancer treatment. While 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 age ≥65 with breast cancer in a trial of adjuvant therapy using patient-reported worsening physical condition.[21] In contrast, functional decline was identified in 90% of adults age ≥70 with advanced non-small cell lung cancer receiving chemotherapy using ADLs.[33] Study populations also differed widely in cancer types and specific treatments evaluated. However, the vast majority of studies included only chemotherapy, revealing a gap in understanding 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 wide spread use of PRO measures to assess FS among patients with cancer mirrors the broader surge of PROs to assess symptoms and adverse events 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 (e.g., previsit questionnaire), remotely without an in-person component (which is increasingly important during the COVID-19 pandemic), and with potentially fewer resources compared to conducting a physical performance test. PROs also allow FS to be more easily studied longitudinally in clinical trials or observational cohort studies where FS is not the primary outcome. Compared to 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 for clinically meaningful functional decline or improvement. Despite half of the included studies measuring FS at ≥3 follow-up assessments, over 60% only analyzed data from two time points, effectively ignoring informative patient-centered information. To illustrate, 48% of studies analyzed longitudinal FS as a change score between two assessments and 14% used a threshold definition of a dichotomous functional decline outcome. While these types of analytic approaches may assist in clinical interpretation (e.g., percent of patients who functionally decline after one cycle of chemotherapy[30]), they do not capture FS trajectories that may include both declines and

improvements. In contrast, Hurria et. al[22] combined more nuanced changes in FS over time and clinically applicable results by conducting four analyses using dichotomous outcomes to examine: Functional decline at the end of adjuvant breast cancer chemotherapy, functional decline at twelve months, improvement of FS among those with decline, and resistance to decline. This study exemplifies an alternative analytic approach that examines several time points as well as 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 adults[66] and associated with functional decline,[24,29,49,5] there may have been residual confounding. We also found that worse PS, pain, anemia, and worse nutrition 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 (e.g., cognition) through geriatric assessment[67] is necessary to comprehensively risk stratify patients. Geriatric assessment results can guide recommendations to address modifiable risk factors via supportive care interventions (e.g., physical therapy for worse PS) and co-management with a multidisciplinary team (e.g., palliative medicine for pain, dietician 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 stressor,[69] or simply the ability to recover to baseline.[22, 70] Understanding characteristics associated with functional improvement can guide conversations regarding cancer treatment as 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.

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

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 are absent from many trials, is equally important. This is especially critical given the rapidly evolving treatment landscape and 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 QOL questionnaires. These data have the potential to greatly expand the

knowledge base on FS changes during cancer treatment and 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 ePrognosis.org collection of prognostic indices.[73, 74] Studies of FS changes among older adults with the same cancer type are also needed to make results less heterogeneous and more clinically applicable.

In conclusion, there is increasing recognition of change in FS as 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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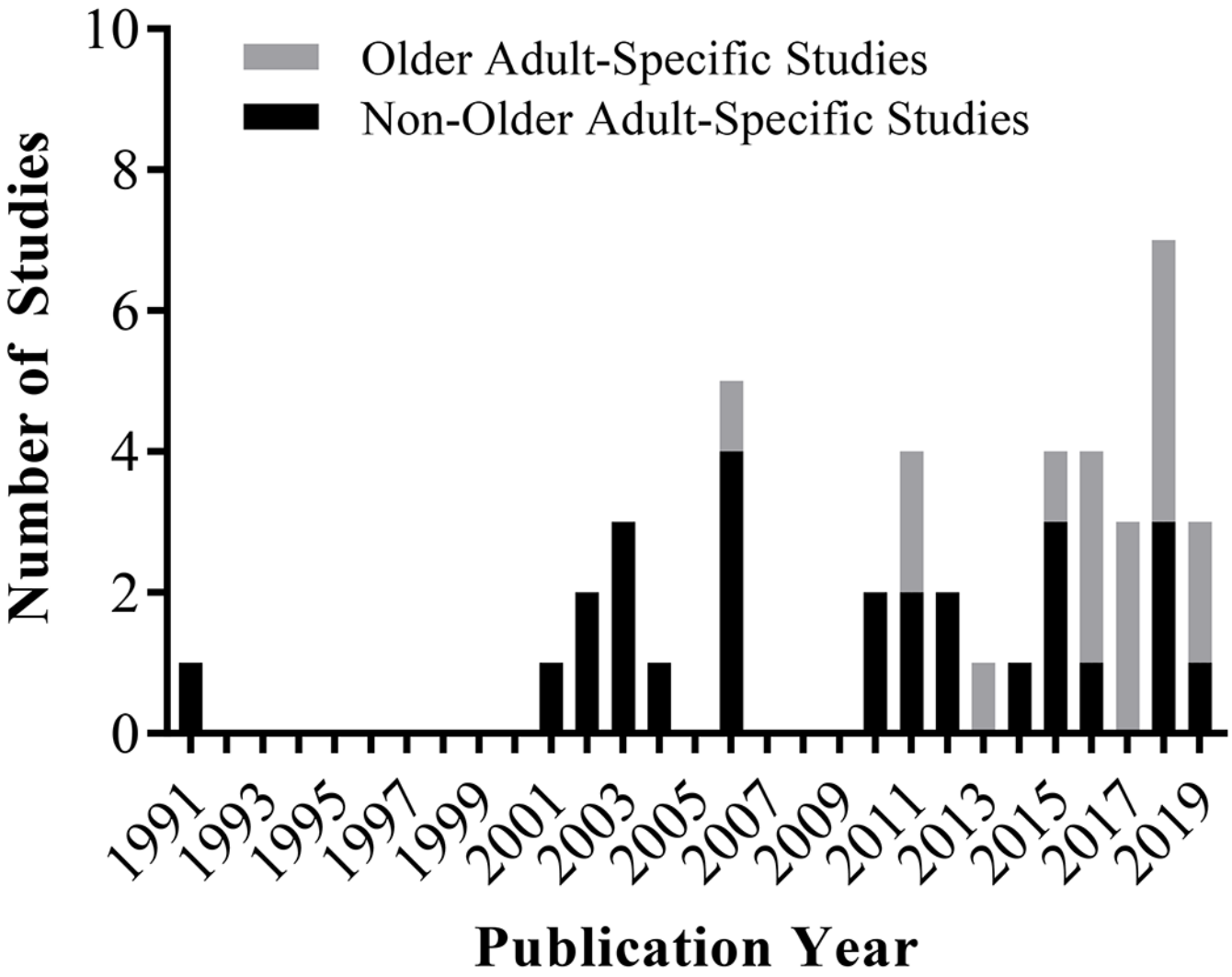

Figure 1.

Included studies by publication year and study type (older adult-specific versus non-older adult-specific study). Systematic review included publications from database inception through January 11, 2019.

Table 1.

Older-adult specific studies meeting inclusion criteria and primary functional status results (N=17).

Age inclusion criteria	Study/ Quality assessment score[a]	Study design	Sample (cancer type(s), stage)	Overall N (systemic therapy n)	Age (age 65+ n if available or age summary statistic – mean/ median)	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 ≥60	Klepin 2016[19]/8	Single center observational cohort (US)	AML	49	Mean age 70 (SD 2); 57.1% age 60-69, 34.7% 70-79, 8.2% ≥80	Chemo	Pepper Assessment Tool for Disability (ADL, IADL, mobility), SPPB, grip strength	Pretx (hospitalization for induction chemo), 8 wks after discharge	Decline using standard cutoffs	-IADL dependence worsened (1.4 baseline vs 2.1 follow-up, p<0.001) -SPPB worsened (7.5 vs 5.9, p=0.02) -Grip strength declined (men: 38.9 vs 34.2, p<0.001; women: 24.5 vs 21.8, p=0.007)	-Unfavorable cytogenetic risk score (p=0.05) and receipt of the most intense chemo (cytarabine/ daunorubicin/ etoposide) (p=0.03) were associated with ADL decline -Higher BMI (p=0.03) and unfavorable cytogenetic risk score (p=0.01) were associated with IADL decline -Depressive symptoms at baseline and follow-up were associated with decline in SPPB score (p=0.03) -Receipt of the most intense chemo (p=0.02) was associated with decline in SPPB gait speed -Higher baseline cognition score was associated with improvement in SPPB balance (p=0.05) -Remission status was not associated with

Age inclusion criteria	Study/ Quality assessment score[a]	Study design	Sample (cancer type(s), stage)	Overall N (systemic therapy n)	Age (age 65+ n if available or age summary statistic – mean/ median)	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
											functional decline
Age ≥65	Doni 2011[20]/9	Multicenter observational cohort (Italy)	All types, all stages	578	Mean age 72.6 (SD 5.0), median 71.9 (range 64.9-100)	Chemo	ADL, ECOG PS	Pretx, before each cycle (for at least 12 wks)	Longitudinal modeling	-Mean ADL score worsened up to wk 20 -Progressive worsening of ECOG PS starting from wks 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)	-At wk 12, hemoglobin change of at least 1 g/dl was associated with ADL decline (p<0.05) -Stage and PS were not associated
Age ≥65	Gajra 2018[21]/10	Multicenter RCT (US)	Breast, stage I-III	145	Median age 71; 40% age 65-69, 54% 70-80, 6% >80	Adjuvant chemo (AC, CMF) vs capecitabine	Subjective Significance Questionnaire (self-reported change in physical condition), EORTC QLQ-C30 PF	Midtx; 1, 12, 18, 24 mos after EOT	Self-report worsening physical condition	-At mid-treatment, 25% reported worse, 49% same, and 26% improved physical condition -At 1 yr, 6% reported worse, 37% same, 57% improved physical condition	-Low preference for chemo was associated with worse physical condition at mid-treatment (p=0.005) but not at the other time points -No association between chemo preference and EORTC QLQ-C30 PF
Age ≥65	Goodwin 2006[1]/10	Multicenter observational cohort (US)	Solid tumor, all stages	26	Mean age 71 (SD 5, range 65-82)	Chemo	Short Functional Dependence Scale ADL and IADL	Pretx, chemo visits 1-9	Longitudinal modeling	-Not reported	-Older age, cancer type, surgery, radiation, and lower hemoglobin were associated with higher functional

Age inclusion criteria	Study/ Quality assessment score[a]	Study design	Sample (cancer type(s), stage)	Overall N (systemic therapy n)	Age (age 65+ n if available or age summary statistic – mean/ median)	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
											dependence across visits
Age ≥65	Hurria 2019[22]/10	Multicenter RCT (US)	Breast, stage I-III	256	Mean age 71.9 (SD 4.7, range 65-85)	Chemo	EORTC-QLQ-C30 PF	Pretx; posttx; 12 mos 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 mos: ≥10 point decrease from pretx to 12 mos after -Resistance to decline: <10 point decrease from pretx to posttx and 12 mos after	-Decline from pretx to posttx: 42% (median decline 20 points, range 11.7-73.3) -Resilience at 12 mos: 47% recovered -Decline at 12 mos: 30% (median decline 20 points, range 13.1-53.3) -Resistance to decline: 49.6%	-Decline from pretx to posttx was associated with baseline fatigue (OR 2.37, p=0.02). Comorbidity was not associated at posttx. -Resilience at 12 mos was associated with being married (OR 2.52, p=0.04), having <4 positive nodes (OR 3.57, p=0.048), and no pre-treatment appetite loss (OR 3.65, p=0.02) -Decline at 12 mos was associated with being unmarried (OR 1.98, p=0.01) and pretreatment dyspnea (OR 2.37, p=0.007). Fatigue, having <4 positive nodes, and older age were not associated with decline at 12 mos. -Resistance to decline was associated with no pretreatment fatigue (OR 2.49, p=0.01)

Age inclusion criteria	Study/ Quality assessment score[a]	Study design	Sample (cancer type(s), stage)	Overall N (systemic therapy n)	Age (age 65+ n if available or age summary statistic – mean/ median)	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
											and no dyspnea (OR 1.94, p=0.03). Comorbidity was not associated.
Age ≥65	Manokumar 2016[23]/9	Single center observational cohort (Canada)	Prostate, stage IV	36	First line: Mean age 77.3 (SD 4.5); Second line: Mean age 71.4 (SD 6.2)	Docetaxel	OARS-IADL, TUG, timed chair stands, handgrip strength, falls (≥1)	Pretx, q3 mos until posttx	Change score	1st-line chemo -IADL: 21% improved, 52% stable, 28% declined -TUG: 22% improved, 39% stable, 39% declined -Timed Chair Stands: 17% improved, 42% stable, 42% declined -Handgrip strength: 11% improved, 61% stable, 29% declined -Falls: 38% experienced one fall	-Vulnerable Elders Survey (VES-13) score ≥3 was associated with greater increase in timed chair stand score
Age ≥65	Miaskowski 2017[24]/9	Multicenter observational cohort (US)	Breast, GI, GYN, lung; all stages	363	Mean age between 70.7 to 72.7 (SD 5.4-6.0)	Chemo	SF-12 PCS	Baseline (chemo within the prior 4 wks), 1 wk and 2 wks post-chemo, then repeat for the subsequent cycle	Change score	-Three classes based on latent class analysis (above, below, and well below the normative norm of individuals aged 65-74) -PCS score remained relatively stable over 2 cycles of chemo	-Unemployment (p<0.001), lower income (p=0.002), and a history of heart disease (p=0.001) were associated with being in the below and well below classes -Exercise on a regular basis (p<0.001), self-reported back pain (p<0.001), lower hemoglobin

Age inclusion criteria	Study/ Quality assessment score[a]	Study design	Sample (cancer type(s), stage)	Overall N (systemic therapy n)	Age (age 65+ n if available or age summary statistic – mean/ median)	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
											(p=0.002), and self-reported depression (p=0.028) were associated with being in the well below class -Age, gender, cancer diagnosis, time since cancer diagnosis, number of metastatic sites, number and types of prior cancer treatments, and chemo cycle length were not associated with latent class membership
Age ≥65	Rier 2018[2]/11	Single center observational cohort study (Netherlands)	All types, all stages	142	Median age 72 (range 69-78)	Chemo	IADL	Pretx, midtx, posttx	IADL independence: ≥8 points; IADL decline: ≥3 points decline at posttx or ≥2 points decline at 1 year posttx	-IADL independence: Pretx (63.9%), posttx (56.3%) -IADL decline: 11.5%	-Age (p=0.05), impaired cognition (0.05), refractory or progressive disease at posttx (vs complete remission, p=0.003), and severe sarcopenia (vs normal, p=0.05) were associated with IADL decline (all univariable analyses) -None were associated with decline on multivariable analysis

Age inclusion criteria	Study/ Quality assessment score[a]	Study design	Sample (cancer type(s), stage)	Overall N (systemic therapy n)	Age (age 65+ n if available or age summary statistic – mean/ median)	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	Verelst 2011[25]/11	Multicenter RCT (Netherlands)	Multiple myeloma, all stages	284	Median age 72 (range 65-84)	Melphalan/ prednisone, melphalan/ prednisone/ thalidomide	EORTCQLQ-C30 PF	Pretx, cycle 3 (3 mos), cycle 8 (9 mos), 12 mos, 18 mos	Change score	-EORTC QLQ-C30 improved in both arms over time, though this was in favor of the 2-drug regimen early during induction phase	-Female sex was associated with lower scores on EORTC QLQ-30 PF (p=0.003)
Age ≥65	Wong 2018[26]/10	Multicenter observational cohort (US)	Breast, GI, GYN, lung; all stages	363	Mean age 71.4 (SD 5.5)	Chemo	SF-12 PCS	Baseline (chemo within the prior 4 wks), 1 wk and 2 wks post-chemo, then repeat for the subsequent cycle	Longitudinal modeling	-PCS scores decreased slightly (0.21 points, p<0.01) at each subsequent assessment	-Higher morning fatigue (p=0.04) and lower enrollment PCS scores (p=0.01) 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, chemotherapy toxicity index, cycle length, evening fatigue, morning energy, evening energy,

Age inclusion criteria	Study/ Quality assessment score[a]	Study design	Sample (cancer type(s), stage)	Overall N (systemic therapy n)	Age (age 65+ n if available or age summary statistic – mean/ median)	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
											pain, anxiety, and attentional function were not associated
Age ≥65	Xue 2015[27]/7	Single center RCT (China)	NSCLC, stage IIIB-IV	24	Mean age 73 (SD 5.3, range 65-83)	Chemo	EORTC QLQ-C30 PF	Pretx (day 1 prior to chemo); 7d, 21d, 42d, 63d post-chemo	Change score	-No change in functioning scale among function-independent and mildly function-impaired patients -For function-dependent patients, PF improved	-Worse baseline functional status was associated with improvement in PF
Age ≥70	Chakiba 2019[28]/11	Multicenter observational cohort (France)	Colon, pancreatic, stomach, ovarian, bladder, prostate, lung, NHL, cancer of unknown primary; all stages	292	Median age 77 (range 70-93); 36% age 70-75, 35% 76-80, 22% 81-85, 7% >85	Chemo	ADL	Pretx, before cycle 2	Decline: 0.5 point decrease	-16% declined, 10% improved, 73% stable ADL score	-Abnormal G8 (≤14) was associated with functional decline (OR 4.3, 95% CI 1.28-14.92; p=0.018) in multivariable model -Age, sex, tumor type, stage, neutrophil count, platelet count, creatinine clearance, albumin, and CRP were not associated
Age ≥70	Fiteni 2016[29]/10	Multicenter RCT (France)	NSCLC, stage III-IV	361	Mean age 77.1 (range 70-88); 49.9% age <77, 50.1% ≥77	Carboplatin/ paclitaxel vs gemcitabine vs vinorelbine	EORTC QLQ-C30 PF	Pretx, 6 and 18 wks	PF MCID: 5 points; time to deterioration	-Median time to deterioration: doublet chemo 2.04 mos (95% CI 1.87-3.88) vs monotherapy 1.71 (95% CI	-Doublet chemo was associated with longer time to PF deterioration (HR 0.57, 95% CI 0.42-0.78, p=0.008) -Female sex (HR 1.53, 95% CI

Age inclusion criteria	Study/ Quality assessment score[a]	Study design	Sample (cancer type(s), stage)	Overall N (systemic therapy n)	Age (age 65+ n if available or age summary statistic – mean/ median)	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
										1.58-1.91), p=0.01	1.09-2.15, p=0.01) and CCI score >2 (HR 1.50, 95% CI 1.08-1.12, p=0.002) were associated with shorter time to PF deterioration -Age, PS, smoking status, BMI, MMSE, ADL, stage, and histology were not associated with time to PF deterioration
Age ≥70	Hoppe 2013[30]/12	Multicenter observational cohort (France)	Colon, pancreatic, stomach, ovarian, bladder, prostate, lung, non-Hodgkin lymphoma, unknown primary origin, all stages	364	Median age 77.3 (range 70-93)	Chemo	Katz ADL	Pretx, before cycle 2	ADL decline: decrease of ≥0.5 in total score	-Decline: 16.7% (median 0.5 points, range 0.5-3) -Improvement: 10.7% (median 0.5 points, range 0.5-2.5)	-High GDS-15 (OR 2.16, p=0.03) and low IADL (OR 2.87, p=0.04) were associated with decline -Age, sex, PS, weight loss, BMI, leukocytes, platelet count, creatinine, CRP, hemoglobin, albumin, tumor type, disease extension, CIRS-G, MAX2 index, ADL, MNA, MMSE, and GUG were not associated with decline
Age ≥70	Kenis 2017[31]/11	Multicenter observational cohort (Belgium)	Breast, CRC, ovarian, lung, prostate, hematologic malignancy; all stages	439	Mean age 75 (range 70-95)	Chemo	Katz ADL, Lawton IADL	Pretx, 2-4 mos after chemo	ADL decline: change of ≥2 in total score, IADL decline: change of ≤1 in total score	-ADL decline: 19.9% -IADL decline: 41.3%	-Abnormal nutritional status (OR 2.02, p=0.007) and baseline IADL dependency (OR 1.76, p=0.037) were associated

Age inclusion criteria	Study/ Quality assessment score[a]	Study design	Sample (cancer type(s), stage)	Overall N (systemic therapy n)	Age (age 65+ n if available or age summary statistic – mean/ median)	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
											with ADL decline -Disease status (progression/ relapsed vs new diagnosis; OR 0.59, p=0.014) was associated with IADL decline -Age, geriatric screening tools, ECOG PS, fall, pain, polypharmacy, living situation, comorbidity, fatigue, baseline ADL, cognition, depression, cancer type, and treatment were not associated with both ADL and IADL decline
Age ≥70	Morikawa 2018[32]/8	Single center observational cohort (Japan)	NSCLC, stage III-IV	18	Median age 74.5 (range 70-82)	Chemo, targeted therapy	Physical activity (accelerometer)	Pretx (prior to hospitalization); during hospitalization; 1, 2, 3 wks after discharge	Hospitalization-associated physical inactivity: decreased mean daily steps both during hospitalization and during the 1st wk as compared with mean daily steps at baseline	-50% walked fewer daily steps during hospitalization and did not recover to baseline level at 1 wk after discharge	-Cachexia and longer hospitalization (≥8 vs <8 days) were associated with hospitalization-associated physical inactivity
Age ≥70	Naito 2017[33]/8	Single center observational cohort (Japan)	NSCLC, stage III-IV	30	Median age 74 (range 70-82)	Chemo, targeted therapy	Barthel ADL	Pretx, each hospital visit	Disabling event defined as decrease in Barthel ADL >10 points;	-90% were disabled at the cutoff date -Disabling events: stair climbing	-Cachexia was associated with shorter disability-free survival (7.5 vs 17.1 mos,

Age inclusion criteria	Study/ Quality assessment score[a]	Study design	Sample (cancer type(s), stage)	Overall N (systemic therapy n)	Age (age 65+ n if available or age summary statistic – mean/ median)	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
									disability free survival	(100%), morbidity (96%), bathing (89%), toilet use (56%), and transferring (41%)	p<0.05) and longer post-disability survival (2.5 vs 0.7 mos, p<0.05)

Abbreviations: ADL, activities of daily living; AC, cyclophosphamide/doxorubicin; AML, acute myeloid leukemia; BMI, body mass index; chemo, chemotherapy; CIRS-G, Cumulative Illness Rating Scale-Geriatrics; CMF, cyclophosphamide/methotrexate/fluorouracil; CRC, colorectal cancer; CRP, C-reactive protein; d, day; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; EOT, end of treatment; GDS-15, Geriatric Depression Scale-15; GI, gastrointestinal; GUG, Timed Get Up and Go; GYN, gynecological; 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; mo, month; mos, months; NHL, non-Hodgkin lymphoma; OARS, Older American's Resource Scale; PCS, Physical Component Summary; PF, physical functioning; posttx, posttreatment; pretx, pretreatment; PS, performance status; RCT, randomized controlled trial; NSCLC, non-small cell lung cancer; SD, standard deviation; SF, short-form; vs, versus; wk, week; wks, weeks; TUG, Timed Up and Go; tx; treatment; yr, year; yrs, years

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

[b]We listed patient characteristics that are associated with functional change as well as 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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Table 2.

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)	Overall N (systemic therapy n)	Age (age 65+ n if available or age summary statistic – mean/ median)	Systemic cancer treatment(s)	Primary measure(s) of functional status	Assessment time points	Definition of functional status change	Change in functional status during treatment	Association of patient characteristics[b] with functional status change
Alibhai 2015[34]/10	Multicenter observational cohort (Canada)	AML	237	59% age <60 (median age 52.9); 41% ≥60 (median age 69.7); range 21-81	Induction daunorubicin, cytarabine	2MWT, chair stands, grip strength, IADL	Pretx; 4-6, 9-12, 13-16 wks; 6, 8, 10, 12 mos	2MWT MCID: 59 ft, grip strength MCID: 4.5 kg (MCID not reported for chair stands and IADL)	-2MWT ($p<0.001$), chair stands ($p<0.001$), and IADLs ($p=0.003$) improved -No change in grip strength	-Younger age was associated with greater recovery in chair stands ($p=0.048$) -Gender, smoking status, baseline PS, and hemoglobin were not associated with change in physical function
Bergman 1991[35]/9	Single center observational cohort (Sweden)	SCLC, all stages	62	Mean age 66 (range 36-80); 35% age ≥70	Chemo	Sickness Impact Profile physical index (ambulation, body care/ movement, mobility)	Pretx; 3, 6, 9, 12 mos	Correlation with physical index change score	-Body care/ movement subscale worsened 5 points at 3 mos and 6.1 points at 6 mos ($p<0.05$); no difference at 12 mos -No change in ambulation or mobility	-Characteristics associated with worsening physical index: worsening ECOG/WHO PS, EORTC pain, EORTC appetite ($p<0.01$); tumor non-response, cisplatin-containing regimen, neutropenia ($p<0.05$) -Age, sex, depression, hair loss, and nausea were not associated
Bezjak 2006[36]/13	Multicenter RCT (global)	NSCLC, stage IIIB-IV	425	Median age 61	Erlotinib vs placebo	EORTC QLQ-C30 PF	Pretx, q4 wks during tx, 4 wks posttx, q12 wks until EOT	PF decline: ≥10 point decrease, improvement: ≥10 point increase, stable: <10 point change	-Erlotinib: 51% declined, 31% improved, 18% stable PF	-Only treatment with erlotinib was associated with improvement in PF ($p=0.006$) -Age, sex, ethnicity, PS, prior treatment, histology, and smoking history

Study/ Quality assessment score[a]	Study design	Sample (cancer type(s), stage)	Overall N (systemic therapy n)	Age (age 65+ n if available or age summary statistic – mean/ median)	Systemic cancer treatment(s)	Primary measure(s) of functional status	Assessment time points	Definition of functional status change	Change in functional status during treatment	Association of patient characteristics[b] with functional status change
										were not associated
Chen 2003[37]/9	Single center observational cohort (US)	Solid tumor, non-leukemic hematologic malignancy, all stages	37	Mean age 75.6 (range 70-87); 38% age 70-74, 54% 75-80, 8% 81-87	Chemo	IADL, ECOG PS	Pretx, EOT (or at 6 mos)	Change score	-Mean 1.44 point decline in IADL score (p=0.04) -No change in ECOG PS	-Severe chemotherapy toxicities were associated with decline in IADL (change score −2.93 vs −0.17; p=0.03) and ECOG PS (change score 0.56 vs −0.11; p = 0.03)
de Jong 2006[38]/12	Multicenter observational cohort (Netherlands)	Breast, stage I-III	157	Mean age 47.3 (SD 8.8, range 25-70)	Adjuvant CMF or doxorubicin-containing regimen	Multidimensional Fatigue Inventory reduced activity subscale	Cycle 1, 3, 5; 4 and 12 wks after last cycle	Longitudinal modeling	-Activity level stable during study period	-Older age and not having children were associated with lower activity level over time -Mastectomy (vs lumpectomy), longer duration of radiation, and fewer total chemotherapy treatments were associated with lower activity level -Chemotherapy type, marital status, education, having a job, hemoglobin, and time between surgery and chemotherapy were not associated with change in activity level
Dodd 2001[39]/10	Multicenter RCT (US)	All types, all stages	93	Mean age 55.4 (SD 14.6)	Chemo (RCT of two mouthwashes for mucositis)	Patient-reported KPS	Pretx, end of cycle 3	Longitudinal modeling	-Pretx mean KPS 84.8 -End of cycle 3 mean KPS 82.7	-Pretx KPS, older age, worse pain, and worse fatigue were associated with worse KPS at the end of cycle 3 -Sleep

Study/ Quality assessment score[a]	Study design	Sample (cancer type(s), stage)	Overall N (systemic therapy n)	Age (age 65+ n if available or age summary statistic – mean/ median)	Systemic cancer treatment(s)	Primary measure(s) of functional status	Assessment time points	Definition of functional status change	Change in functional status during treatment	Association of patient characteristics[b] with functional status change
										insufficiency was not associated
Dodd 2010[40]/8	Multicenter RCT (US)	Breast, stage I-III	112	Mean age 50 (SD 9.3)	Chemo (RCT of exercise intervention during chemo, after chemo, vs usual care)	Patient-reported KPS	Before cycle 2, EOT, 1 yr	Association with symptom clusters (pain, fatigue, sleep disturbance, depression) at each assessment	-Not reported	-Before cycle 2, All Low symptom cluster was associated with better KPS vs Moderate cluster (p=0.002) -At EOT, All Low cluster was associated with better KPS vs all other clusters (p<0.0001) -At 1 yr, Mild cluster associated with better KPS vs Moderate and All High clusters (p<0.005)
Doorenbos 2006[41]/10	Multicenter RCT (US)	Solid tumor, all stages	237	Mean age 60 (SD 10, range 31-87)	Chemo (RCT of cognitive behavioral theory guided intervention vs usual care)	SF-36 PF	Baseline; 10, 20, 32 wks	Longitudinal modeling	-Baseline mean PF 64.2 (SD 29.5), wk 20 mean PF 70.6 (SD 28.1) -At wk 20, women with breast cancer had higher PF than women with lung cancer (p=0.001); men with lung cancer had higher PF than women with lung cancer (p=0.02)	-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=0.02) -Lower depressive symptoms and lower symptom limitations were associated with increased intervention effect on PF -Age, sex, stage, and tumor type were not found to mediate intervention effect on PF

Study/ Quality assessment score[a]	Study design	Sample (cancer type(s), stage)	Overall N (systemic therapy n)	Age (age 65+ n if available or age summary statistic – mean/ median)	Systemic cancer treatment(s)	Primary measure(s) of functional status	Assessment time points	Definition of functional status change	Change in functional status during treatment	Association of patient characteristics[b] with functional status change
Fallowfield 2002[42]/12	Multicenter RCT (global)	Solid tumor or non-myeloid hematologic malignancies, all stages	375	Epoetin arm: Mean age 58.1 (SD 14.2, range 18-84) Placebo arm: Mean age 59.2 (SD 14.3, range 21-88)	Non-platinum chemo (RCT of epoetin alfa vs placebo)	CLAS daily activities, SF-36 PCS	Randomization; 4, 16, 28 wks	Change score at last available assessment	-Mean CLAS daily activities change score: Epoetin arm 7.78 vs placebo arm −1.96 (p<0.04). -No difference in mean SF-36 PCS change score by arm: Epoetin arm 1.27 vs placebo arm 0.05 (p=0.33)	-Higher hemoglobin level was associated with higher CLAS daily activities and SF-36 PCS over time (p<0.01) -Higher baseline endogenous erythropoietin was associated lower CLAS daily activities over time (p<0.05) -Lower reticulocyte count and pre-study transfusion dependency were associated with higher SF-36 PCS over time (p<0.05) -Older age was associated with lower SF-36 PCS score over time (p<0.01) -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
Frodin 2011[43]/9	Single center observational cohort (Sweden)	Myeloma, lymphoma, testicular, sarcoma, AML; all stages	96	Mean age 54 (SD 12)	auto-SCT	EORTC QLQ-C30 PF	Pretx; wkly during wks 1-4; monthly during mos 2, 3; 6 mos; q6 mos up to yr 3	Longitudinal modeling	-At wk 2, 42% declined in PF -PF improved back to baseline by month 2	-At wk 2, a diagnosis of myeloma (vs lymphoma) was associated was better PF (p=0.001)

Study/ Quality assessment score[a]	Study design	Sample (cancer type(s), stage)	Overall N (systemic therapy n)	Age (age 65+ n if available or age summary statistic – mean/ median)	Systemic cancer treatment(s)	Primary measure(s) of functional status	Assessment time points	Definition of functional status change	Change in functional status during treatment	Association of patient characteristics[b] with functional status change
Frodin 2015[44]/10	Single center observational cohort (Sweden)	Any hematologic malignancy, all stages	94	Mean age 48	Allogenic SCT, reduced intensity conditioning	EORTC QLQ-C30 PF	Pretx, wkly during wks 1-4, monthly during mos 2, 3; 6 mos; q6 mos up to yr 3	Change score	-Pretx PF mean: 81 -At 3 wks, change score −36 ($p<0.05$ compared with pretx) -At 3 mos, change score −20 ($p<0.05$) -At 1 yr, change score −8 -At 3 yrs, change score −5	-Extensive chronic GVHD was associated with worse PF compared with limited chronic GVHD and no chronic GVHD at 1.5, 2, and 2.5 yrs (all $p<0.01$)
Gaston-Johansson 2015[45]/11	Single center observational cohort (US)	Breast, all stages	30	Mean age 52.7 (SD 10.2, range 32-72)	Chemo	FACT-Breast physical and functional well-being	Pretx, midpoint, EOT	Longitudinal modeling	-Physical and functional well-being decreased at midpoint and EOT compared with pretx (all $p<0.001$)	-Worst pain intensity was associated with worse functional well-being at EOT -No association with age or stage
Given 2002[46]/10	Multicenter RCT (US)	Solid tumor and NHL, all stages	113	Mean age 58 (SD 10.5)	Chemo (RCT of nursing symptom management intervention vs usual care)	SF-36 Physical role functioning	Baseline (within 8 wks of chemo initiation); 10, 20 wks	Longitudinal modeling	-Intervention arm: Mean physical role functioning score 11 (SD 22) at baseline, 50 (SD 41) at 20 wks -Control arm: Mean physical role functioning score 11 (SD 22) at baseline, 31 (SD 36) at 20 wks	-Intervention was associated with improved physical role functioning at 20 wks (mean score 50 vs 31) -Diagnosis of breast cancer (vs non-breast cancer) was associated with improved physical role functioning at 20 wks
Greimel 2006[47]/10	Multicenter RCT (Germany, Austria)	Ovarian, stage IIB-IV	416	Mean age 56.6 (SD 10.1)	Cisplatin/ paclitaxel vs carboplatin/ paclitaxel	EORTC QLQ-C30 PF	Pretx; cycle 2, 4; EOT; q6 mos	Longitudinal modeling	-Mean PF change score 9.4 (carboplatin/ paclitaxel) vs 1.7 (cisplatin/ paclitaxel)	-Carboplatin/ paclitaxel arm had better EOT PF -Characteristics associated with worse PF over time: anemia, neurotoxicity, GI toxicity, older age

Study/ Quality assessment score[a]	Study design	Sample (cancer type(s), stage)	Overall N (systemic therapy n)	Age (age 65+ n if available or age summary statistic – mean/ median)	Systemic cancer treatment(s)	Primary measure(s) of functional status	Assessment time points	Definition of functional status change	Change in functional status during treatment	Association of patient characteristics[b] with functional status change
										-Hematologic toxicity, pain, and treatment arm were not associated with change in PF over time
Kim 2010[48]/8	Single center observational cohort (Korea)	Diffuse large B cell or follicular lymphoma, all stages	32	Mean age 55.9 (range 21-79)	Chemo	SF-36 PCS	Pretx, 2nd visit during chemo, last visit after cycle 6	PCS score <40	-Pretx: 12 patients had a PCS score <40 −2nd visit: 12 patients had a score <40 -Last visit: 5 patients had a score <40	-Neuropathy at 2nd visit was associated with lower PCS score at the last visit (PCS score 44.5 for neuropathy vs 49.9 for non-neuropathy, p=0.02)
Kinsey 2018[49]/12	Multicenter RCT (global)	NSCLC, stage III-IV	236	37.5% age ≥ 65	Chemo	Stair climb power	Pretx, day 84	% Loss	≥10% loss: 31% 0 to <10% loss: 18% ≥0 to <10% gain: 10%, ≥10% gain: 31%	-Taxane (vs non-taxane therapy, p=0.023) and prior smoking (vs current use, p=0.027) were associated with functional decline -Prior weight loss, disease response, lean body mass, ECOG PS, disease stage, age, gender, and comorbidities were not associated with functional decline
Land 2004[50]/12	Multicenter RCT (US, Canada)	Breast, stage I-II	160	50.6% age ≤ 49, 32.5% 50-59, 16.9% ≥ 60	Chemo	SF-36 return to normal activity	Pretx, start of each chemo cycle (several time points from wk 3-52)	Change score	-Return to normal activity score did not change during chemotherapy	-Lumpectomy and radiation (vs mastectomy) were associated with lower return to normal activity score (1.11 points lower, p=0.02) -Chemotherapy (CMF vs AC), tamoxifen, surgery, tumor size, and

Study/ Quality assessment score[a]	Study design	Sample (cancer type(s), stage)	Overall N (systemic therapy n)	Age (age 65+ n if available or age summary statistic – mean/ median)	Systemic cancer treatment(s)	Primary measure(s) of functional status	Assessment time points	Definition of functional status change	Change in functional status during treatment	Association of patient characteristics[b] with functional status change
										age were not associated with return to normal activity score
Mohamedali 2012[51]/10	Single center observational cohort (Canada)	AML	103	Younger: Median age 52.0 (range 21-59) Older: Median age 69.7 (range 60-80)	Induction daunorubicin, cytarabine	EORTC-QLQ-C30 PF, handgrip strength, timed chair stands, 2MWT	Time of dx; 4-5 wks, 8-10 wks, 12-16 wks (after each cycle of chemo)	Change scores; MCID 10 points	-No statistically significant change in EORTC PF -Handgrip strength decreased	-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<0.001) but older adults did not (20.3 to 19.8, p=0.36) -Both groups improved on the 2MWT (p<0.001) -Younger patients had less decline or greater improvement in all three PF tests over time compared to older patients
Morita 2003[52]/10	Multicenter RCT (Japan)	NSCLC, stage IIIB-IV	377	Median age 61 (range 35-75)	Chemo	QOL-ACD physical well-being, ECOG PS	Pretx; day 8, 15, 22	Change scores	-Maximum decrease in score for each domain was observed at wk 1 -More severe deterioration of PS was observed in wks 1 and 2, while a noticeable number of patients experienced improved PS in wk 4	-Nausea/vomiting (p<0.001), anorexia (p<0.001), diarrhea (p<0.001), and PS deterioration (p=0.001) were associated with decline of physical well-being -Age, gender, and treatment arm were not associated

Study/ Quality assessment score[a]	Study design	Sample (cancer type(s), stage)	Overall N (systemic therapy n)	Age (age 65+ n if available or age summary statistic – mean/ median)	Systemic cancer treatment(s)	Primary measure(s) of functional status	Assessment time points	Definition of functional status change	Change in functional status during treatment	Association of patient characteristics[b] with functional status change
Oechsle 2011[53]/9	Single center observational cohort (Germany)	All types, stage II	53	Median age 58 (range 29-76)	Chemo	Questionnaire for Measurement of Habitual Physical Activity (work, sports, leisure indices), EORTC-QLQ-C30 PF, International Physical Activity questionnaire	Baseline; 4 wks	Change score	-Work index: decreased from 2.25 to 0.56 (p<0.001) -Sports index: decreased from 2.91 to 2.47 (p<0.001) -Leisure time index: increased from 2.81 to 3.01 (p<0.01) -Median time of sportive activities decreased (1.6 hour to 0.8 hour, p<0.01) -No change in EORTC-QLQ-C30 PF	-Sports index prior to cancer diagnosis was higher among men (p<0.05) but no difference in sports index during chemo by gender -No gender differences in EORTC QLQ-C30 PF
Revicki 2012[54]/9	Multicenter RCT (global)	Melanoma, stage III-IV	676	Mean age 56.2 (SD 57)	Ipilimumab/gp100 vs ipilimumab alone vs gp100 alone	EORTC-QLQ-C30 PF	Pretx; 12 wks	No change: 0–5 points; a little change: 5–10 points; moderate change: 10–20 points; very much >20 points	Change scores: -Ipilimumab plus gp100: −6.2 -Ipilimumab alone: −5.1 -Gp100 alone: −10.1	-Older and younger patients (<65 vs ≥ 65 yrs) had similar PF decline in the ipilimumab plus gp100 and ipilimumab alone groups
Shallwani 2016[55]/8	Single center observational cohort (Canada)	NSCLC, stage IIIA-IV	47	Mean age 63.3 (SD 12.2)	Chemo	SF-36 PCS, 6MWT, 1 minute chair rise test, grip strength	Pretx, post-cycle 2	SF-36 MCID: 5 units; 6MWT MCID: 54 meters. Longitudinal modeling	-SF-36 PCS worsened overall: Pretx 40.8, posttx 38; p=0.02. 20% had clinically significant improvements; 33% deteriorated −6MWT worsened overall: Pretx (454.5), posttx (414.3); p<0.01. 9% had	-Nutritional status, fatigue, and 6MWT were not associated with SF-36 PCS

Study/ Quality assessment score[a]	Study design	Sample (cancer type(s), stage)	Overall N (systemic therapy n)	Age (age 65+ n if available or age summary statistic – mean/ median)	Systemic cancer treatment(s)	Primary measure(s) of functional status	Assessment time points	Definition of functional status change	Change in functional status during treatment	Association of patient characteristics[b] with functional status change
									clinically significant improvements; 14% deteriorated -Chair rise test stable: Pretx (21.4), posttx (20.7); p<0.25 -Grip strength worsened: Pretx (27.4), posttx (26.5); p=0.03	
Timilshina 2019[56]/9	Multicenter observational cohort (Canada)	AML	71	Median age 52 (IQR 41-58)	Intensive chemo	EORTC QLQ-C30 PF, grip strength, 10 timed chair stands	Pretx; 11 time points over 3 yrs	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 meters, timed chair stand MCID: 3.4 seconds)	-EORTC QLQ-C30 PF unchanged: Baseline (80.6), 12 mos (85.2), 24 mos (82.5), 36 mos (90.0) -EORTC QLQ-C30 PF: 72% returned to normal at 1 yr and 77% at 3 yrs -Grip strength unchanged: Baseline (30.3), 12 mos (31.2), 24 mos (31.8), 36 mos (32.0) -Grip strength: 50% returned to normal at 1 yr and 54% at 3 yrs -Chair stands/min improved: Baseline (25.6), 12 mos (35.0), 24 mos (39.0), 36 mos (40.7); p=0.002 -Chair stands: 44% returned to	-Older age (time x age interaction, p=0.01) and male gender (time x gender interaction, p=0.002) were associated with slower recovery in timed chair stands -Age and gender were not associated with recovery for other functional status measures

Study/ Quality assessment score[a]	Study design	Sample (cancer type(s), stage)	Overall N (systemic therapy n)	Age (age 65+ n if available or age summary statistic – mean/ median)	Systemic cancer treatment(s)	Primary measure(s) of functional status	Assessment time points	Definition of functional status change	Change in functional status during treatment	Association of patient characteristics[b] with functional status change
									normal at 1 yr and 64% at 3 yrs	
Verdonck-de Leeuw 2014[57]/10	Single center observational cohort (Netherlands)	HNSCC, all stages (curative only)	164	Median age 59 (range 40-84)	Chemoradiation (generally cisplatin)	EORTC QLQ-C30 PF	Pretx (1 wk before tx); 6 wks; 6, 12, 18, 24 mos post-RT	Change score	-EORTC QLQ-C30 worsened in the first 6 wks, then improved in survivors -EORTC QLQ-C30 worsened in non-survivors	-Comorbidity (p=0.03) and non-survivors were associated with lower EORTC QLQ-C30 PF over time
Watters 2003[58]/10	Single center observational cohort (Canada)	Breast, all stages	65 (45 young, 25 old)	Old (65+): mean age 70 (SD 5, range 65-80) Young (>65): mean age 55 (SD 6, range 31-64)	5-FU, doxorubicin, cyclophosphamide	EORTC QLQ-C30 PF, SF-36 PF, KPS, handgrip strength	Pretx; prior to cycle 3; 3 wks post-cycle 6; 6 mos, 12 mos	Change score	-EORTC QLQ-C30 and SF-36 PF were lower at completion of chemo ($p<0.01$ and $p<0.05$, 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 +/− 11, $p<0.001$) -KPS did not differ from baseline to follow-up -No change in handgrip strength	-Younger age was associated with greater decline in EORTC QLQ-C30 PF ($p<0.05$) -Age was not associated with changes in SF-36 PF
Williamson 2018[59]/10	Single center observational cohort (US)	Lung, all stages	101	Mean age 64.5 (SD 11.6)	Chemo, immunotherapy, targeted therapy, combination	FACT-L TOI (physical/ functional well-being)	Baseline (study entry), 6 wks, 12 wks	Change score	-Baseline: 51.37 −6 wks: 33.17 −12 wks: 44.55	-Lower baseline physical/functional well-being ($p<0.001$), being unmarried ($p=0.017$), non-Hispanic White race ($p=0.004$), higher internalized

Study/ Quality assessment score[a]	Study design	Sample (cancer type(s), stage)	Overall N (systemic therapy n)	Age (age 65+ n if available or age summary statistic – mean/ median)	Systemic cancer treatment(s)	Primary measure(s) of functional status	Assessment time points	Definition of functional status change	Change in functional status during treatment	Association of patient characteristics[b] with functional status change
										stigma (p=0.045) were associated with lower physical/functional well-being at 6 wks -Lower baseline physical/functional well-being (p<0.001) was associated with lower physical/ functional well-being at 12 wks -Age, sex, education, smoking history, months since diagnosis, cancer stage/type, prior surgery, prior chemotherapy, 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 weeks
Yang 2018[60]/10	Single center observational cohort (Taiwan)	NSCLC, stage IIIB-IV	344	Gefitinib: mean age 63.7 (SD 11.2); erlotinib: mean age 61.9 (SD 12.8); afatinib: mean age 60.8 (SD 10.2)	Gefitinib, erlotinib, afatinib	WHOQOL-BREF physical, mobility, daily activities	Baseline; q2-4 wks during tx up to 25 mos (no specific time point)	Change score	-Physical, mobility, and daily activities scores were lower in the afatinib arm	-ECOG PS 2-4 (vs 0-1) was associated with worse scores on physical, mobility, and daily activities (p<0.001) -EGFR exon 19 deletion was associated with worse scores on physical (p<0.05), mobility (p<0.05), and daily activities

Study/ Quality assessment score[a]	Study design	Sample (cancer type(s), stage)	Overall N (systemic therapy n)	Age (age 65+ n if available or age summary statistic – mean/ median)	Systemic cancer treatment(s)	Primary measure(s) of functional status	Assessment time points	Definition of functional status change	Change in functional status during treatment	Association of patient characteristics[b] with functional status change
										(p<0.01) -Brain metastasis was associated with worse scores on mobility (p<0.05) -Disease progression was associated with worse scores on physical, mobility, and daily activities (p<0.001) -Afatinib (vs gefitinib) was associated with worse scores on physical (p<0.05), mobility (p<0.01), and daily activities (p<0.01) -Sex, education, employment, marital status, comorbidities, and recurrence were not associated with any decline

Abbreviations: 2MWT, two-minute walk test; 6MWT, six-minute walk test; 5-FU, fluorouracil; AC, cyclophosphamide/doxorubicin; AML, acute myeloid leukemia; chemo, chemotherapy; CLAS, Cancer Linear Analogue Scale; CMF, cyclophosphamide/methotrexate/fluorouracil; d, day; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; EOT, end of treatment; FACT-L TOI, Functional Assessment of Cancer Therapy-Lung Trial Outcome Index;GI, gastrointestinal; HNSCC, head and neck squamous cell carcinoma; IADL, instrumental activities of daily living; MCID, minimal clinically important difference; mo, month; mos, months; NHL, non-Hodgkin lymphoma; 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; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; SCT, stem cell transplant; SD, standard deviation; SF, short-form; vs, versus; wk, week; wks, weeks; tx; treatment; WHO, World Health Organization; WHOQOL-BREF, World Health Organization Quality-of-Life Brief; yr, year; yrs, years

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

[b]We listed patient characteristics that are associated with functional change as well as those that are not associated. We did not list patient characteristics if they were only included as covariates without a reported result.

Table 3.

Measures of functional status, assessment time points, and analytic approach by study type.

Characteristic	Overall No. (%) (N=44)	Older adult-specific studies No. (%) (n=17)	Non-older adult-specific studies No. (%) (n=27)	p-value[a]
Measures of functional status				
Patient-reported outcome[b]	43 (98)	17 (100)	26 (96)	1.00
EORTC QLQ-C30	15 (34)	5 (11)	10 (37)	
ADL	9 (20)	7 (16)	2 (7)	
IADL	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)	
Walking test	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				
Pretreatment and 1 follow-up	9 (20)	3 (18)	6 (22)	0.91
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				
Change score between two assessments	21 (48)	6 (35)	15 (56)	0.008
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: ADL, activities of daily living; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; IADL, instrumental activities of daily living; KPS, Karnofsky Performance Status.

[a] Fisher's exact test comparing older adult-specific studies and non-older adult-specific studies.

[b] Only the three most common measures of functional status within each subgroup are shown.

[c] Other assessment schedule: Initial assessment occurred after initiation of systemic therapy.

[d] Other analysis: Association with patient-reported change in physical condition.

Table 4.

Common characteristics associated with functional decline during systemic cancer treatment (N=36 studies that examined functional decline).

Characteristic	Total no. of studies examining characteristic and functional decline	No. of studies reporting an association with functional decline	No. of studies reporting no association	No. of studies including characteristic as a covariate without reporting association	Characteristic variable details[a]
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]	-Categorical age: 65-69 vs 70-74 vs 75-84[1] 25-45 vs 46-70[38] <60 vs ≥60[51] <65 vs ≥65[58] -Continuous age[42] -Age details not specified[2,39,47]
Worse performance status	11	4[35, 39, 52, 60]	6[20, 26, 29–31, 49]	1[19]	-ECOG PS: 0-1 vs 2-4[60] -Continuous KPS score[39] -Change in ECOG/WHO PS[35,52]
Progressive disease status	8	4[2, 31, 35, 60]	4[19, 42, 49, 60]		-Refractory/progressive disease at treatment completion vs complete remission[2] -Disease progression/relapse vs new diagnosis[31] -Tumor response: Partial/complete response vs progressive/stable disease[35] -Disease progression: Yes vs no[60]
Pain	7	4[24, 35, 39, 45]	3[26, 31, 47]		-Back pain: Yes vs no[24] -EORTC QLQ-C30 pain: Quite a bit/very much vs not at all/a little[35] -Quality of Life-Cancer pain score[39] -Pain-O-Meter worst pain intensity score[45]
Anemia	7	4[1, 20, 24, 47]	3[26, 30, 38]		-Categorical hemoglobin level: 7.3-10.9, 11.0-12.9, 13.0-13.9, 14.0-15.6[1] -Continuous hemoglobin level[24] -Hemoglobin change ≥1 g/dl[20] -Anemia CTCAE grade 0-2 vs 3-4[47]
Worse nutritional status	6	4[2, 31–33]	2[30, 49]		-Sarcopenia: Severe (low muscle mass, slow gait speed, and low handgrip strength) vs none[2] -Mini-Nutritional Assessment-Short Form score: ≤11 vs >11[31] -Cancer cachexia: Unintentional weight loss >5% in last 6 mos (or >2% if BMI <20 kg/m^2) or presence of muscle depletion vs no cachexia[32,33]

Abbreviations: BMI, body mass index; CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; dl, deciliter; g, gram; kg, kilogram; KPS, Karnofsky Performance Status; m, meter; mos, months; PS, performance status; vs, versus; WHO, World Health Organization.

[a]Characteristic variable details shown for studies that reported an association with functional decline.