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Older adults with cancer and their caregivers — current landscape and future directions for clinical care

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Abstract

Despite substantial improvements in the outcomes of patients with cancer over the past two decades, older adults (aged ≥65 years) with cancer are a rapidly increasing population and continue to have worse outcomes than their younger counterparts. Managing cancer in this population can be challenging because of competing health-related and ageing-related conditions that can influence treatment decision-making and affect outcomes. Geriatric screening tools and comprehensive geriatric assessment can help to identify patients who are most at risk of poor outcomes from cancer treatment and to better allocate treatment for these patients. The use of evidence-based management strategies to optimize geriatric conditions can improve communication and satisfaction between physicians, patients and caregivers as well as clinical outcomes in this population. Clinical trials are currently underway to further determine the effect of geriatric assessment combined with management interventions on cancer outcomes, as well as the predictive value of geriatric assessment in context of treatment with contemporary systemic therapies, such as immunotherapies and targeted therapies. In this Review, we summarize the unique challenges of treating older adults with cancer and describe current guidelines as well as investigational studies underway to improve the outcomes of these patients.

TOC blurb

The number of adults aged ≥65 years with cancer is rapidly growing; these individuals continue to have worse outcomes than younger adults with cancer. The authors of this Review summarize the unique challenges of treating older adults with cancer owing to competing health-related and

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Author contributions

The authors contributed equally to all aspects of preparation of the article.

Competing interests

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ageing-related conditions, and describe describe current guidelines as well as investigational studies underway to improve the outcomes of these patients.

Introduction

The average global life expectancy is predicted to increase to approximately 80 years by 2040.[1] Cancer is an ageing-related disease, and thus its prevalence will also increase with the ageing of the population. Older adults with cancer are a unique, heterogeneous population: they often have multiple competing health and ageing-related conditions, as well as distinct preferences that influence treatment decision-making and affect cancer outcomes. Tools are available to guide treatment decision-making and supportive care for older patients, although important knowledge gaps remain regarding how best to manage these patients. In this Review, we discuss the epidemiology of cancer in older adults and disparities in the care of this population, and describe how ageing-related conditions affect cancer-specific outcomes, how geriatric assessment can assist in treatment decision-making and management strategies for geriatric syndromes, including addressing caregiver needs. We also discuss limitations of current guidelines and highlight clinical trials assessing unmet needs in this population.

Epidemiology

By 2030, 70% of all cancers will be diagnosed in older adults (a term that in this article refers to individuals aged ≥65 years, unless indicated otherwise). Currently, 70% of lung cancers, 59% of colorectal cancers and 59% of prostate cancers are diagnosed in individuals in this age group[2,3]. Adults aged ≥85 years account for 8% of all new cancer diagnoses and 17% of cancer-related deaths[4]. Furthermore, owing to advances in cancer diagnosis and treatment, the number of cancer survivors is growing (FIG. 1). The majority of cancer survivors (64%) are older adults, and this percentage is projected to increase to 73% by 2040, with the group of individuals aged >85 years being the fastest growing among cancer survivors[4,5].

Despite remarkable scientific progress in cancer control, diagnosis and treatment over the past two decades, these advances have not been equally distributed[6]; disparities according to age, sex and ethnicity remain[7,8]. Using data from nine registries in the Surveillance, Epidemiology and End Results (SEER) database, Zeng et al compared cancer-specific death for patients diagnosed with cancer between 1994–2009 and showed that patients aged 50–64 years compared with those aged ≥65 years had greater improvements in survival from colorectal, breast, prostate, lung and liver cancer[9]. The hazard ratios for cancer-specific death during years 2005–2009 compared with 1990–1994 in patients aged 50–64 years versus those aged 75–85 years were: 0.57 (95% CI 0.55–0.60) versus 0.88 (95% CI 0.84–0.92) for colorectal cancer; 0.48 (95% CI 0.45–0.51) versus 0.88 (85% CI 0.82–0.95) for breast cancer; 0.67 (95% CI 0.63–0.71) versus 0.76 (95% CI 0.69–0.84) for liver cancer; 0.95 (95% CI 0.73-0.77) versus 0.84 (95% CI 0.81-0.86) for lung cancer; and 0.32 (95% CI 0.30–0.36) versus 0.65 (95% CI 0.61–0.70) for prostate cancer. Compared with adults aged 65–84 years, those aged ≥85 years are diagnosed at later stages, are less likely to receive

guideline-concordant care (including surgery) and often receive treatment deemed inadequate[4]. For example, the percentage of patients with breast cancer aged ≥85 years who received surgery in 2019 was estimated to be 65% compared with 89% of patients aged 65–84 years.

Further inequities emerge when evaluating cancer incidence and mortality on a global scale. LMICs in regions such as Africa, India and Latin America, where almost 400 million older adults live, have the highest cancer incidence and mortality when compared to other regions, such as North America and Europe[10,11]. In the USA, cancer incidence and mortality also vary by ethnicity: among older adults, the overall incidence of cancer, as well as that of late-stage or unstaged disease, is higher in those of African-American or other black ethnic backgrounds than in white individuals[12]. In addition, older black individuals have lower 5-year relative survival rates for all cancers combined compared with older white individuals (59.9% versus 54.5%)[12].

Cancer disparities, combined with the limited participation of older adults and/or individuals from ethnic minorities in clinical trials, leave patients in these groups vulnerable to suboptimal cancer treatment and an increased risk of poor outcomes. Ludmir et al.[13] identified significant ageing-related disparities in an analysis of 302 randomized clinical trials, with the median age of participants in these trials being 6.5 years younger than the median age of the general population (P <0.001). Similarly, in an analysis of 34,957 patients involved in 69 phase II or III Canadian Cancer Trials Group studies, Hernandez-Torres et al. found that in Canada, only 40.8% of patients aged ≥65 years and 12% of patients aged ≥75 years were enrolled in clinical trials compared with 56.1% of patients diagnosed with cancer (30% aged ≥75 years; P <0.001)[14]. Factors contributing to ageing-related disparities in oncology clinical trial participation include the specification of upper age limits in the inclusion criteria of clinical trials, restrictive exclusion criteria on the basis of factors such as comorbidities, organ function and functional status, and the uncertainty of oncologists regarding treatment-related adverse events (TRAEs) in older adults[14-16]. The inequity in clinical trial participation is more profound in ethnic minorities, and this gap has been steadily widening over the past decade[17-19] Greater emphasis must be placed on ensuring the appropriate representation of ages, sexes and/or gender and ethnicities of participants in clinical trials to help to improve our knowledge of how to appropriately treat every patient. The paucity of studies outside of high-income countries further demonstrates the need for global research initiatives for older adults in lower middle-income countries (LMICs) that consider the unique needs of patients in those areas[11].

Ageing-related conditions in cancer

Prevalence in older adults with cancer

Among older adults with cancer, substantial heterogeneity exists in overall health status and functional status (so-called ‘physiological age’), even among those of similar chronological age. Older age is associated with an increased prevalence of chronic illnesses (or comorbidities), ageing-related conditions (or geriatric syndromes) and frailty.

Comorbidities are defined as additional medical conditions in the context of an index illness (such as cancer), whereas multimorbidity refers to the simultaneous occurrence of several medical conditions, functional limitations and/or geriatric syndromes in one person[20]. Comorbidities are highly prevalent in individuals with cancer and their prevalence increases with age[21]. In the USA, 80% of older adults with cancer have a chronic condition, such as heart disease, stroke or chronic lower respiratory disease, and 50% have more than two chronic conditions[22]. In older adults with cancer, the prevalence of comorbidities is similar to that in older adults without cancer, but seems to differ among patients with different cancer types[7,23,24]. For example, patients with lung or colorectal cancer have a higher prevalence of comorbidities (52.9% and 40.7%, respectively) than patients with breast or prostate cancer (32.2% and 30.5%, respectively), for whom the prevalence is similar to that in individuals without cancer (31.8%)[7,24]. These differences might be attributable to risk factors, such as smoking or various lifestyle habits, which contribute to the risk of both cancer and other chronic conditions.

Geriatric syndromes do not fit into discreet disease categories and are caused by several underlying factors involving multiple organ systems to cause “accumulated effects of impairments in multiple domains”[23] that make older adults “vulnerable to additional insults or challenges”[25] (TABLE 1). Geriatric syndromes are more prevalent in older adults with a history of cancer than in younger adults with cancer and in older adults without cancer. In a study of Medicare beneficiaries (n = 12,480), the percentage of older adults reporting at least one geriatric syndrome was higher among those with cancer than in those without cancer (60.3% versus 53.2%; P <0.001). In particular, older adults with cancer had a statistically significant higher prevalence of hearing impairment, incontinence, osteoporosis, depression and falls (all P <0.023)[26]. Polypharmacy, which increases in association with comorbidities, is also highly prevalent in older adults with cancer. A pharmacist-led retrospective analysis of older adults with cancer (n = 248) found a high prevalence of polypharmacy (5–10 medications), excessive polypharmacy (>10 medications) and inappropriate use of medications (40%, 38% and 21%, respectively); patients were receiving a mean number of 9.2 medications[27]. The prevalence of polypharmacy varies across studies and geographic regions (35–96%) but the prevalence of inappropriate used of medications is similar[28-31]. On the basis of SEER–Medicare data, cognitive impairment is present in 4–7% of patients with cancer, although this value is probably an under-estimate owing to the lack of data capture in insurance claims, and because mild cognitive impairment is usually not accounted for in these claims[32]. Indeed, in a study published in 2019[33], 39.2% of 3,140 older adults with cancer who had a Mini Mental Status Exam (MMSE) prior to starting cancer treatment screened positive for cognitive impairment (score <24, indicating at least mild dementia). Sensory impairments, such as vision and hearing loss, occur in almost one-third of older patients with cancer[34]. In a prospective cohort study of malnutrition using the Mini-Nutritional Assessment (MNA) in community-dwelling adults aged ≥70 years prior to initiating cancer treatment[35], 43.5% of patients were classified as being at risk of malnutrition (MNA score 17–23.5), and 20.7% met criteria for malnutrition (MNA score 0–16). Older adults with cancer experience changes in body composition leading to decreases in bone mass, muscle mass and strength, and increased adiposity[36,37]. On the basis of femoral neck bone mineral density, the US National Osteoporosis Foundation estimates that

10.3% of adults aged ≥50 years in the USA (>10 million people) have osteoporosis, 43.9% (>30 million people) have low bone mass and one-third of older women suffer a fracture[38,39]. In a cross-sectional study of men with prostate cancer (n = 390, mean age of 68 years), 35.4% of hormone-naive patients had osteoporosis[40]. Sarcopenia, characterized by the loss of muscle mass and strength, is believed to occur in 15–50% of older adults with cancer[41].

Frailty is a geriatric syndrome that encompasses the most extreme disparity between chronological and physiological age; as a result, it remains multidimensional, dynamic, and is affected by both physical and psychosocial risk factors[42]. No consensus definition of frailty exists, and it is measured in different ways. A common definition used in geriatrics is the Fried physical phenotype of frailty[43], which defines frailty as fulfilling three out of five criteria including unintentional weight loss, exhaustion, slow walking speed, a low level of physical activity and/or weakness. This measure has not been validated in older adults with cancer and its use in geriatric oncology has been limited. The Balducci criteria were developed to specifically identify older adults with cancer who are frail and unlikely to withstand and benefit from oncology treatments deemed aggressive[44]. The criteria include dependency on a carer for activities of daily living (ADLs) and instrumental activities of daily living (IADLs), ≥3 comorbid conditions, the presence of geriatric syndromes or age ≥85 years. Observational studies have revealed that older adults with cancer classified as ‘frail’ using the Balducci criteria tend to be at higher risk of death across various cancers, such as colorectal cancer and diffuse large B cell lymphoma[45-47].

Several other methods of measuring frailty in older adults with various malignancies have also been developed[48]. The Carolina Frailty Index (CFI) was developed by Guerard et al.[49] using a cancer-specific geriatric assessment on the basis of the principle of deficit accumulation — that is, frailty increases in correlation with the number of health deficits. The CFI was predictive of all-cause mortality in older adults with cancer, independent of age, sex, cancer type, stage and number of comorbidities. Ferrat et al.[50] evaluated the performance of four frailty classifications (Balducci, International Society of Geriatric Oncology (SIOG) 1, SIOG2 and latent class analysis) in older adults with cancer. SIOG1, developed by the SIOG Prostate Cancer Working Group, uses comorbidities, ADL and IADL status and nutritional status, to classify patients as ‘fit’, ‘vulnerable’, ‘frail’ or ‘too sick’, in order to determine best treatment options for older adults with prostate cancer[51]. SIOG2 is an update of SIOG1 in which the ‘too sick’ category was removed and only patients with an abnormal result in the Geriatric 8 (G8) health status screening tool were evaluated[52]. Latent class analysis was derived statistically using the geriatric assessment to classify older adults into four health profiles from ‘relatively healthy’ to ‘globally impaired’[53]. When these four classifications were compared, limited agreement was found in how patients were categorized as ‘fit’, ‘vulnerable’ or ‘frail’. However, all four frailty classifications had good discrimination performance for 1-year mortality (C-index ≥0.70) and 6-month rate of unscheduled hospital admissions (C-index ≥0.70). Discrimination varied by disease site, presence of metastatic disease and prognosis, suggesting that frailty measures might need to be adjusted for tumour site and stage. On the basis of their analysis, the authors suggest that definitions of frailty should include, at least, disability, number of severe comorbidities and malnutrition.

The prevalence of frailty is 15.3% in older adults and >30% in adults aged ≥80 years, with women, ethnic minorities and adults with lower income being most affected[54]. However, the prevalence of frailty in older adult with cancer ranges between 6–86% depending on the definition used[55]. Applying the Balducci frailty criteria in a study of older Medicare beneficiaries (n = 12,480), Mohile et al.[26] found that the prevalence of frailty was significantly higher among those with cancer than in those without cancer (79.6% versus 73.4%; P <0.001). Using the CFI, Guerard et al.[49] found that, among 546 older adults with cancer, 18% were ‘frail’ and 24% were ‘pre-frail’.

Effects on cancer-specific outcomes

The complex interplay between cancer, comorbidities, geriatric syndromes and frailty has wide-ranging implications on cancer disease course and outcomes. Comorbidities increase cancer burden and are competing causes of death in patients with cancer. Comorbidities have been associated with poorer overall survival (OS) in adults with cancer in a study of 6,325 older individuals, and with worse cancer-specific survival in patients with lung or colon cancer[56,57]. Williams et al.[58] found that 60% of 539 older patients with cancer (with a mean age of 72 years) reported a functional limitation related to comorbidity and that the risk of death increased by 5% for each unit increase in comorbidity burden score.

Comorbidities affect decisions related to cancer screening and treatment. Conditions such as diabetes, cognitive decline, psychiatric disorders and hip fractures have been associated with a trend towards lower uptake of screening for breast, cervical and colorectal cancers[59,60]. Several studies suggest a complicated relationship between comorbidity and cancer stage at diagnosis, with several individual comorbidities (such as diabetes and other endocrine disorders, psychiatric disorders, and haematological disorders) and/or the severity of comorbidities affecting a patient’s risk of being diagnosed with advanced-stage disease[61,62]. In a study of 14,096 patients with prevalent solid tumours, dementia had the strongest individual effect on the risk of having advanced-stage or unknown stage at diagnosis[63]. Comorbidities are also associated with decreased use of chemotherapy, and studies have reported higher rates of grade 3–4 toxicities, mainly haematological, in patients with higher numbers of comorbidities[64,65]. For example, in a study of 4,040 patients with colorectal cancer, patients with ≥2 comorbidities had significantly higher odds of not receiving chemotherapy than those with no comorbidities (OR 2.55, 95% CI 1.36–4.78) and patients aged ≥75 years with >1 comorbidity had even greater odds of not receiving chemotherapy compared with younger patients with no comorbidities (OR 23.2, 95% CI 10.3-52.5)[66]. In women with breast cancer aged ≥60 years, Zauderer et al.[67] found a statistically significant association between comorbidity and any grade 3–4 toxicity (OR 2.15; P = 0.04) and non-haematological grade 3–4 toxicities (OR 2.97; P ≤0.01). Finally, comorbidities are associated with an increased symptom burden and decreased physical and mental quality of life (QOL) in vulnerable older adults with cancer[68].

Geriatric syndromes also influence cancer-related outcomes in older adults (TABLE 1). These syndromes include cognitive impairment[69,70], polypharmacy[71], malnutrition[72], sarcopenia[37,41], falls[73], depression[74] and frailty. Notably, older adults with cancer are one of the highest risk groups for suicide[75]. Similarly, frailty has been shown to affect mortality and

is a predictor of the risk of TRAEs in older adults with cancer. Using the CFI, Guerard et al. [49] found that in older adults with cancer, estimated 5-year survival decreased from 72% in 'robust' patients to 58% in 'pre-frail' patients and 34% in 'frail' patients. Frail patients had >2-fold increased risk in all-cause mortality compared with robust patients[49]. In a study involving 50 adults with newly diagnosed advanced-stage non-small-cell lung cancer (NSCLC), Ruiz et al.[76] found that having ≥3 impairments in baseline frailty according to the Fried Frailty Index was associated with higher risk of TRAEs during the first cycle of chemotherapy (OR 7.0, 95% CI 1.1–44.6). Frailty has also been shown to be associated with decreased QOL in older adults with cancer. For example, in older women with breast cancer undergoing treatment (n = 63), pre-frail and frail patients reported worse physical function and more fatigue, depression and sleep disturbance than robust wormen[77]. Pooling data across several studies, geriatric assessment tools can help to identify older patients with cancer who have significantly higher risk of mortality, perioperative complications and TRAEs[78].

Geriatric assessment in decision-making

A geriatric assessment is a diagnostic process of evaluating an older adult's comorbidities, medications, physical and cognitive function, nutritional status, psychological state, and social support. A comprehensive geriatric assessment (CGA) expands on this concept. This multidimensional, multidisciplinary approach incorporates the geriatric assessment to identify care needs in older adults, and involves developing and implementing interventions to improve outcomes in vulnerable and frail older adults (TABLE 2)[79]. Numerous studies in the general geriatric population have evaluated the role of the CGA on improving outcomes for community-dwelling older adults[80,81] as well as hospitalized patients[82-84]. On the basis of this data, the use of CGA has been extrapolated to older adults with cancer[85].

The application of the geriatric assessment to older adults with cancer has led to validated risk prediction models for TRAEs in older adults with cancer, such as the Cancer and Aging Research Group (CARG) tool[73]. The Chemotherapy Risk Assessment Scale for High-age patients (CRASH) can also be helpful and seems to perform similarly to the CARG tool in terms of discriminatory value[70,86]. The choice of a geriatric assessment tool to characterize frailty or identify which older adults might be more susceptible to adverse events during cancer treatment depends on several factors, including the time and resources available, familiarity with the domains and measures used, and whether existing standardized protocols already are in place. Moreover, inherent differences exist in the performance of a given tool within specific cancer types, whether in isolation or in comparison with other tools[87,88].

Performing the geriatric assessment can lead to clinically significant changes in treatment plans for older adults with cancer. For example, in an analysis of 35 geriatric assessment-driven cancer research studies, initial cancer treatment plans were subsequently modified in 28% of patients, and in most cases (7 of 8 studies which described differences in treatment choice) lead to attenuation of overall treatment intensity[89,90]. A positive effect on treatment completion and on TRAEs and/or complications was observed in 75% and 55% of studies, respectively. A later prospective study has corroborated that multidisciplinary geriatric oncology team-based approach in cancer care can influence the cancer treatment decisions

for older adults with cancer[91]. The degree to which assessment-guided geriatric interventions have been implemented varies across studies but seems to be more common in those with a protocol-driven set of interventions or those incorporating formal geriatrics consultations and/or team-based care[89,90].

Incorporation of the geriatric assessment into cancer treatment decision-making remains challenging, because this step can be considered time-consuming and resource intensive[92]. Screening of older adults with cancer to identify those who are vulnerable or frail and might be more susceptible to TRAEs is an alternative approach that is less demanding in terms of time and resources than performing a CGA on all older adults above a certain age threshold (TABLE 3). Susceptible patients identified through such screening might benefit from a subsequent CGA. The G8 screening tool and the Flemish version of the Triage Risk Screening Tool (fTRST) have been shown to enable prediction of worse functional outcomes and worse OS in older adults with cancer[93,94]. In a systematic review published in 2019, more than half of G8-based studies demonstrated an association between frailty (G8 score ≤14) and worse OS[95]. The Vulnerable Elders Survey-13 (VES-13) is more commonly used in the USA than in other countries, where it was initially found to predict disability and unfavourable survival in community-dwelling older adults[96]. In older adults with cancer, VES-13 has been demonstrated to correlate with toxicities or tolerance of cancer treatment as well as OS, albeit in fewer geriatric oncology studies than the G8 screening tool[97-100].

Several geriatric evaluation screening tools and CGA formats exist and, importantly, no single tool or approach is favoured by SIOG or ASCO[85,101]. In the latest update of the SIOG position statement regarding such screening tools, any one is encouraged as an initial first step for clinicians to help better identify at-risk older adults with cancer prior to starting treatment[102]. We must emphasize that these tools do not replace a CGA, which will offer further clinically important insights to inform decision-making on anticancer treatment. The ASCO guidelines similarly do not recommend one screening tool over another (for example G8 versus VES-13), but they do encourage clinicians to routinely incorporate geriatric measures to assess baseline function and other geriatric domains, such as evaluating IADLs and falls, in older patients with cancer receiving or considering chemotherapy[85].

Management of ageing-related conditions

High-priority interventions for each geriatric assessment domain have been identified through two Delphi consensus studies led by US-based and European-based panels[103,104] (TABLE 2), and these results were incorporated into the 2018 ASCO Guidelines for Geriatric Oncology[85]. A large, cluster-randomized, multisite study of community oncology practices published in 2019 demonstrated that the use of CGA with management recommendations improves communication about ageing-related issues as well as patient and caregiver satisfaction[105]. Overall, 541 participants aged ≥70 years with advanced-stage cancer who had impairment in one geriatric assessment domain were enrolled across the USA; 414 caregivers were also involved. Oncology practice sites were randomly allocated to deliver the intervention (a tailored geriatric assessment summary with management recommendations for each patient) or usual care (notification to oncologist only in situations of depression or cognitive impairment). The primary outcome was satisfaction with

communication about ageing-related concerns, evaluated with a modified Health Care Climate Questionnaire (score range 0–28, with higher scores indicating greater satisfaction). Compared with usual care, patients and caregivers in the intervention group were more satisfied (difference in mean score of 1.09 points; 95% CI 0.05–2.13 points; $P = 0.04$) and patient satisfaction remained higher after 6 months of follow up (difference in mean score of 1.10 points). Conversations about concerns were more frequent during clinical encounters in the intervention group[105].

Several smaller pilot studies have evaluated the feasibility of implementing geriatric assessment with management recommendations in the oncology setting and explored various models to deliver this type of care. A large-cohort, single-arm study of patients aged ≥70 years with cancer in Belgium evaluated a model of care where geriatric expertise was available to patients as an inpatient or outpatient service and care remained under their primary oncologist[106]. Overall, 710 patients were evaluable and a median of two geriatric assessment management recommendations per patient were provided. However, only 35% of all geriatric assessment management recommendations were acted upon, with the most frequent being referrals to dietician, social work or psychologist services. A British prospective study evaluated the effect on cancer-related outcomes (including TRAEs, treatment changes and OS) of geriatric assessment with management interventions, delivered directly by geriatricians, in 65 older adults with cancer versus standard oncology care in 70 patients[107]. Patients receiving geriatric assessment with management interventions were more likely to complete cancer treatment (33.8% versus 11.4%; OR 4.14; $P = 0.006$) with fewer treatment modifications (43.1% versus 68.6%; OR 0.34; $P = 0.006$), although the frequency of TRAEs were not different between both groups (43.8% versus 52.9%; $P = 0.29$).

Smaller, randomized pilot studies have also been conducted to evaluate the feasibly of delivering geriatric assessment with management recommendations and the preliminary effect of these interventions on cancer outcomes. A single-institution randomized trial involving 71 patients with advanced-stage solid tumours tested an algorithm-based model for implementing geriatric assessment-guided management recommendations[108]. A trained coordinator conducted and scored the geriatric assessment with predetermined impairment cutoffs, and subsequently used an algorithm to provide geriatric assessment-guided management recommendations to the primary oncology team for implementation. Of the 37 patients randomly allocated to the intervention group, 34 (92%) had a geriatric assessment completed and recommendations were provided to the oncology team within the targeted time frame (1 week from the assessment), demonstrating the feasibility of this model of care. In total, 409 geriatric management recommendations were provided, of which only 35% were ultimately implemented by the primary oncology team. This result further suggests that additional support might be required to optimize the implementation of geriatric assessment-guided management recommendations, as opposed to sole reliance on the primary oncology team. A second randomized pilot study, conducted in Canada, also evaluated the feasibility of a programme of geriatric assessment-guided management and its effects on QOL and cancer therapy modification in older adults aged ≥70 years with stage II–IV gastrointestinal, genitourinary or breast cancer who were receiving chemotherapy[109]. One group of patients had a baseline geriatric assessment and subsequently received

predefined evidenced-based geriatric assessment-guided interventions deemed necessary by the study team; priorities of the older adults and their caregivers were incorporated into these recommendations. The control group received standard oncology care. This model was deemed feasible: 64% of patients approached were enrolled, 86% of whom remained on the study. The primary outcome was measured with the EORTC core QOL Questionnaire, with a change of ≥10 points indicating an important clinical change. Geriatric assessment with management intervention improved QOL, with greater benefit in patients who survived >6 months. In these patients, the median change in baseline QOL score after 3 months of intervention was −2.78 points versus −9.75 points in the control group. This type of intervention has also been evaluated in a randomized trial in the pre-operative setting to determine its effect on post-operative complications[110]. In this trial[110], 122 older patients scheduled for elective colorectal surgery were randomly allocated to receive geriatric assessment with management or usual care. After adjusting for prespecified prognostic factors, the geriatric assessment-guided management intervention was significantly associated with a reduction in the total number of post-operative complications (OR 0.33, 95% CI 0.11–0.95).

Finding of several additional randomized controlled trials have further elucidated the effect of geriatric-assessment-guided management interventions on care outcomes of older adults with cancer. Corre and colleagues[111] evaluated the utility of integrating the geriatric assessment into cancer therapy decision-making for older adults with NSCLC. In this multicentre study, 494 patients aged ≥70 years with stage IV NSCLC were randomly assigned to receive geriatric assessment-guided treatment options (carboplatin-based doublet for fit patients, docetaxel for vulnerable patients and best supportive care for frail patients) or usual care (carboplatin-based doublet if performance status ≤1 and age ≤75 years or docetaxel if performance status of 2 and age >75 years). OS was equivalent in both arms (6.5 months versus 6.1 months in the usual care and intervention arm, respectively), despite nearly a quarter of frail patients in the intervention arm receiving best supportive care only. Significantly fewer patients in the intervention arm had TRAEs (85.6% versus 93.4%; $P = 0.015$) and treatment failure as a result of toxicities (4.8% versus 11.8%; $P = 0.007$)[111]. These findings suggest that geriatric assessment can better allocate the appropriate therapy for individual patients, without compromising survival outcomes and, thus, future therapeutic trials for older adults should incorporate geriatric assessment[112]. Three randomized control trials were presented at the 2020 ASCO Annual Meeting demonstrating the benefit of a geriatric assessment-guided intervention on TRAEs. A large, multicentre study (NCT02054741) conducted by Mohile et al. showed that, compared with the usual care arm, providing geriatric assessment summary and intervention recommendations for patients with advanced-stage solid tumors or lymphomas and starting a new treatment reduced the percentage of patients with grade 3–5 adverse events (71% versus 50%). The relative risk of grade 3–5 TRAEs for intervention versus usual care was 0.74 (95% CI 0.63–0.87; $P = 0.0002$), mostly owing to the occurrence of non-haematological toxicities (RR 0.73; 95% CI 0.53–1.0; $P \leq 0.05$). No significant differences were observed in OS (71% versus 74%; $P = 0.03$)[113]. Similarly, Li et al. found that, compared with standard of care, geriatric assessment-guided interventions reduced TRAEs by 9.9% (95% CI 1.6–18.2%)[114]. Soo et al. additionally found that these interventions led to a lower frequence of early

treatment discontinuation, reduced unplanned hospitalizations and improved QOL[115]. Multicentre studies are underway to determine models of geriatric assessment-guided management interventions delivered by a geriatrician with nurse follow up (NCT02704832, NCT03154671)[116,117]. These studies are all relevant because they use different models of care that are informed by specific health care systems and populations, and utilize outcomes important to older adults.

Caregiver assessment and interventions

Prevalence and roles

Owing to the presence of comorbidities and/or physical, cognitive and functional impairments, older adults with cancer often require supportive care. In the USA, 63% of home care to older adults with cancer is provided by informal caregivers, who are often family members, female and unpaid[118-120]. With the increase in the ageing population of patients with cancer and the improvement of oncology treatments, the number of informal caregivers is also expected to increase. Informal caregivers provide an average of 32 hours of care per week. These caregivers have crucial roles in treatment decision-making, patient advocacy and end-of-life care. They provide nursing care with limited training, including managing cancer symptoms and TRAEs, while also assisting with self-care household tasks and providing emotional support. In comparison with non-cancer caregivers, cancer caregivers provide significantly more help with ADLs and IADLS[119].

Caregiver burden

Caregivers of older adults with cancer also tend to be older (63–66 years on average), ~40% have comorbidities and they are more likely to report their health as fair to poor[121,122]. Given the care that is required by older adults with cancer, caregivers experience substantial physical and emotional challenges that can lead to caregiver burden[121]. In comparison with non-caregivers of the same age, caregivers of older adults with cancer are more likely to experience deterioration in physical health and to have poor health-related behaviours (including decreased exercise, sleep and poor eating habits), and are less likely to engage in preventative care[123-126]. In addition, caregivers are more likely to report symptoms of anxiety and depression, with 19% reporting moderate-to-severe anxiety and 24% reporting moderate-to-severe depression in a study of caregivers of older adults with cancer[127]. Patient characteristics that lead to greater anxiety and depression in caregivers include poor Eastern Cooperative Oncology Group (ECOG) performance status, solid tumours (as opposed to haematological malignancies), requiring assistance with ADLs and/or IADLs, having greater symptom burden and having greater emotional distress[120,128,129]. Caregiver characteristics associated with increased psychological symptoms were younger age, being a spouse, poor health status, lower social support and having poor coping skills (FIG. 2).

In a study of older adults with cancer[120], 75% of their caregivers reported some degree of burden. In a study of 392 older spousal caregivers, Schulz et al.[124] found that those who reported physical and mental strain from caregiving had a 63% greater 4-year mortality risk than non-caregivers. In 2019, data from two studies have demonstrated that worse QOL in caregivers is associated with poor patient performance status, higher number of impairments

in the patient's geriatric assessment, caregiver depression and less social support[122,130]. Caregiver burden, in turn, is associated with increased all-cause mortality in patients, as well as an increased risk of hospitalization and more intensive and/or inappropriate end-of life care[131,132].

Caregiver interventions

While researchers have clearly established that caregivers of older adults with cancer are at high risk for a heavy caregiver burden and negative physical and psychological outcomes, testing of interventions in this specific population is scarce. As previously discussed, in one study evaluating a geriatric assessment intervention for older adults with advanced-stage cancer and one geriatric assessment domain impairment, caregivers of these patients reported higher levels of satisfaction with treatment and communication with the oncologist than those of patients assigned to receive usual care[105]. Data from interventions involving caregivers of adults of all ages with cancer are available[133-136], but whether the findings from these studies can be applied to older caregivers of older persons with cancer is not known[137,138]. In a systematic review of 22 psychosocial intervention studies involving caregivers, the mean age of caregivers ranged from 39–61 years, suggesting that older caregivers are underrepresented in such research[133]. One potential promising area is focused on testing the effectiveness of existing caregiver interventions in caregivers of older adults with cancer, either as originally developed or tailored to the specific needs of this population. In a systematic review of a wide range of interventions (categorized as cognitive behavioural, complementary or alternative medicine, family or couples, interpersonal, problem solving or skill building, psychoeducational, subspecialty palliative care, and supportive therapy), the authors concluded that "structured, goal-oriented, and time-limited interventions that are integrative appear to be the most feasible and to offer the greatest benefit"[121]. In a Cochrane Review that included 19 trials of psychosocial interventions for caregivers of patients with cancer[139], the authors stated that differences across studies prevented drawing conclusions and identified a need for rigorous trials that are adequately powered and examine a wide range of robust, validated and reliable caregiver outcome measures.

Interventions that are provided to both the patient and the caregiver might be of particular benefit because the patient's health is related to the QOL and emotional status of their caregiver[140]. Including caregivers and older patients in the design of the interventions might improve their acceptability and feasibility[141]. Selecting interventions that include a needs assessment and that target the priority areas identified by individuals (such as problem-solving therapy or skills training) could be a particularly effective approach, given that the needs of patients and caregivers are widespread and varied.

Future clinical and research directions

The current guidelines in geriatric oncology have several limitations, and these gaps should guide future clinical and research directions for older patients with cancer and their caregivers[85,101,102]. First, guidelines are primarily focused on older adults receiving chemotherapy owing to the lack of robust data from geriatric assessment of those receiving

other systemic therapies (such as immune-checkpoint inhibitors (ICIs) and targeted therapies). Nonetheless, studies evaluating the predictive value of geriatric assessment for other treatment modalities are emerging[142,143]. In a real-world evaluation of ICIs in 75 older patients aged ≥70 years with advanced-stage NSCLC, ICIs were generally well tolerated and rates of immune-related adverse events (irAEs) were similar to those reported in landmark trials (37% of patients experiencing any grade irAEs and 8% of patients experiencing grade ≥3 irAEs). However, these patients had a higher rate of treatment discontinuation owing to TRAEs (16% versus 3–10% in landmark trials), and had high rate of hospitalization during ICI treatment (72%)[142]. In 28 patients aged ≥65 years with solid tumours receiving ICIs who underwent a geriatric assessment, Welaya et al. found a high prevalence of impairments (75% had ≥1 impairment) and patients with IADL impairments received fewer cycles of ICIs (median 2 versus 7 cycles; $P = 0.02$)[143]. Second, guidelines do not specify how frequently the geriatric assessment should be performed[85,101]. Currently, the benefits associated with performing these tools longitudinally are unclear[144]. Third, while guidelines recommend specific geriatric assessment domains and tools, they do not provide practical information on who should be performing these assessments or how the geriatric assessment can be done.

The uptake and implementation of geriatric assessment in clinical practice is low[145] because health-care professionals often perceive it to be time-consuming and resource intensive[146,147]. Gulasingam et al.[146] identified barriers to use of the G8 tool and selected four mechanisms to facilitate change: conducting local consensus discussions, identifying and preparing a champion, using educational materials, and preparing patients to be active participants. In order to promote uptake of the geriatric assessment, several practice models have also been implemented: (1) consultative geriatric assessment, whereby patients are referred to a geriatric oncology clinic led by a geriatric oncologist, geriatrician or nurse practitioner; (2) having a geriatric oncologist as the primary oncologist who can perform a geriatric assessment and provide treatment; (3) co-management between an oncologist and a geriatric oncology health-care professional; and (4) integration of nursing clinicians to guide geriatric management in clinical care[148-150]. Advances in technology have led to an increase in the use of electronic medical records and mobile health tools to facilitate the administration and delivery of geriatric assessment-guided interventions[151-153]. For example, the Electronic Rapid Fitness Assessment (eRFA) was developed to efficiently capture data across multiple geriatric assessment domains as part of preoperative evaluation of older cancer patients by having patients complete an online assessment on an electronic tablet and have the data available for clinician review[154]. The median time to complete the eRFA (11 minutes) is considerably shorter than the time to complete a paper-version of the complete geriatric assessment (30 minutes), and has been shown to be feasible and effective in identifying geriatric assessment impairments[154]. Shahrokni et al. subsequently developed the Memorial Sloan Kettering-Frailty Index (MSK-FI) which uses the eRFA to assess frailty in older cancer patients undergoing surgery[155]. They demonstrated that, in cancer patients aged ≥75 years who were undergoing surgery, each 1-point increase in the MSK-FI (indicating greater frailty), was associated with longer lengths of stay (0.58 days, 95% CI 0.22–0.95 days; $P = 0.002$), higher odds of intensive care unit admission (OR 1.28, 95% CI 1.04–1.58; $P = 0.02$), and increased 12-month risk of death (5% for a score of 0 versus 20%

for scores ≥4; $P = 0.005$). The eRFA has also been successfully implemented in older patients undergoing haematopoietic cell transplantation[156]. Finally, a pilot study has shown that delivery of geriatric assessment-guided interventions (such as monitoring of medication in patients screened positive for polypharmacy) is feasible and acceptable among older adults with cancer[153].

Incorporating a geriatric assessment in clinical trials is feasible and such assessments are being incorporated in an increasing number of trials (Supplementary Table 1). Geriatric assessment has been included in single-centre observation and treatment trials, as well as in national cooperative group clinical trials[157]. In the CALGB 360401 study, 93 older patients who were already enrolled on cooperative group clinical trials completed an adapted geriatric assessment. This process was quick, easy to complete, and a large majority of patients found it satisfactory[158]. This study met the prespecified end point, which was feasibility of geriatric assessment implementation (completed before receiving treatment by 70% of patients enrolled), and laid the basis for the use of geriatric assessment in subsequent cooperative trials, including the Alliance A041202 study[159], a multi-site study investigating the use of ibrutinib in 547 older adults with chronic lymphocytic leukemia. Although geriatric assessment was not the primary end point of Alliance A041202, virtually all individuals (95%) assigned to undergo one completed them[160].

Cancer clinical trials often prioritize end points such as OS and progression-free survival (PFS). While such outcomes are important, older patients also prioritize physical function, cognition and QOL[161,162], which are often not captured in clinical trials. In response to this need, an increasing number of studies involving older adults with cancer have started to incorporate geriatric assessment and patient-reported outcomes (Supplementary Table 2)[159,163,164]. For example, in the FOCUS2 trial, Seymour et al.[165] developed and used a novel composite measure of clinical benefit, tolerability, QOL and patient values, the Overall Treatment Utility (OTU), to determine the benefit of chemotherapy in frail and older adults with colorectal cancer. The authors assessed the benefit of treatment (response rate (RR), PFS, OS, QOL, and OTU) with 80% reduced-dose chemotherapy with either fluorouracil or capecitabine with or without the addition of oxaliplatin. Good OTU indicated no clinical and/or radiologic disease progression and no major negative effects of treatment (toxicity or patient acceptability); intermediate OTU indicated disease progression without negative effects of treatment or negative effects of treatment without disease progression; and poor OTU indicated disease progression and major negative treatment effects[165]. When comparing groups with good and intermediate and poor OTU, better OTU was strongly associated with improved PFS and OS and enabled better discrimination between different chemotherapy regimens than PFS and OS alone. The addition of oxaliplatin to fluorouracil or capecitabine showed a significantly increased response rate (RR 35% versus 13%; $P \leq 0.0001$) but did not significantly improve PFS or OS, and the increased toxicity negatively affected QOL. However, the addition of oxaliplatin was significantly associated with good OTU (47% versus 36%; $P = 0.003$) suggesting overall benefit with oxaliplatin. In comparison, no benefit was found with capecitabine over fluorouracil: the OTU score was not superior, no differences in RR, PFS, OS or QOL were found and TRAEs were more frequent. The analysis of baseline patient characteristics, including geriatric assessment data, was feasible and enabled predictors of favourable OTU to be determined[165]. The OTU has

subsequently been shown to be a beneficial measure in other clinical trials, namely the phase II 321GO and the phase III GO2 studies designed to optimize chemotherapy for frail and older adults with advanced-stage gastroesophageal cancer[166,167]. In addition to providing relevant and practical outcome data in older adults, access to clinical studies and their publications will help to boost awareness and implementation of the geriatric assessment in daily practice[168].

While current guidelines provide recommendations on how to conduct the geriatric assessment and which relevant tools and assessments can be used[85], implementation in daily oncology practice remains poor owing in part to limited practice or institutional availability and resources. The geriatric assessment needs to be integrated into clinical trials involving older adults in order to define the standards of care for this population. We advocate for the education of geriatric and oncology care providers, including at the fellowship level. In addition, novel and practical study designs utilizing the geriatric assessment might facilitate implementation and warrant further exploration.

Conclusions

Older adults with cancer are a growing population with unique needs and challenges. Tools for geriatric screening and geriatric assessment can assist in identifying patients who are most at risk of poor outcomes from oncology treatment. Geriatric assessment has been shown to affect treatment decision-making and improve communication with older adults and their caregivers as well as their satisfaction with care. Several larger, multicentre studies are underway to determine the effects of geriatric assessment-guided management intervention on other cancer-related outcomes, such as survival, TRAEs or QOL. Improving enrolment of older adults in therapeutic trials and promoting novel trial designs that incorporate outcomes important to older adults will help to improve the disparity in care and outcomes in older adults with cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points

- Cancer is a disease of ageing; older adults (aged ≥65 years) account for the majority of new cancer diagnoses and the majority of cancer survivors.
- In comparison with older adults without cancer, those with cancer have an increased prevalence of comorbidities and ageing-related conditions that substantially affect cancer diagnosis, treatment and outcomes.
- A comprehensive geriatric assessment is a multidimensional, multidisciplinary approach used to evaluate health and functional status in older adults, identify patients at increased risk of poor outcomes from cancer treatment, and guide decision-making and management recommendations.
- Management of geriatric conditions in older adults with cancer might improve their outcomes; to achieve such advances, further therapeutic trials utilizing the geriatric assessment and novel trial designs incorporating outcomes important to this population are required.

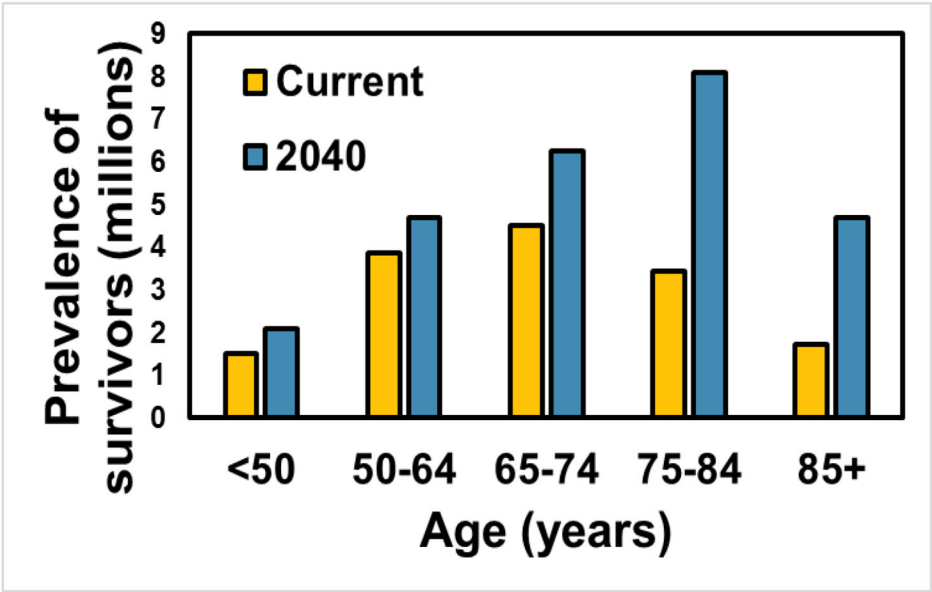

Figure 1: Increasing Number of Older Survivors of Cancer

*Adapted from: Bluethmann SM, Mariotto AB, Rowland JH. Anticipating the "Silver Tsunami": Prevalence Trajectories and Comorbidity Burden among Older Cancer Survivors in the United States. *Cancer Epidemiology Biomarkers & Prevention*. 2016;25(7):1029-1036.

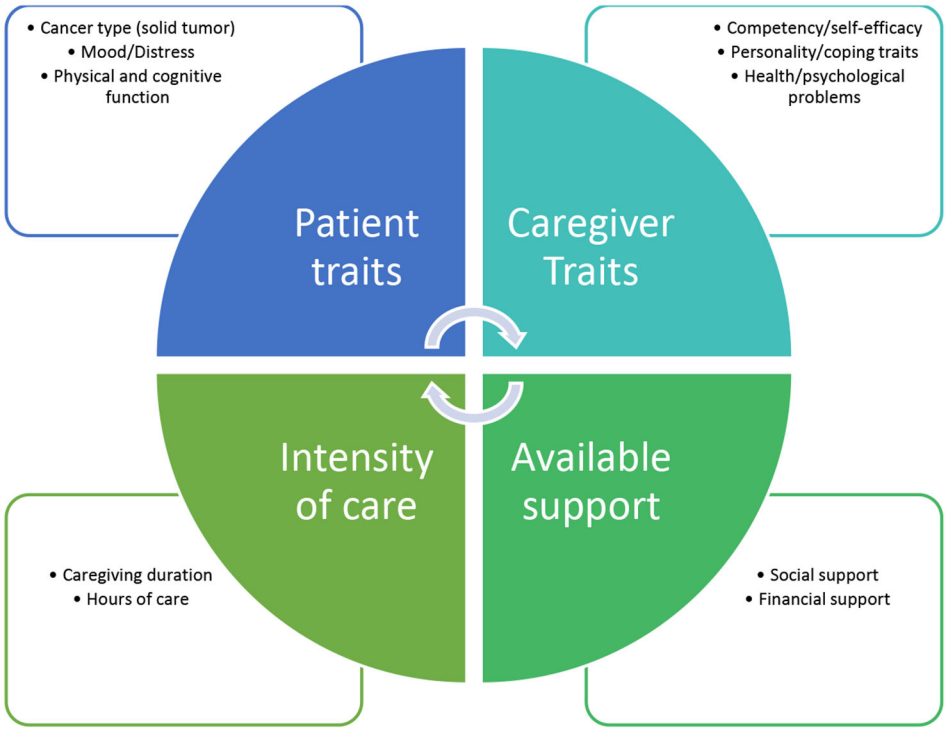

Figure 2: Factors affecting caregiver distress

Table 1 |

Geriatric syndromes in older adults (aged ≥65 years) with cancer

Ageing-related condition	Prevalence	Effects of condition
Polypharmacy (>5 prescribed medications)	40%[27]	Adverse events owing to drug–drug interactions Increased risk of TRAEs Non-adherence to medication Increased risk of falls Functional decline Increased hospitalization rate Increased risk of mortality
Cognitive impairment	3–4% (SEER–Medicare data)[32] 39% (patients with MMSE score <24)[33]	Increased risk of TRAEs Increased discontinuation of chemotherapy Increased incidence of delirium Increased risk of hospitalization
Sensory (hearing and visual) impairments	30%[34]	Functional, psychological and cognitive deficits Increased risk of TRAEs
Malnutrition	13% (patients with non-GI cancer)[35] 29% (patients with GI cancer)[35]	Increased risk of TRAEs Functional decline Reduced QOL Increased mortality
Depression	26%[26]	Increased mortality Increased risk of hospitalization Increased symptom burden Poor adherence to treatment Functional deficits Decreased QOL
Sarcopenia	12.5–57.7%[37]	Increased risk of TRAEs Increased risk of hospitalization Increased risk of death
Falls	13–50%[169]	Increased risk of severe TRAEs
Frailty	18%[49]	Perioperative complications Increased risk of TRAEs Increased risk of death

GI, gastrointestinal; MMSE, Mini Mental Status Exam; QOL, quality of life; SEER, Surveillance, Epidemiology, and Ends Results; TRAE, treatment-related adverse event.

Table 2 |

Geriatric assessment domains, tools and intervention recommendations[85]

Domain	Tools	Description	Intervention recommendations
Function	ADL	Self-reported dependence on others for any task necessary to independently care for oneself, including eating, bathing and mobility	Modify treatment choice or intensity Referral to social work and home health services
	IADL	Self-reported dependence on others for any task necessary for living independently, including driving, shopping and finances	
Physical performance	SPPB	A three-part test of lower body function that includes a timed walk, repeated chair stands and standing balance	Evaluate for other risk factors for falls, such as polypharmacy or sensory impairment Physical therapy and/or occupational therapy referral for strength and balance training, and home exercise programmes Home safety evaluation Fall counselling education
	Fall history	Self-reported history of falls within the past 6 months	
Cognition	Mini–Cog	A test to screen for cognitive problems that includes a word recall and clock drawing	Referral to a specialist for more comprehensive cognitive assessment Assess decision-making capacity Identify health-care proxy and involve in decision-making Medication review to minimize medications associated with a higher risk of delirium Delirium risk counselling for patient and caregivers
	BOMC	A six-item measure that evaluates orientation, attention, and memory	
Comorbidities	Chart review	Robust review of chronic medical conditions through routine history	Involve primary care physician in co-management of comorbidities Consider referral to geriatrician
Polypharmacy	Medication review	Review all prescription and nonprescription medications (including over-the-counter medications and herbal or supplementary agents)	Brown bag medication review (patients bring all their medications and supplements to medical appointments for clinician review) Assess medication adherence Review medications for duplications and potentially inappropriate medications for older adults De-prescribe potentially inappropriate medications Involve pharmacist
	Beers criteria	A list that identifies potentially inappropriate medications that should be avoided in older adults	
Psychological status	GDS	Self-reported 15-item screening tool for depression in older adults	Referral to psychosocial services Pharmacological therapy
	GAD-7	Self-reported 15-item measure used to screen for and determine the severity of generalized anxiety disorder	
	Distress Thermometer	A self-reported measure to screen for psychological distress in patients with cancer	
Nutrition	Unintentional weight loss	Measures unintentional weight loss within the last 6 months	Referral to nutritionist or dietician Recommend support with grocery delivery and meal preparation
	Mini Nutritional Assessment	A six-item screening measure to determine nutritional impairments and patients at risk of malnutrition	
Social support	MOS-SS survey	A self-reported measure of 19-items that assesses four social domains: emotional support, tangible support, affectionate support and medical outcomes	Modify treatment or dose intensity Referral to social work and home health services Transportation assistance
	Medical Social Support Section (subscale of OARS)	Self-reported measure of the number of support individuals involved in the patient's medical care and the degree of involvement of the support individuals	

ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living; BOMC, Blessed Orientation Memory Concentration Test; GAD-7, Generalized Anxiety Disorder 7; GDS, Geriatric Depression Scale; MOS-SS, Medical Outcomes Survey Social Support survey; OARS, Older Americans Resources and Services; SPPB, Short Physical Performance Battery.

Table 3 |

Geriatric screening tools[102]

Geriatric assessment domain	Items	Score range
G8: score range 0–17; score ≤14 indicates impairment		
Nutrition	Decreased food intake over the past 3 months	0, severe decrease 1, moderate decrease 2, no decrease
	Weight loss over the past 3 months	0, weight loss >3 kg 1, does not know 2, weight loss between 1–3 kg 3, no weight loss
	BMI	0, BMI <19 1, BMI 19–21 2, BMI 21–22 3, BMI ≥23
Functional status and mobility	Mobility	0, bed bound or chair bound 1, able to get out of bed or chair but does not go out 2, goes out
Cognition and mood	Neuropsychological problems	0, severe depression or dementia 1, mild depression or dementia 2, no neuropsychological problems
Polypharmacy	Taking ≥3 prescription medications	0, yes 1, no
Self-reported health status	In comparison with other people of the same age, how does the patient compare his or her health status?	0, not as good 0.5, does not know 1, just as good 2, better
Age	–	0 >85 years 1 80–85 years 2, <80
fTRST: score range 0–6; score ≥1 indicates impairment		
Cognition	Presence of cognitive impairment (disorientation, dementia or delirium)	0, no 2, yes
Social support	Lives alone, or no caregiver is available, willing or able	0, no 1, yes
Functional status and mobility	Has difficulty with walking or transfers or history of falls in the past 6 months	0, no 1, yes
Hospitalization	History of hospitalization in the past 3 months	0, no 1, yes
Polypharmacy	Taking ≥5 medications	0, no 1, yes
VES-13: score range 0–10; score ≥3 indicates vulnerable		
Age	–	1, 75–84 years 3, ≥85 years
Self-reported health	In comparison with other people of the same age, how does the patient compare his or her health status?	0, excellent, very good or good 1, fair or poor
Functional status and mobility	Considerable difficulty with: stooping, crouching or kneeling, lifting or carrying 10 lbs, reaching or extending arm above shoulder, walking a quarter of a mile, doing heavy housework Needs assistance with: shopping for personal items, managing money, walking across the room (use of cane or walker is accepted), doing light housework, bathing or showering	1 point for each item, maximum of 2 points 4, one or more items

fTRST, Flemish version of the Triage Risk Screening Tool; G8, Geriatric 8 health screening tool; VES-13, Vulnerable Elders Survey-13.