Part 1 Key principles in geriatric oncology

Part 1
Chapter 1

Key principles in geriatric oncology

Geriatric assessment for the older adult with cancer

Arti Hurria and Harvey Jay Cohen

A. The aging population in the United States and worldwide

Cancer is a disease associated with aging. Approximately 60 percent of cancer incidence and 70 percent of cancer mortality occur in adults over 65 years of age.[1] Thus the principles of geriatrics are particularly relevant in today's field of oncology and will become even more relevant as the United States and world populations age.

Over the past century, the population of individuals aged 65 years and older grew 10-fold, increasing from 3.1 million in the year 1900 to 35 million in the year 2000.[2] This number is expected to double from 2000 to 2030 as baby boomers (born 1946–1964) start to reach age 65 in 2011 (Figure 1.1). By 2030, the population aged 65 years and older is projected to account for almost 20 percent (about one in five) of the population.[2] Along with the increase in the absolute number of older adults, life expectancy is also increasing. From 1900 to 2000, average life expectancy in the United States increased from 47.3 to 76.9 years.[2] After 2030, the population considered to be the oldest old (aged 85 years and older) is projected to increase rapidly as baby boomers reach and surpass age 85.

Similar growth in the older population is projected to take place across the world. In the year 2000, 420 million people worldwide were aged 65 years and older, representing 7 percent of the world's population. By 2030, this number is projected to double to 974 million, with 70 percent of older adults living in developing countries.[2] Projecting into the future, from 2100 to 2300, centenarians (those individuals aged 100 years and older) will be the fastest-growing segment of the world population, with an anticipated ninefold increase in the proportion of the population (from 0.2% to 1.8%).[3]

B. The association between cancer and aging

There is a clear association between cancer and aging. The median age of diagnosis for cancer at all sites is 67 years, and the median age of death from cancer is 73.[1] The aging of the U.S. population is expected to contribute to an increase in the total yearly cancer incidence. From 2010 to 2030, the total projected cancer incidence will increase 45 percent, from 1.6 million in 2010 to 2.3 million in 2030. This increase in cancer incidence is largely driven by an increase in cancer in older adults, with a 67 percent increase in cancer incidence anticipated in older adults compared with an 11 percent increase in younger adults.[4] The most common tumor types are those that commonly afflict older adults, that is, prostate, lung, and colon cancer in men and breast, lung, and colorectal cancer in women.[a]

C. Assessment of older adults with cancer: Integrating geriatric principles in oncology care

Along with increasing age comes a decrease in physiologic reserve; however, the aging process is heterogeneous and occurs at variable rates among different individuals. It is not uncommon to hear doctors use the phrase "a young 80-year-old" or "an old 80-year-old," implying that factors other than age affect an older adult's life expectancy. Understanding or objectively quantifying an older adult's physiologic reserve is an important part of cancer treatment planning; however, there is no standard tool in oncology practice with which to assess an older adult's physiologic reserve, to help weigh the risks and benefits of cancer treatment in the older adult, or to guide treatment decisions.

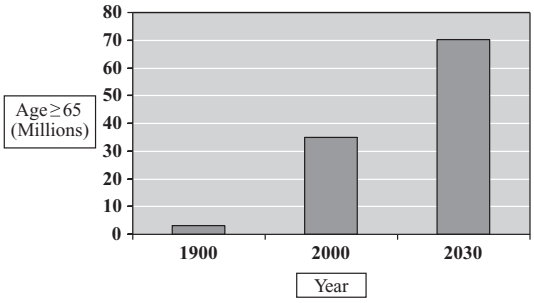

Figure 1.1 Projected aging of the U.S. population.[147,148]

Geriatricians utilize a geriatric assessment in daily practice as a means of quantifying this physiologic reserve and understanding other factors that may influence overall survival, treatment tolerance, quality of life, or the ability to follow a particular treatment regimen. This assessment consists of an evaluation of functional status, comorbid medical conditions, cognitive function, psychological state, and social support. The patient's medication list is also reviewed to assess for drug interactions, duplicative or unnecessary medications, or drugs that may carry a high risk of side effects, with consideration for discontinuing or substituting medications, as appropriate. Consideration is also given to the potential costs of therapy and the ability of the patient to absorb these costs.

One could argue that a geriatric assessment should be performed for patients of all ages, particularly those with cancer who are facing a possibly life-threatening diagnosis that may require intensive treatment. However, this assessment is especially valuable in the older adult, in whom competing causes of morbidity and mortality (often a consequence of the aging process) need to be considered to weigh the potential risks and benefits of cancer therapy. In this chapter, we review the domains of a geriatric assessment with a particular focus on emerging literature that demonstrates how an understanding of these factors can support the care of an older adult with cancer. In addition, we summarize the evolving literature that demonstrates the potential for incorporating physiologic and biologic markers as part of the assessment.

C.1. The role of functional status

The Karnofsky Performance Status (KPS) Scale[5] or the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale is commonly used to assess functional status in oncology practice.[6] These scales predict morbidity and mortality among all patients with cancer. They require the clinician to choose a number that best describes the patient's overall level of daily activity and need for assistance with activities. A decline in function is presumed to be secondary to the cancer and cancer-associated symptoms. This assessment does not provide a detailed evaluation of the patient's baseline level of functioning (regardless of cancer), which is an independent predictor of morbidity and mortality in the geriatric population.

A geriatrician's evaluation of functional status includes an assessment of the patient's ability to complete activities of daily living (ADLs) and instrumental activities of daily living (IADLs). ADLs are basic self-care skills required to maintain independence in the home such as the ability to bathe, dress, toilet, transfer, maintain continence, and feed oneself.[7] IADLs are skills required to maintain independence in the community such as the ability to take transportation, prepare meals, use the telephone, manage money, take medications, shop, travel, and do laundry.[8] Requiring assistance with ADLs or IADLs is associated with an increased risk of further functional decline,[9] hospitalization,[9] nursing home placement,[9] cognitive dysfunction,[10] and mortality.[9,11–14] In a study of community-dwelling older adults, patients who required assistance in one or more ADLs had 9.8-fold (95% confidence interval [CI] 6.8–14.0) increased odds of being institutionalized and 8.6-fold (95% CI 6.6–11.0) increased odds of mortality within 6 years. Patients who required assistance with one or more IADLs had 6.7-fold (95% CI 4.6–9.6) increased odds of being institutionalized and 6.6-fold (95% CI 5.1–8.6) increased odds of mortality within 6 years (Figure 1.2).[9]

Measuring functional status at only one time point provides just part of the picture. Emerging reports demonstrate the importance of functional transitions and the impact of transient versus permanent declines in physical function. Declines in physical function that persist over time are associated with poorer overall survival and increased risk of subsequent hospitalization compared with declines in physical function that are transient.[9,15] These data suggest that measuring functional status at several points along the trajectory of illness provides valuable prognostic information.

From a practical standpoint, assessing an older adult's functional status should be an integral part of determining whether the patient can comply

Baseline: Functional Status (1984)	Follow-up (1990)	
	Risk of Institutionalization Odds Ratio (95% CI)	Risk of Mortality Odds Ratio (95%CI)
IADL Assistance	6.7 (4.6, 9.6)	6.6 (5.1, 8.6)
ADL Assistance (Moderate)	9.8 (6.8, 14.0)	8.6 (6.6, 11.0)
ADL Assistance (Severe)	17.0 (9.1, 32.0)	30.0 (18.0, 15.0)

Figure 1.2 Association of baseline functional status with risk of institutionalization and mortality 6 years later.[9] Abbreviations are as follows: CI, confidence interval; IADL, instrumental activities of daily living; ADL, activities of daily living.

with an oncology treatment plan. For example, when planning a daily radiation schedule, the physician needs to know whether the patient can drive to the appointment or whether he or she has other means of transportation. This is particularly important for the oncology population because a diagnosis of cancer is associated with an increased need for assistance with ADLs and IADLs, and this increased need for assistance continues among cancer survivors (Figure 1.3).[16,17] In studies of older adults with cancer, requiring assistance in ADLs and IADLs is particularly common. For example, in a study of 363 older patients with cancer, 9 percent required assistance with ADLs and 38 percent required assistance with IADLs,[18] despite that all patients had an ECOG performance score of less than 2. In another study of older adults with metastatic breast cancer, 26 percent of patients required assistance with ADLs and 73 percent required assistance with IADLs.[19] The need for assistance with ADLs is even greater among patients who are hospitalized. For example, in a study of older adults with cancer who were admitted to an acute care for elders unit, 45 percent of patients required assistance with ADLs.[20]

A survey of oncologists and primary care providers demonstrated that health status (functional status plus comorbid conditions) plays a significant role in adjuvant treatment decisions for older adults with breast cancer.[21] Although functional impairment influences treatment decisions and is common among the oncology population, there is no standard tool used in daily practice to determine how functional status affects the risks and benefits of cancer therapy with an older adult and how this unique health status should be integrated into treatment decisions. Emerging data do suggest that the ability to complete IADLs is associated with cancer prognosis and risk of toxicity to chemotherapy. Among older adults with advanced lung cancer, for example, requiring assistance with IADLs and pretreatment quality of life were reported as independent

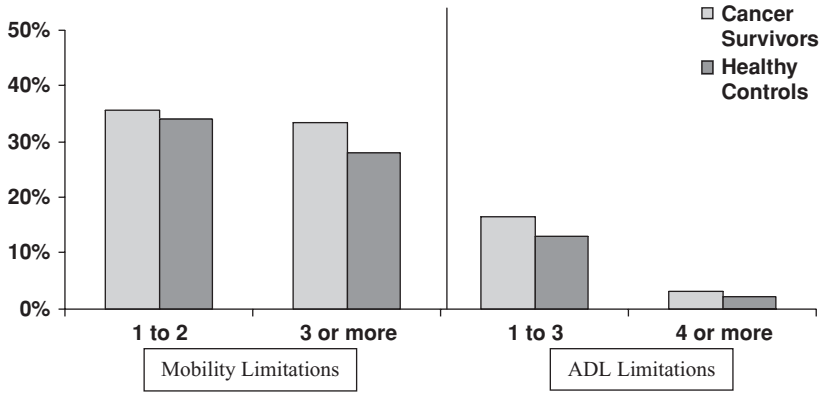

Figure 1.3 More mobility limitations and ADL limitations of cancer survivors.[17]

predictors of median survival.[22] In another study of 63 patients with acute myelogenous leukemia across all ages (range 19–85, median 61), requiring assistance with IADLs, KPS score, and the presence of unfavorable cytogenetics were independent predictors of overall survival.[23]

C.2. Comorbidity

With increasing age, there is an increase in the number of comorbid medical conditions that may have an impact on a patient's risk of morbidity, mortality, and tolerance to cancer therapy. Therefore an integral part of oncology decisions is to decide whether the patient's life expectancy is more likely to be limited by the cancer or another comorbid medical condition, whether a comorbid medical condition will affect treatment tolerance, and what the interactions of the comorbid medical conditions with the patient's cancer will be. Studies in the cancer literature suggest a low correlation between measures of comorbidity and functional status,[24] with each being an independent prognostic factor for overall survival.[25]

Among patients with cancer, comorbid medical conditions influence overall survival. This was illustrated in an observational prospective cohort study of 17,712 patients with a variety of cancers, in which the severity of comorbidity was significantly associated with survival, independent of cancer stage.[26] In another study of patients with early-stage breast cancer, patients with three or more comorbid conditions (out of seven selected comorbid medical conditions) were 20 times more likely to die of a cause other than breast cancer.[27] A similar impact of comorbidity on overall survival was demonstrated in another study of older adults with stage I breast cancer who received tamoxifen and were randomized to postlumpectomy radiation versus no radiation.[28] Whereas radiation decreased the risk of local recurrence, radiation had no impact on overall survival, with most patients dying of another cause. In a study of patients with advanced lung cancer, increased comorbidity (as assessed by the Charlson Comorbidity Index[29]) was associated with poorer overall survival (Figure 1.4).[30]

On the other hand, the risk from cancer might outweigh the risk of dying from another comorbid illness, underscoring the importance of treating an older adult with a cancer that carries a poorer prognosis. This was demonstrated in a study of patients aged 65 years and older with breast cancer (the majority with node-positive disease) who were randomized to a standard adjuvant polychemotherapy regimen versus an experimental arm of oral monochemotherapy to decrease the risk of relapse. With 2.4 years of follow-up, patients who received standard chemotherapy had a statistically significant improvement in overall and disease-free survival. Therefore treatment affected breast cancer–specific mortality within a relatively short period of follow-up, and within this follow-up period, only 2 percent of patients enrolled in the study died of a cause not related to breast cancer or treatment.[31]

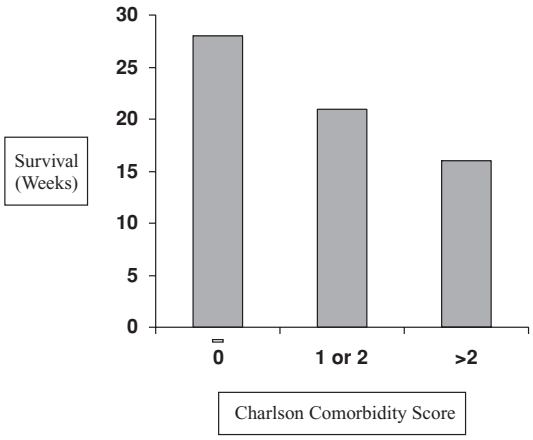

Figure 1.4 Increased comorbidity associated with decreased survival in advanced lung cancer.[30]

Common treatments in the oncology population may exacerbate or unmask comorbid illnesses. For example, steroids are often prescribed as chemotherapy premedications to prevent nausea or an allergic reaction. They may also be included as a part of the cancer treatment regimen such as in the cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen for lymphoma. These steroids could exacerbate diabetes or unmask glucose intolerance. In addition, comorbid conditions place the patient at risk for treatment-associated side effects. Taxanes or other neurotoxic drugs can exacerbate underlying neuropathy. A diagnosis of hypertension (present in almost half of all adults aged 70 years or older[32]) is a known risk factor for trastuzumab-associated cardiomyopathy.[33,34] In addition, hypertension is a risk factor for anthracycline-associated cardiomyopathy.

Comorbid medical conditions could influence whether a patient is able to complete a prescribed chemotherapy course. In a study of patients with advanced lung cancer randomized to poly- or single-agent chemotherapy, comorbidity (defined

as a Charlson score greater than 2, compared to 2 or less) was associated with increased likelihood of discontinuing treatment.[30] In a study of patients with breast cancer, comorbidity was a better predictor of the toxicity risk from adjuvant chemotherapy than age alone.[35] Comorbid medical conditions also influence cancer prognosis. In a large randomized study of adjuvant chemotherapy for colon cancer, patients with diabetes experienced a significantly higher rate of disease recurrence and overall mortality, independent of predictors for colon cancer recurrence.[36]

Several tools are available to assess the prognostic impact of comorbidity among older adults in general; however, few tools have been developed specifically for older adults with cancer. Piccirillo and colleagues evaluated the prognostic importance of comorbidity among patients with cancer (46.3% aged 65 years or older) using the Adult Comorbidity Evaluation–27, which yields an overall comorbidity level (none, mild, moderate, or severe).[26] This comorbidity level is used to estimate the hazard ratio for overall survival within a variety of tumor types. Other tools evaluate the risk of mortality among all older adults and have included a diagnosis of cancer as one variable in the model. For example, Walter and colleagues developed and validated a prognostic index for 1-year mortality among older adults who have been hospitalized. A diagnosis of cancer (solitary vs. metastatic) was among the six risk factors (male sex, ADL dependency, congestive heart failure, cancer, creatinine value, and albumin level) considered for 1-year mortality.[37] In another index developed by Lee and colleagues, a diagnosis of cancer was 1 of 12 variables (including age, sex, comorbid medical conditions, and functional status) that predicted a 4-year risk of mortality.[38] The Charlson Comorbidity Index ranks and compares comorbid medical conditions that increase the 1-year risk of mortality; it also includes a diagnosis of cancer among the comorbid illnesses included in the index.[39] A Charlson Comorbidity Index that takes into account the impact of age in addition to comorbid conditions is also available.[40]

C.3. Cognition

In the geriatric population, the prevalence of cognitive impairment increases with age and is associated with an increased risk for functional decline and an increased risk of mortality.[41–43] In a study of older adults with chronic medical illnesses (including cancer), the effects on mortality of cognitive impairment and chronic medical illnesses are additive.[44] Patients with cancer may be predisposed to cognitive problems for a variety of reasons, including symptoms, fatigue, pain, and depression.[45] Cognitive problems often go unrecognized. In a study of older adults with cancer admitted to an acute care for elders unit, 27 percent of patients scored above the abnormal range on the short "Blessed Test," while 36 percent of patients did not have delirium or dementia documented in their charts.[20]

Cognitive impairment may lead to a delay in cancer diagnosis and variations in cancer treatment patterns. In a study utilizing the Surveillance, Epidemiology, and End Result (SEER)-Medicare database, patients with colon cancer and dementia were twice as likely to have colon cancer reported after death (on an autopsy or death certificate). Of those who were diagnosed while they were alive, patients with dementia were less likely to obtain a pathologic diagnosis, undergo surgical resection, or receive adjuvant chemotherapy.[46] Cognitive impairment is associated with a lower likelihood of receiving cancer therapy. In a study of older adults with cancer, advanced age and decreased mental status were associated with a decreased likelihood of surgery.[47]

Cancer therapy may be associated with cognitive side effects, which have been described in the breast cancer literature[48–58]; however, few studies have specifically focused on older adults or on patients with baseline cognitive problems.[56,59] Nevertheless, among older adults, the impact of therapy on cognitive or functional status significantly influences the patients' preferences for life-sustaining therapy. This was demonstrated in a study of patients aged 60 years and older who had a limited life expectancy because of cancer or other chronic illness (congestive heart failure or chronic obstructive pulmonary disease). In this survey, patients responded that they would forego a life-sustaining therapy if the outcome was survival but severe cognitive (88.8%) or functional (74.4%) impairment.[60]

Studies of the impact of cancer and/or cancer therapy on cognitive function of cancer survivors have reported conflicting results.[17,61,62] A population-based sample of patients aged 55 years and older demonstrated no difference in self-reported cognitive function in cancer survivors (survived cancer 4 or more years) versus controls.[17] Neuropsychological and radiology studies demonstrate a different result. In a study of twins aged 65 years and older, of which one was

a cancer survivor and the other had no history of cancer, the cancer survivor twin was more likely to have cognitive dysfunction than the unaffected twin.[62] Another study of survivors of breast cancer and lymphoma demonstrated that survivors treated with systemic chemotherapy scored lower on neuropsychological tests than survivors who had not received chemotherapy.[61] Furthermore, positron emission tomography scans of the brain in breast cancer survivors 5–10 years after chemotherapy demonstrated altered activity in the frontocortical, cerebellar, and basal ganglia compared with subjects who had not received chemotherapy.[63] Another study of breast cancer survivors demonstrated that those who had received chemotherapy had differences in information processing on electrophysiologic tests.[64]

From a practical standpoint, an assessment of cognitive function is necessary prior to prescription of cancer therapy to ensure that the patient can provide informed consent and understand the risks, benefits, and alternatives of the therapy. The health care team needs to be sure that the patient understands the side effects of therapy and the indications of when to seek help. In addition, with the increase in oral cancer therapies, an assessment of cognitive function is necessary to be sure that the patient will comply with the schedule. Taking too few pills could be ineffective, and in some cases, taking too many pills could be lethal. Enlisting the patient's social support for assistance can be critical to ensuring success of the cancer treatment and minimizing the risk of toxicity.

C.4. Nutritional status

Among community-dwelling older adults, a low body mass index (BMI), weight loss, and weight cycling (loss and subsequent gain or vice versa) increase the risk of mortality.[65,66] In a study of 4,317 nonsmoking men and women aged 65–100 years, there was an inverse relationship between BMI and mortality. Women with a BMI less than 20 were at highest risk for 5-year mortality.[67] A study of 4,714 older adults demonstrated that weight loss of 5 percent or more was associated with an increased risk of mortality.[68] In another study of 247 patients aged 65 years and older, weight loss of more than 4 percent of body weight was an independent predictor of mortality.[66,67]

Weight loss and malnutrition are common among patients with cancer. A study of 3,047 patients enrolled in ECOG protocols demonstrated that weight loss prior to initiation of chemotherapy varied from 31 percent in patients with favorable non-Hodgkin's lymphoma to 87 percent in patients with gastric cancer. Weight loss was associated with decreased performance status, lower chemotherapy response rates, and decreased median survival.[69] Weight loss prior to diagnosis or treatment has been associated with poor outcomes in multiple tumor types, including an association between weight loss and poorer quality of life.[70,71] Patients with mild cognitive impairment or dementia are at increased risk for malnutrition.[72] As part of a nutritional evaluation, it is important to distinguish whether reversible factors associated with weight loss are present, including difficulty chewing because of poorly fitting dentures or mucositis, inability to shop or cook, or medication side effects. Nutritional intervention should be tailored to the individual patient, depending on the cancer treatment and the patient's clinical condition and nutritional status. The intervention can range from evaluating and treating reversible causes to diet counseling, oral supplementation, or enteral or total parenteral nutrition.[73]

C.5. Psychological state and social support

Depression in older adults is associated with functional decline, increased need for informal caregiving, and increased utilization of health care resources.[74–78] The number of comorbid conditions is associated with an increased risk of depression and anxiety among older adults.[79] Patients with cancer may be at particular risk, secondary to the potentially life-threatening nature of the diagnosis, associated symptomatology, or need for aggressive therapy. A study of 2,924 outpatients with cancer demonstrated that 7.8 percent reported thinking in the past 2 weeks that they would be better off dead or had thoughts of hurting themselves, with risk factors including clinically significant emotional distress ($p < .001$), substantial pain ($p < .001$), and older age ($p = .029$).[80] A case-control study of adults aged 65 years and older with a variety of medical illnesses demonstrated that the only medical illness associated with an increased risk of suicide was cancer (odds ratio 2.3, 95% CI 1.1–4.8). Older adults with concomitant psychiatric disorders, including affective disorder, anxiety/personality disorder, treatment with antidepressants, and treatment with opioid analgesics, were also at an increased risk for suicide.[81]

The psychological impact of cancer may be further heightened by social isolation. Social isolation and loneliness are associated with increased morbidity and mortality in older adults.[82–86] Shifts in the configuration and structure of family networks (such as dissolution of a joint-family living arrangement and geographic dispersion of families) may have an impact on an older adult's available social support during cancer treatment. The presence of social support may play a role in the type of cancer treatment received and the cancer prognosis. A study utilizing the SEER-Medicare database of women aged 65 years and older demonstrated that unmarried women were more likely to be diagnosed with a higher stage of breast cancer, were less likely to receive definitive therapy, and were at an increased risk of death from breast cancer after controlling for cancer stage and size at diagnosis.[87] In addition, a lack of social support can influence a patient's psychological state, as described previously, as can the patient's adherence to medication.[88]

C.6. Performing a geriatric assessment in oncology practice

There are several potential approaches to performing a geriatric assessment in an oncology practice. The approach depends on the goal of the assessment (clinical care vs. research tool) as well as on the time and resources available to perform this assessment and to act on the results. The National Comprehensive Cancer Network practice guideline in *Senior Adult Oncology* outlines a brief approach to a geriatric assessment, including a description of several screening tools for each geriatric assessment domain and potential action based on a "positive" screen.[89] Others have utilized a mailed geriatric assessment that can be completed prior to the office visit and subsequently reviewed by the clinical team.[90,91] A primarily self-administered geriatric assessment for inclusion in cooperative group clinical trials is being evaluated within the Cancer and Leukemia Group B (CALGB).[92]

D. Age-related changes in physiology

Physiologic and biologic predictors of aging and vulnerability among the general geriatric population may be particularly applicable to the oncology population. Either cancer or cancer treatment can be considered a physiological stressor, and age-related diminution in physiologic reserve may affect tolerance to cancer treatment. Furthermore, patients may be affected by physiologic derangements that are distinct from clinically diagnosed conditions. Recognizing that everyone experiences a spectrum of health across multiple domains, the National Institute on Aging Comorbidity Task Force proposed that comorbidity be considered as the total burden of biologic dysfunction, including subclinical dysfunction and physiologic changes as well as clinically diagnosed chronic conditions.[61]

D.1. Age and organ function

Aging is associated with a decline in organ function that occurs at a unique pace in each individual. With increasing age, there is a decrease in cerebral blood flow, loss of neurons, and a decrease in brain weight.[93–95] Age-related neurological changes include a slowing of reaction time and a decrease in the ability to learn or acquire new material; however, delayed recall is preserved.[96–98] Normal age-related neurological changes do not affect usual daily functioning. Aging is also associated with a decrease in both vision and hearing, with the formation of cataracts, presbyopia (impaired ability to focus on near objects), decreased contrast sensitivity, impaired dark vision, and loss of high-frequency hearing.[99] Practical suggestions to compensate for these age-related changes include speaking slowly and clearly, turning toward the patient when speaking, using adequate lighting, and writing instructions in large letters using black ink on white paper to maximize contrast. In addition, removal of cataracts and utilizing glasses or a hearing aid can help with eyesight and hearing.

Cardiovascular changes with aging include arterial stiffening and an increase in systolic blood pressure. While resting heart rate does not change, there is a decrease in the maximum heart rate in response to stress.[100] Similarly, the ejection fraction response to stress is blunted.[101] Aging is associated with changes in pulmonary physiology, including a decrease in FEV1 (forced expiratory volume in 1 second), vital capacity, and diffusing capacity.[102] With increasing age, a change in body composition accompanies a loss of muscle and bone mass.[103] Renal and hepatic mass and blood flow decrease with age. Biopsies of the liver demonstrate a decrease in cytochrome P450 with age[104]; however, aging is not associated with a change in liver function tests. Similarly,

age-related decreases in renal function are not evident when checking a serum creatinine alone—measurement of the glomerular filtration rate provides a more accurate estimate of renal function.[105,106] The age-related decrease in glomerular filtration rate is estimated at 0.75 mL/minute/year; however, approximately one-third of all patients will have no change in glomerular filtration rate with aging.[107]

D.2. Age and bone marrow

There is a decrease in bone marrow reserve and an increase in bone marrow fat with age. Although the aged marrow has less proliferative capacity,[108] under steady state conditions, peripheral blood counts remain within normal limits. In the geriatric population, the presence of anemia is associated with an increased risk of morbidity and mortality. For example, in a study of community-dwelling people aged 85 years and older, anemia was an independent predictor of mortality (mortality risk 1.60 [95% CI 1.24–2.06] for women and 2.29 [95% CI 1.60–3.26] for men).[109] In another study of residents in a skilled nursing facility, the presence of anemia was associated with increased risk of hospitalization.[110]

Among older adults with cancer, the age-related decrease in bone marrow reserve is associated with an increased risk of myelosuppression and myelosuppressive-associated complications from chemotherapy.[111,112] In patients receiving adjuvant chemotherapy for breast cancer, Silber and colleagues found that the first-cycle nadir neutrophil count predicted subsequent neutropenia, treatment delays, or dose reduction.[113] Dees and colleagues performed a prospective pharmacologic evaluation of patients receiving adjuvant AC (doxorubicin 60 mg/m^2 IV and cyclophosphamide 600 mg/m^2 IV every 21 days) and demonstrated an age-related decrease in nadir absolute neutrophil count. After four cycles of AC, the mean nadir absolute neutrophil count was significantly lower for patients aged 65 years and older than for those aged less than 65 years ($p = .01$).[114]

For patients with cancer, the presence of anemia is associated with an increased susceptibility to myelosuppression with certain antineoplastic drugs. For example, the epipodophllotoxins, anthracyclines, and camptothecins are heavily bound to red blood cells. With a progressive decrease in hemoglobin, the distribution volume of these drugs increases.[115] In a cohort of older adults receiving adjuvant chemotherapy for breast cancer, a greater decrease in white blood cell count, absolute neutrophil count, or hemoglobin level from cycle 1 to cycle 2 was associated with increased risks of grade 3 or 4 toxicity, including febrile neutropenia and hospitalization.[116]

D.3. Inflammation, coagulation, and physiologic dysregulation in older adults

It has been hypothesized that aging is associated with a dysregulation in inflammation and coagulation. There is an age-associated increase in levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) and C-reactive protein (CRP).[117–119] Physiologic dysregulation in the domains of inflammation and coagulation has been associated with functional decline and mortality.[120–127] Among 1,723 older persons in the Duke Established Populations for Epidemiologic Studies of the Elderly, those with higher levels of D-dimer and IL-6 at baseline were significantly more likely to subsequently experience functional decline or death.[128] In a prospective longitudinal study of healthy nondisabled older adults, higher circulating levels of IL-6 and CRP were associated with an increased risk of mortality. The joint elevation of both values was associated with a 2.6 times greater mortality compared with lower values of both.[120]

Serum levels of inflammation and coagulation have been associated with poorer physical function and clinical frailty. Serum measures of inflammation (CRP) and coagulation (factor VIII, D-dimer) were associated with clinical frailty among 4,735 community-dwelling adults aged 65 years and older participating in the Cardiovascular Health Study.[126] In a different analysis derived from the same study population, the authors found an inverse relation between inflammation and physical activity.[129] In another study of 880 highly functional older men and women who participated in the MacArthur Studies of Successful Aging, a higher IL-6 and CRP level was associated with poor walking speed and grip strength; however, there was no correlation between these measures and subsequent functional decline over a 7-year period in those who were able to participate in the follow-up physical function testing. Of note, those who died or were unable to undergo testing had higher baseline IL-6 and CRP levels and slower walking speeds.[123] Serum markers of inflammation, especially IL-6 and CRP, are prospectively associated with cognitive decline in well-functioning older adults.[130] Inflammatory markers have also been associated with coronary

artery disease,[131] insulin resistance,[117] risk for type 2 diabetes,[132] changes in bone density,[133] and renal insufficiency.[134]

D.4. Inflammation, coagulation, and physiologic dysregulation in patients with cancer

The importance of elevated levels of CRP, IL-6, and D-dimer has also been demonstrated in the oncology literature. Chronic inflammation may produce reactive oxygen species that result in DNA damage, activation of growth factors, and inhibition of apoptosis.[135–137] Increased levels of IL-6 may be associated with a worse prognosis for patients with breast cancer as well as a higher likelihood of metastasis by up-regulating the expression of adhesion molecules on endothelial cells as well as increasing the production of vascular endothelial growth factor (VEGF.)[138] In a study of patients with prostate cancer, elevated levels of IL-6 were seen in patients with clinically evident hormone refractory disease compared with patients who were normal controls or who had prostatitis, benign prostatic hypertrophy, or localized and recurrent disease.[139] Higher IL-6 levels in patients with advanced non-small-cell lung cancer were associated with poorer survival and poorer performance status.[140] Higher preoperative levels of CRP were associated with poorer overall survival in a study of patients with localized renal cancer.[141] In a study of patients with metastatic renal cell cancer, an "inflammation-based prognostic score" consisting of CRP and albumin level demonstrated that an elevated CRP level and low albumin were associated with cancer-specific survival.[142]

Baseline D-dimer levels were a stronger predictor of overall survival and disease progression than CEA levels among patients with metastatic colon cancer.[143] Among patients with operable breast cancer, elevated plasma D-dimer levels were markers of lymphovascular invasion, clinical stage, and lymph node involvement.[144] Some studies have suggested that CRP is associated with cancer risk, although higher levels of CRP were not associated with breast cancer among the 27,000 plus women in the Women's Health Study.[145,146]

In summary, markers of inflammation and coagulation have been associated with an increased risk of mortality and functional decline in the aging population. Emerging data are demonstrating the applicability of these biomarkers in older adults with cancer.

E. Conclusion

The fields of geriatrics and oncology unite through the care of older adults with cancer. Chronological age tells relatively little about an older adult's physiological age. The factors covered in a geriatric assessment measure independent clinical predictors of morbidity and mortality in older adults and hence provide a more comprehensive understanding of an older adult's health status. Understanding age-related changes in physiology and biomarkers of aging also provides insight into the functional age of an older adult. Incorporating this geriatric knowledge into oncology care would facilitate decision making regarding the risks and benefits of cancer therapy, help identify vulnerable older adults at risk for chemotherapy toxicity, and guide rational interventions to decrease risk. The ultimate goal of applying geriatric principles to an aging oncology population is to preserve the function and well-being of older adults with cancer.

Endnote

a. Excludes squamous and basal cell skin cancers and in situ carcinomas except urinary bladder.