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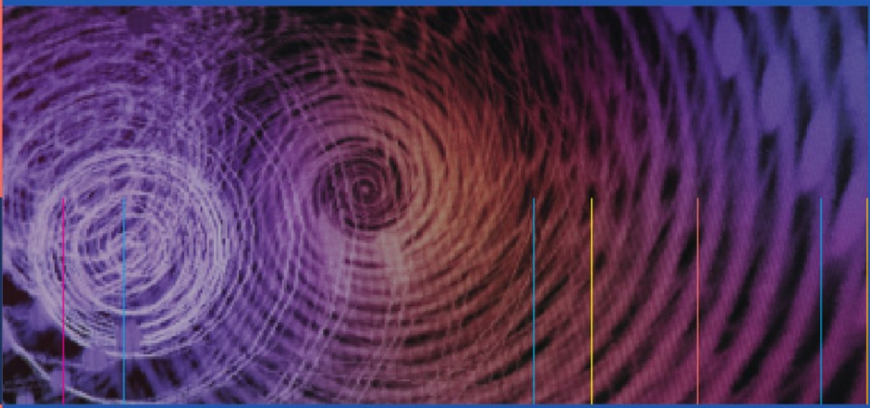

Geriatric Oncology

Treatment, Assessment and Management

Springer

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Editors
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Preface

Cancer and aging are integrally related. Cancer incidence and mortality increase with age, with most cancer diagnoses and deaths occurring in patients aged 65 and older. The aging of the Baby Boomer population, along with an overall increase in life expectancy, points to a doubling of the U.S. population over age 65 by the year 2030. This demographic shift, combined with the known association of cancer and aging, is expected to bring about a rapid growth in the older cancer-patient population. It is clear that geriatric principles must become part of oncology care.

The evaluation and development of treatment recommendations for an older adult with cancer can be challenging for many reasons. Tumor biology and response to therapy are affected by age. In addition, age-related factors may impact treatment patterns, tolerance, and efficacy. These age-related factors include functional status declines, comorbid conditions, changes in cognitive function, weakening of organ function, decreases in physiologic reserve, and faltering social support. In addition, preferences and desires for therapy can be influenced by a person's life expectancy. Palliative care considerations and family caregiver needs may also need to be an integral part of decisions involving cancer therapy. Another important aspect of managing cancer in older individuals includes the goals of treatment. While cure and prolongation of survival are the main goals of cancer treatment for patients of all ages, the prolongation of active life expectancy is particularly relevant to the older patient, especially individuals receiving adjuvant treatment for cancer. Given the complex interweaving of these factors, oncologists should be armed with tools that help them to comprehensively evaluate older adults in order to provide thoughtful, timely, and effective treatment recommendations.

This book is designed to guide oncologists with the integration of proven geriatric principles. Recommendations, risks, and benefits of cancer screening, assessment, and treatment of older adults with cancer are discussed in detail. Chapters detail the physiologic, psychological, and social aspects of aging and discuss ways to incorporate this information into cancer therapy decisions with older adults. Palliative care considerations in the challenging context of aging are also discussed, along with the issues that caregivers face when dealing with a geriatric cancer patient. An understanding of the unique interaction between cancer and aging will ultimately enhance cancer care for the growing population of older adults.

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Aging and Cancer: What Oncologists Need to Know

Arti Hurria and Lodovico Balducci

Cancer is a disease associated with aging. Approximately 60% of cancer diagnoses and 70% of cancer mortalities occur in patients age 65 or older. By 2011 in the United States, the "Baby Boomer" generation will be turning 65. The aging of these baby boomers, along with a rise in the overall life expectancy, is leading to a rapid growth of the older U.S. population. By 2030, one in five Americans will be age 65 or older. These demographics, along with the known association between cancer and aging, will contribute to an enormous rise in the number of older adults with cancer. Incorporating geriatric principles of care will be increasingly essential to cancer treatment.

Planning cancer therapy in older adults can be complex for several reasons. First, the very biology of cancer may differ from younger to older adults. For some cancers, such as breast cancer, older age is associated with a more indolent biology [1, 2], while for other cancers, such as acute myelogenous leukemia, older age is associated with an aggressive biology that is more likely to be refractory to standard therapy [3]. Understanding the tumor's biological characteristics is essential to treatment planning.

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In addition to considering disease-related biology, the clinician must weigh host-related factors that may influence both life expectancy and treatment tolerance. These include physiologic changes that accompany aging, as well as factors traditionally captured in a geriatric assessment, such as functional status, comorbid medical conditions, psychological state, social support, and cognitive function.

Perhaps the most important part of planning cancer therapy is to understand the individual's wishes for treatment and acceptance of the side effects he or she will endure in order to achieve a cancer cure or remission. One of the greatest barriers to providing optimal care for older adults with cancer is the underrepresentation of older adults in clinical trials, which set the standards for oncology care [4–6]. Because older adults, particularly those at the extremes of age, rarely take part in clinical trials, the benefits and risks of cancer therapy for them are extrapolated from a younger patient population, which generally experiences a lower incidence of side effects to cancer therapy [7]. This makes therapy planning a challenge in the older adult.

This chapter summarizes the key principles of geriatric medicine, principles that oncologists can incorporate into their care of an older adult. Subsequent chapters will examine each of these topics in detail.

Physiologic Changes with Aging: Practical Considerations in Prescribing Cancer Therapy in Older Adults

The aging process is characterized by a progressive loss in physiologic reserve [8, 9]. Declines in organ function that occur with aging can affect the dosing and side effects of cancer therapy. In particular, with increasing age, renal function decreases. Renal blood flow diminishes by 1% per year after age 50, and renal mass goes down by 25%–30% over a lifespan [10]. Beginning around age 40, the glomerular filtration rate ebbs at an estimated

0.75 ml/min/yr [11]. At the same time, age-related declines in renal and hepatic function are not typically evident in standard blood work. For example, serum creatinine is a poor reflection of renal function with increasing age because of an age-related loss in muscle mass [12]. Therefore, only a creatinine clearance can quantify an older adult's renal function in order to accurately prescribe cancer therapy that is renally metabolized.

With increasing age, hepatic mass and blood flow decrease [8, 13]; however, the impact of this decline on hepatic organ function is not certain [14–16]. Liver biopsy studies have shown a decrease in cytochrome p450 content with aging [17]; however, age-related changes do not show up in serum liver function tests. Surrogate measures of liver function are still being studied [14].

Age-related changes in gastrointestinal absorption can influence the bioavailability of oral cancer therapy and supportive medications. For example, with increasing age, there are splanchnic blood flow decrease, mucosal atrophy of the gastrointestinal system, and a decrease in gastric motility and enzyme secretion [18, 19]. In addition, age-related changes in body composition can influence the volume of distribution of medications. With increasing age, there is an increase in total body fat, leading to an increase in the volume of distribution of drugs that are lipid-soluble [10]. Conversely, with increasing age, total body water decreases, leading to a diminution in the volume of distribution for hydrophilic drugs. Malnutrition and hypoalbuminemia also alter the distribution of drugs that are heavily bound to albumin [10].

Perhaps one of the most significant changes with aging is the diminished response to hematopoietic stress, placing older adults at greater risk for myelosuppression [7, 20–23]. Age >65 is a risk factor for febrile neutropenia [21, 24], and myelosuppression-associated complications occur most frequently during the first cycle of therapy [25]. Early initiation of white blood cell growth factor can help to decrease the risk of febrile neutropenia and decrease the risk of hospitalization resulting from neutropenia-associated complications [26].

Cancer treatment can also cause anemia, which may contribute to fatigue and functional decline [27, 28].

Domains Other Than Chronological Age That Affect Life Expectancy and Treatment Tolerance

Aging and Functional Decline

Aging is associated with a progressive loss in physical function. The need for assistance with daily activities is predictive of morbidity and mortality in older adults [29, 30]. Older patients with cancer are also more likely to require assistance with daily functioning than those without cancer [31]. Furthermore, this increased need for assistance persists in cancer survivors [32]. Among patients with cancer, the need for functional assistance is also predictive of survival, chemotherapy toxicity, and post-operative complications [31–33]. From a practical standpoint, understanding someone’s functional status is essential in order to determine if an individual can seek medical attention if he or she develops cancer symptoms or therapy side effects. For example, can he use the telephone without assistance, or take transportation to clinic visits or to an emergency room? If he is unable to perform these tasks, then a support system (such as a family member, visiting nurse, or lifeline) must be enlisted to ensure that the patient can get help if he notices warning signs of toxicity.

ADLs and IADLs

The assessment of functional status should also include an evaluation of the ability to complete activities of daily living (ADLs) or 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, transfer, maintain continence, and feed oneself. The need for assistance in ADLs is common among hospitalized patients with cancer.

In one study, 45% of older adults with cancer who were admitted to the hospital required assistance with ADLs. In another study of cancer survivors, patients with a history of cancer were more likely to continue to require assistance with ADLs than patients who had no history of cancer [32].

IADLs are activities required to maintain independence in the community, such as the ability to do housekeeping, take transportation, do laundry, use the telephone, manage finances, and take medications. Among patients with advanced non-small lung cancer, the need for assistance with IADLs has been associated with poorer survival [34]. Among patients with ovarian cancer, the need for assistance with daily functioning has also been associated with increased risk of chemotherapy toxicity [35].

These observations highlight the importance of evaluating functional status in older adults with cancer in order to estimate both the tolerance to cancer therapy and mortality. In addition, it is critical to evaluate a patient's social support, which may compensate to some degree for a patient's functional impairment.

Age and Comorbidity

The Role of Comorbidity in Treatment and Prognosis

The number of competing comorbid medical conditions rises with increasing age. Comorbid medical conditions have an impact on life expectancy [36–40] as well as on treatment tolerance [37, 41, 42]. In addition, certain comorbid medical conditions such as diabetes or obesity may play a role in cancer prognosis [43–47]. A thorough understanding of a patient's coexisting medical conditions is necessary in order to weigh the impact of the cancer on life expectancy versus other comorbid medical conditions. In addition, the impact of comorbid medical conditions on cancer treatment tolerance must be considered.

Comorbidity Scales

Several validated scales have measured comorbidity. Karampeazis and Extermann provide a thorough review of comorbidity scales in their chapter (Chapter 5). In addition to comorbidity scales, other authors have recommended prognostic indexes that include factors other than comorbidity (such as age, functional status, and gender). The comorbidity index utilized will depend on the question being considered. For example, Lee and colleagues developed a prognostic index for the risk of four-year mortality, which includes comorbid medical conditions, functional status, and age [48]. Charlson and colleagues developed an index that ranks and weighs conditions that increase the risk of one-year mortality among patients hospitalized on an inpatient medicine service, and includes the age of the patient [49]. Walters and colleagues developed a prognostic index for the risk of one-year mortality among older adults who are hospitalized, which includes comorbid conditions (including a diagnosis of cancer), gender, functional status, and laboratory values [50].

Aging and Changes in Social Support

Among older adults, a lack of social support is an independent predictor of mortality [51]. Older adults are particularly vulnerable in this regard because the aging process is associated with losses in the social support system: the loss of a spouse, the loss of family members, and the loss of friends. In addition, adult children often live far from their parents and are consumed with daily work and their own activities. A lack of social support can be particularly problematic for older adults undergoing cancer therapy, which can require frequent doctor or hospital visits. Treatment-related side effects can require immediate attention, making an adequate support system crucial.

The Role of Social Support After Therapy

Social support also plays an important role following the completion of cancer therapy. A lack of social support is associated with poorer psychological adjustment in cancer survivors. Among breast cancer survivors, a mean of nearly seven years after therapy, having less social support, being divorced, or being separated were significant predictors of increased psychological distress [52]. In another study of breast cancer survivors, 20 years after adjuvant therapy, a lack of social support was associated with a higher prevalence of posttraumatic stress disorder [53].

On the other hand, while social support may benefit patients, emerging literature details the burdens experienced by their caregivers. In a study of 101 patients with advanced cancer, 39% of the spouse caregivers reported symptoms of depression. In contrast, only 23% of the patients reported significant symptoms of depression [54]. In another study of 310 Korean caregivers of patients with cancer, 67% of the caregivers reported high depression scores. The most significant predictor of depression was the feeling of care burden. Other predictors of caregiver depression included caring for a spouse with a poor performance status, being female, being a spouse of the patient, having poor health, adapting poorly, and being unable to function normally [55]. These findings suggest that a significant proportion of caregivers are at risk for depression, and attention should be paid to minimizing caregiver burdens.

Aging and Psychological State

Approximately one third of patients with cancer experience psychological distress. The prevalence of clinically significant depression in the older population with cancer is estimated to be 3-25% [56]. Depression in the older person is associated with an increased risk of subsequent functional decline and increased resource requirement [57]. For example, in a survey of 6,649 patients over the age of 70, the presence of depression was associated with the need for increased hours of informal caregiving [58].

While some studies report that older patients with cancer experience similar or less psychological distress than younger patients, other studies are now identifying older age as a psychological risk factor [56, 59]. In a study of 2,924 patients with cancer, 8% reported thoughts of hurting themselves or feeling that they would be better off dead. In multivariate logistic regression, risk factors included age > 65 ($p = 0.29$), clinically significant emotional distress ($p < 0.001$), and substantial pain ($p < 0.001$).

Other studies have reported that older adults who are more vulnerable to psychological distress are those with inadequate social support. For example, in a study of breast cancer survivors, older age was associated with less distress; however, patients with less adequate social support experienced greater distress [53]. A case-control study of suicide risk in older adults revealed that the risk of suicide is higher among older adults with cancer than among older adults with other illnesses [60].

Aging and Cognitive Decline

With increasing age, there is an increased risk of cognitive decline. A diagnosis of dementia is associated with shortened survival [61]. Patients with cancer who have a diagnosis of dementia are likely to be diagnosed with cancer at a more advanced stage and are less likely to receive curative therapy [62, 63]. This was illustrated in two studies from the SEER Medicare database, which reported that older adults with either breast or colon cancer and a diagnosis of dementia were less likely to receive curative therapy.

While cancer or cancer therapy may have an impact on general cognitive function, few studies have focused on the impact of cancer therapy on the cognitive function of older adults. In a study of older adults receiving adjuvant chemotherapy for breast cancer, half of these patients described a decline in cognitive function from before therapy to six months after chemotherapy [64]. Other studies in a general population, however, suggest no differences in the self-reported cognitive status of cancer survivors and controls [32].

Cognitive Status Related to Treatment Choices

Older adults report that the impact of a therapy on cognitive status is an important part of the informed-consent process. In one survey of older adults, 88% stated that they would forego life-saving treatment if the outcome was survival with cognitive decline [65].

From a practical standpoint, an understanding of someone's cognitive status is required prior to prescribing cancer therapy in order to determine whether the person understands the risks and benefits of cancer therapy and is able to provide informed consent. In addition, the treating oncologist needs to determine whether the patient can remember the complex instructions regarding therapy, supportive medications, and the indications for seeking medical attention.

Understanding Treatment Goals

Perhaps the most important part of an oncologist's care in an older adult is understanding his or her treatment goals. Clinical trials to date have utilized traditional endpoints of disease-free and overall survival as measures of efficacy. While these endpoints are important for patients of all ages, additional endpoints may be considered equally as relevant by the geriatric population. The quality of survival and the impact of therapy on daily function and cognition have been highlighted as factors of concern in an older adult's decision-making process [65], and these factors are rarely studied in clinical trials.

The principle of "prolongation of active life expectancy" is especially relevant to the geriatric population with cancer, where the goal of treatment is to control or prevent disease in order to allow the person to maintain daily function and cognitive capacities. This process involves assessing the impact of therapy on daily life and exploring whether the trade-offs of cancer or therapy-associated loss of function or cognition are worth the prolongation of survival. An evaluation of the longitudinal impact of therapy on function and cognition should be considered a relevant endpoint for clinical trials in older adults in order to guide decisions involving the risks and benefits of cancer therapy.

Conclusions

Cancer is a disease associated with aging. This chapter highlighted the key factors to consider when treating an older adult with cancer. First, determine whether age-related changes in tumor biology will impact either the risk of cancer on life expectancy or the treatment efficacy. Second, consider age-related changes in physiology that may affect dosing and the tolerance to cancer therapy, including age-related declines in renal and hepatic function, changes in the absorption and volume of distribution of medications, and decreased bone marrow reserve. Third, evaluate factors other than chronological age that may impact life expectancy and tolerance to cancer therapy. These include functional status, comorbid medical conditions, psychological state, social support, and cognitive function. Fourth, understand the patient's goals with therapy, and prescribe treatment with these goals in mind.

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Assessing the Older Cancer Patient

Melissa Cohen, David Reuben, and Arash Naeim

Introduction

By 2030, one in every five individuals will be over the age of 65. Because the incidence of cancer increases with age, over 60% of all new cancer cases and 80% of deaths from cancer occur in people over 65 years of age in the United States and Europe [1–3]. Despite recent advances in geriatric care, elders still remain at risk for adverse events in all settings where cancer is treated. Because elderly patients are largely underrepresented in large cooperative trials [4, 5], there is limited evidence-based information for decision making to help guide the oncologist when caring for the older cancer patient. This can result in either suboptimal or overly toxic treatment.

Important issues need to be addressed before selecting and initiating treatment in elderly patients with cancer. Aging involves changes in the functional, cognitive, emotional, and socioeconomic domains. It is also associated with an increased incidence of comorbidities and geriatric syndromes [6]. Common geriatric syndromes such as delirium, gait imbalance, malnutrition, and incontinence can complicate cancer therapy and, thus, increase patient morbidity and costs of care. Furthermore, cancer treatment can worsen geriatric

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syndromes and comorbid conditions. Often, it is difficult to determine if declining health status is a result of cancer treatment or the patient's underlying disease. A baseline assessment of these multiple dimensions may facilitate the detection of decline, which may be remediable, and improve outcomes [3].

Increasingly, cancer patients are utilizing their oncologist as a primary care physician [7]. Therefore, it is important for the oncologist to become competent in assessing and addressing the geriatric patient, both to determine the most appropriate cancer treatment as well as to create an individualized intervention plan to deal with the multiple health problems that coexist in many elderly cancer patients and improve treatment tolerability. Just as an oncologist strives to make a pathologic diagnosis and assess the stage of disease to prognosticate, it is equally important to assess the characteristics of the elderly patient that may place him or her at risk for adverse outcomes during cancer treatment [6].

Comprehensive Geriatric Assessment

Over the past 15 years, geriatricians have developed and validated a more holistic approach to evaluate the elderly population called the *comprehensive geriatricassessment*(CGA). The CGA is a multidisciplinary, intensive evaluation of a patient who is at significant risk for subsequent functional decline [8]. It measures aspects such as functional status, comorbid medical conditions, nutritional status, psychological state, social support, and geriatric syndromes (Table 1). It involves a multidisciplinary interpretation as well as implementation. The CGA has proven to have benefits including prolongation of life [9, 10], prevention of institutionalization to nursing homes and hospitals [11], prevention of geriatric syndromes [12, 13], and improvement of subjective well-being [14]. Such a comprehensive approach often reveals information missed by routine history and physical alone [6, 15, 16].

Table 1 Components of the comprehensive geriatric assessment [8]

Parameter	Assessment	Administration	Time required
Function	• Activities of daily living (ADL)—eating, dressing, continence, grooming, transferring, using the bathroom	Self- or interviewer-administered	5–10 min
	• Instrumental activities of daily living (IADL)—using transportation, managing money, taking medications, shopping, preparing meals, doing laundry, doing housework, using the telephone		5–10 min
	• Performance status		
Comorbidity	• Number of comorbid conditions • Seriousness of comorbid conditions (comorbidity index)	Self- or interviewer-administered	15 min
Socioeconomic issues	• Living conditions • Presence and adequacy of caregiver • Income • Access to transportation • Financial counsel to discuss cost, coverage options, etc.	Self-administered	15 min
Geriatric syndromes	• Dementia—Mini-Mental Status (MMS)	Interviewer-administered	10 min
	• Depression—Geriatric Depression Scale (GDS)		15 min

Table 1 (continued)

Parameter	Assessment	Administration	Time required
	• Delirium • Falls (all falls should have an assessment) • Osteoporosis (spontaneous fractures) • Neglect and abuse • Failure to thrive • Persistent dizziness		
Polypharmacy	• Number of medications • Drug-drug interactions	Self- or interviewer-administered	10 min
Nutrition	• Nutritional risk—Mini-Nutritional Assessment	Interviewer-administered	<5 min

Evidence for the value of integrating geriatric perspectives into oncology is increasingly being documented in the literature [17–22]. The main objectives of performing geriatric assessments in oncology are to

(a) provide a gross estimation of life expectancy and help the oncologist understand the impact of the patient's cancer during his or her remaining life,
(b) identify cancer patients for whom we could expect the greatest benefit from treatment,
(c) identify medical and social problems that may decrease the tolerance of cancer treatment and/or be amenable to intervention,
(d) formulate appropriate treatment and management strategies,
(e) monitor clinical and functional outcomes.

The National Comprehensive Cancer Network (NCCN) recently issued guidelines that recommend that all cancer patients over 70 years of age should receive some form of a geriatric assessment [15]. The tools for this assessment, however, have not been well specified. Due to its time-intensive nature and the volume of patients seen in a busy oncology clinic, it is not feasible to complete a CGA on every cancer patient older than 70 years.

Who to Screen?

Currently, "elderly" refers to people aged 65 years and over. However, this does not distinguish between people at different stages of the aging process. Chronological age is an unreliable predictor of life expectancy, functional reserve, or the risk of treatment complications in a population [23]. Aging is a very heterogeneous process, and it is unclear why some elderly maintain their physical and cognitive abilities throughout a long life while others lose these same abilities rather early.

The estimated average remaining life expectancy (RLE) has been split into quartiles of longevity by age and health status [24]. A substantial variability in life expectancy exists at each age based on health status. For example, a 75-year-old man in the lower quartile has a remaining life expectancy of 4.9 years, while a man of the same age but in a higher quartile can have an RLE of 14.2 years. Information obtained from a CGA can assist a patient's classification into the upper, middle, or lower quartiles and thus help guide treatment decisions [24, 25].

Screening

In the past few years, there have been many attempts to identify a reliable and sensitive prescreening instrument to help determine which cancer patients would benefit most from a CGA:

- A self-administered CGA instrument, the Gero-Oncology Health and Quality of Life Assessment, was developed and proved to be a feasible method of obtaining a CGA in a Veteran's Administration (VA) population. The results were remarkably similar to data obtained by CGA performed by trained health professionals [26] (Table 2).

- An abbreviated CGA (aCGA), which included items from the Geriatric Depression Scale, mini-mental state examination, activities of daily living and independent activities of daily living scales, was used to identify those patients who would require further intensive evaluation with the full, multidisciplinary CGA [27, 28].
- A "minimal" CGA was developed and evaluated in elderly patients with prostate cancer. The study revealed many geriatric problems that were not clear prior to the prescreening process, such as drug interactions, cognitive problems, depressive symptoms, and malnutrition, that can all impact cancer treatment [29] (Table 3).
- The Vulnerable Elders Survey, VES-13, a 13-item, function-based, self-administered survey that consists of one question

Table 2 Gero-oncology health and quality-f-life assessment [26]

Domain	Instrument	No. of Questions	Citation
Comorbid conditions	OARS Comorbidity Scale	32	[100]
Activities of daily living	EORTC QLQ-C30 subset	5	[101]
Functional status	OARS-IADL	7	[102]
Functional status	Exercise Scale	3	[103]
Pain	Visual Analog Pain Thermometer	1	[104]
Financial	OARS Finanical	3	[100]
Social	MOS Social Support Scale	20	[105]
Emotional	Hospital Anxiety and Depression scale	14	[106]
Spiritual	SOBI	15	[107]
Quality of life	EORTC QLQ-30	30	[101]

OARS: Older American Resources and Services; EORTC: European Organization for Research and Treatment of Cancer; QLQ: Quality of Life Questionnaire; IADL: Instrumental Activities of Daily Living; SOBI: Systems of Belief Inventory; MOS: Medical Outcomes Study.

Table 3 Minimal comprehensive geriatric assessment [29]

Domain	Instrument	No. of Questions	Citation
Comorbid conditions	CIRS-G	14	[44]
Functional status	Katz ADL	6	[54]
Functional status	Lawton IADL	8	[108]
Functional status	Karnofsky	1	[109]
Cognition	MMSE	11	[110]
Mood	Geriatric Depression Scale	30	[70]
Nutrition	Mini-Nutritional Assessment	19	[111]
Mobility	Timed Up and Go	1	[112]

CIRS-G: Cumulative Illness Rating Scale-Geriatrics; MMSE: Mini-Mental Status Exam; IADL: Instrumental Activities of Daily Living; ADL: Activities of Daily Living.

for age and 12 items that assess health, function, and physical status. The higher the score, the greater the risk for functional decline and/or death. The authors found that the clear cutoff values of the VES-13 tool enabled them to easily stratify their patients as healthy, at average risk; vulnerable, at moderately increased risk; or frail, at extreme risk [25, 30].

- A combination of the self-administered questionnaire and a brief physician assessment, including measures of functional status, falls, comorbidity, cognition, nutritional status, psychological state, social function, and social support, proved feasible to identify the needs of geriatric oncology patients in less than a half-hour (Table 4) [31, 32].
- An instrument that borders between a screening test and an abbreviated CGA is the EASYCare instrument. A tool developed to assess disability in the elderly, it is a compilation of other, validated instruments and assigns an overall disability score from 1 (low disability) to 100 (high disability) (Table 5) [33].
- Fried and colleagues developed an index of frailty that includes five components, the presence or absence of

Table 4 Hurria et al. brief geriatric assessment [31, 32]

Domain	Instrument	No. of Questions	Citation
Comorbid conditions	OARS Comorbidity Scale	32	[100]
Functional status	MOS–ADL	10	[105]
Functional status	OARS–IADL	7	[102]
Functional status*	Karnofsky–Physician	1	[109]
Functional status	Karnofsky–Self-report	1	[113]
Functional status*	Timed Up and Go	1	[112]
Functional status	No. of falls in last six months	1	[114]
Cognition*	Blessed Orientation-Memory-Concentration	6	[115, 116]
Psychological	Hospital Anxiety and Depression Scale	14	[106]
Social	MOS Social Support Scale	20	[105]
Social	Seeman and Berkman Social Ties	4	[98]
Nutrition*	Body-Mass Index	1	[117]
Nutrition	Percent unintentional weight loss in six months	1	[84, 86]

*Needs to be administered by a health-care professional.
OARS: Older American Resources and Services; EORTC: European Organization for Research and Treatment of Cancer;QLQ: Quality of Life Questionnaire; IADL: Instrumental Activities of Daily Living; SOBI: Systems of Belief Inventory; ADL: Activities of Daily Living; MOS: Medical Outcomes Study.

which stratifies the elderly into non-frail, pre-frail, and frail. A person is frail if three or more criteria are met. Pre-frail is defined as meeting one or two criteria [34]. Using this stratification can help guide cancer treatment decisions because elements of the frailty syndrome may help identify older patients likely to develop severe toxicity and side effects in response to treatment. Because of

Table 5 EasyCare instrument [33]

Domain	Instrument	No. of Questions	Citation
Comorbid conditions	CIRS-G	14	[44]
Functional status (ADL/IADL)	GARS-3	18	[118]
Mobility	Timed Up and Go	1	[112]
Quality of life	MOS-20	20	[105]
Mood	MOS-20 subscale		[105]
Well-being	Cantril self-anchoring ladder	10	[119]
Cognition	MMSE	11	[110]
Social	Loneliness Scale	14	[120]

CIRS-G: Cumulative Illness Rating Scale-Geriatrics; GARS-3: Groningen Activity Restriction Scale; MOS: Medical Outcomes Study; MMSE: Mini-Mental Status Exam; IADL: Instrumental Activities of Daily Living; ADL: Activities of Daily Living.

the possibility that the pre-frail elderly may have the most unpredictable response to stressors, they may be the population that would benefit most from a CGA (Table 6).

- Lastly, Rockwood and colleagues defined a frailty index using data from the Canadian Study of Health and Aging (CSHA) by using 70 deficits from the clinical examination (individual items available at http://myweb.dal.ca/amitnits.CHSAclinical-variables.jpg) to classify patients as “robust,” “pre-frail,” or “frail,” showing that a phenotypic definition of frailty is predictive of survival [35].

Evaluate Comorbidities

The presence of comorbid conditions increases with age and can have important implications for patients with cancer. Clinical studies in elderly cancer patients have shown that the presence of

Table 6 Fried frailty screener [34]

Research criteria used to define frailty		
Variable	Question	Criteria
Weight loss	"In the past year, have you lost more than 0 lbs unintentionally (i.e., not due to dieting or exercise)?"	If yes, then subject is frail for weight loss criterion.
Exhaustion	Using the CES depression scale, the following two statements are read. (a) I felt that everything I did was an effort. (b) I could not get going. The question is asked: "How often in the last week did you feel this way?"	Subjects answering "2" or "3" to either of these questions are categorized as frail by the exhaustion criterion.
Physical activity	Based on the short version of the Minnesota Leisure Time Activity questionnaire, subjects are asked about whether they do walking, chores (moderately strenuous), mowing the lawn, raking, gardening, hiking, jogging, biking, exercise cycling, dancing, aerobics, bowling, golf, singles or doubles tennis, racquetball, calisthenics, swimming.	Men: those with physical activity <383 Kcal/wk are frail. Women: those with physical activity <270 Kcal/wk are frail.

Table 6 (continued)

Research criteria used to define frailty		
Variable	Question	Criteria
Walk time (cutoffs are gender and height-specific)	Men	Cutoff for time to walk 15 ft is criterion for frailty
	Height ≤ 173 cm	≥ 7 seconds
	Height > 173 cm	≥ 6 seconds
	Women	
	Height ≤ 159 cm	≥ 7 seconds
	Height > 159 cm	≥ 6 seconds
Grip strength (cutoffs are gender and BMI-specific)	Men	Cutoff for grip strength (kg) is criterion for frailty
	BMI ≤ 24	≤29
	BMI 24.1–26	≤30
	BMI 26.1–28	≤30
	BMI > 28	≤32
	Women	
	BMI ≤ 24	≤17
	BMI 23.1–26	≤17.3
	BMI 26.1–29	≤18
	BMI > 29	≤21

BMI = body mass index; CES = Center for Epidemiological Studies.
Adapted from Fried L, Tangen C, Walsoton J, et al. Frailty in older adults: Evidence for a phenotype. J Gerotol Med Sci 2001;56A:M146–56.

comorbidity has a negative impact on prognosis, treatment tolerance, disability, as well as the risk of mortality among cancer patients [36–39]. Recently, it has been reported that the presence of multiple comorbidities impacts five-year survival in patients with endometrial, prostate, larynx, and rectal cancer [40, 41]. A pilot study using the CGA in elderly breast cancer patients helped identify new health problems over those detected by traditional history and physical alone [18]. There have been systematic attempts to develop management guidelines for cancer patients with comorbid conditions. The Charlson Comorbidity scale [42, 43] (Table 7) and Cumulative Illness Rating Scale-Geriatrics (CIRS-G) [44] are the most common comorbidity indices in geriatrics [17].

Table 7 Modified Charlson Comorbidity Index (CCI)

6 points each for metastatic solid tumor or AIDS

3 points each for moderate to severe liver disease

2 points each for hemiplegia, moderate-to-severe renal disease, diabetes with end-organ damage, and cancer (including leukemia or lymphoma)

1 point each for every decade over 40

1 point each for coronary artery disease, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disorder, peptic ulcer disease, mild liver disease, diabetes

Modified CCI Score	Annual Mortality Rate
Low (<3)	0.03
Moderate (4–5)	0.13
High (6–7)	0.27
Very High (≥8)	0.49

Adapted from www.eperc.mcw.edu/fastFact/ff_191.htm and Beddhu et al. Am J Med 2000 108:609–13.

Evaluate the Patient's Functional Status

Functional impairment is the inability of an older person to function normally in daily life activities and has been found to be an independent predictor for use of health-care resources, morbidity, and mortality [45–48]. A recent survey indicated that 10–13% of older persons between ages 65–69 have difficulty getting out of bed, and 6–10% need help with routine care. This increases as older people age, with 24–29% of those over the age of 80 needing help getting out of bed, and 29–42% needing help with routine care [49]. Cancer is also associated with increased functional dependence above and beyond that associated for the equivalent age in the population. The prevalence of functional limitations in older cancer patients has been reported as being up to twice as high as that reported in large cohorts of community-dwelling elderly [27, 50].

Functional assessment instruments, such as the Karnofsky Index and Eastern Cooperative Oncology Group Performance Status Scale (ECOG-PS), are widely used to help predict prognosis in cancer patients [51]. However, these instruments do not seem as effective in older patients [17, 52, 53]. In geriatrics, more accurate measures of performance status are the activities of daily living (ADL) and instrumental activities of daily living (IADL) scales. Measurement of ADLs provides a general evaluation of self-sufficiency and mobility. They include six basic functions: bathing, dressing, toileting, continence, transferring, and feeding [54, 55]. IADLs are a measure of eight higher-level functions: using the telephone, transportation, shopping, meal preparation, laundry, performing housework, taking medications, and managing money [56]. Functional status in the elderly patient with cancer may reflect tolerability to chemotherapy, progression of cancer, or general health status [57]. An accurate assessment of functional status can help the oncologist to determine if the patient can comply with medical instructions in addition to identifying potential remediable problems. For example, transportation dependence may contribute to difficulty keeping appointments.

Evaluate Geriatric Syndromes

Another important component of the CGA is to evaluate the patient for the presence of geriatric syndromes: cognitive dysfunction (dementia and delirium), vision and hearing impairment, gait and balance difficulties, malnutrition, incontinence, depression, osteoporosis, and sleep disorders. Impairments in any of these syndromes can have a profound effect on cancer treatment and quality of life.

Cognitive Syndromes (Dementia and Delirium)

In older persons, the two most important cognitive problems are dementia and delirium. Dementia is defined as a significant decline in two or more areas of cognitive functioning, including one or more functions of memory, recall, and recognition for visual/verbal information, judgment, language, and problem solving [58]. The incidence of dementia increases with age. It has been reported that as many as 50% of all patients over the age of 80 will have dementia [59]. A diagnosis of dementia usually contributes to increased mortality [60].

Delirium is defined as a disturbance of consciousness with a decreased ability to focus and poor attention that develops over a short period of time and fluctuates. It often is associated with changes in cognition and perceptual disturbances, classically visual disturbances. The prevalence of delirium among patients over the age of 65 presenting to the emergency room ranges from 10–24%. Among hospitalized older persons, it is 25–60% and is a predictor of poor prognosis, with an increased risk of short-term mortality by 2–20-fold [61, 62]. Risk factors for delirium include preexisting dementia, severe medical illness, alcohol abuse, diminished functional ability, depression, and hearing and visual impairment [63].

Cognitive function and capacity are important issues to consider in decision making with older patients. The oncologist is obligated to determine whether a patient can follow directions to comply with chemotherapy treatment plans and make informed decisions about treatment. Furthermore, as the patient's underlying cancer progresses or complications of treatment occur, the older patient may become unable to make health-care decisions. Therefore, issues regarding advance directives, establishing health-care proxies, and potential intensity levels of treatment should be discussed early in the course of cancer care and revisited if the patient's disease progresses.

Conversely, cognitive dysfunction can occur secondary to cancer treatment. Dementia has been reported following treatment of brain tumors with radiotherapy, administered alone or in combination with nitrosourea-based chemotherapy [64]. More often, though, chemotherapy predisposes to delirium [65]. In addition, delirium might be the first presenting sign of infection (with or without neutropenia), dehydration, electrolyte disorders (especially hyponatremia), and malnutrition either directly from the tumor or as a side effect from the chemotherapy.

Depression

Depression, clinical or subclinical, is associated with increased mortality [66]. In community-dwelling elderly patients, the prevalences of depressive symptoms and major depressive disorder are 15% and 1–3%, respectively [67]. Factors associated with depression in the elderly include gender, alcohol and substance abuse, polypharmacy, family history, and medical conditions such as stroke, Alzheimer's disease, cancer, and heart disease [67]. Since older patients often deny depressive symptoms, present with somatic complaints, or have comorbid anxiety or cognitive impairment, it is often difficult to recognize depression in an older patient.

A diagnosis of cancer, particularly those that are incurable, may lead to depressive symptoms. For example, increased dependency or the anticipation of reduced life expectancy can precipitate symptoms. Many of the symptoms of depression, such as appetite change, weight loss, and loss of energy, are similar to cancer symptoms [68]. Affect assessment is particularly important to assess during cancer treatment because depressed patients are less likely to adhere to treatment regimens. There is a marked tendency for oncologists to underestimate the level of depressive symptoms on routine history and physical [69]. A simple inquiry can be used as a screen, such as "Do you often feel sad or depressed?" This single question, however, tends to be overly sensitive and should be used in conjunction with the Geriatric Depression Scale, available in 5-, 15-, and 30-item varieties [70].

Falls Risk: Assess Gait and Balance Impairment

Older patients are more likely to have gait and balance impairments, which increase their risk of falling [71]. There is a high rate of injury as a result of falls among older persons who do not have cancer, and it is likely that older cancer patients are at an even higher risk for serious injury due to several factors. First, cancer patients frequently have fatigue, dizziness, dehydration, or other symptoms that increase the likelihood of a fall. In addition, cancer patients with bony metastases to the hip, wrist, or vertebral body have a higher chance of a fracture due to structural weakness of the bone. Also, for patients with a low platelet count, the chances for serious morbidity and mortality are greater.

The treatment of an older patient with chemotherapy may also contribute to gait and balance instability. Side effects (e.g., cerebellar toxicity, peripheral neuropathy, dizziness, dehydration, and fatigue) of commonly used oncology agents include the increased chance of instability and falls [72] (Table 8). The risk of falling can be assessed by asking all older patients if they have fallen in the last year, and then performing a multifactorial falls assessment by testing balance, gait, and lower extremity strength. Performing this assessment on patients who screen positive for falls, and then treating their risk factors, can reduce falls by 30–40% [73]. For all these reasons, the older cancer patient should be assessed for gait and balance instability prior to and during the course of chemotherapy.

Table 8 Chemotherapy side effects that contribute to falls

Cisplatin	Delayed peripheral neuropathy Sensory impairment Loss of proprioception
Taxanes, Vinca Alkaloids	Peripheral neuropathy (exacerbated with cisplatin)
Flurouracil (5-FU)	Cerebellar toxicity
Cytarabine (Ara-C)	Cerebellar toxicity

Vision Impairment

The prevalence of visual impairment defined as a visual acuity of 20/40 or worse is 4–5% among persons over the age of 65 and 10–21% for those over the age of 75 [74]. Among older persons, the prevalence of common causes of visual impairment is 36% for cataracts, 14% for macular degeneration, 7% for diabetic retinopathy, and 5% for glaucoma [75]. The leading cause of blindness among African-Americans is cataracts, whereas for Caucasians it is macular degeneration.

Cancer treatment of an older patient with poor visual acuity poses additional risks beyond the normal complications of chemotherapy. First, many chemotherapy regimens and underlying malignancies can cause symptoms of fatigue, dizziness, and peripheral neuropathy, which, combined with visual impairment, can greatly increase the risk of a fall. Furthermore, the morbidity (e.g., hip fractures) and mortality of such a fall may be greater, especially in patients with low platelet counts, bleeding disorders, or bony metastases [76]. Medication compliance may also be hindered if the patient lives alone and cannot see well enough to read the labels [77].

Hearing Impairment

The prevalence of hearing impairment in the community is about 25–40% in persons over the age of 65 and 70–80% in those over the age of 75. The prevalence is even higher in nursing home settings, about 80–85% [78, 79].

Hearing impairment is relevant to cancer care because of the ototoxicity of chemotherapeutic agents and because of the effect of hearing impairment on treatment. Several chemotherapeutic agents and other medications that are used commonly in oncologic practice have substantial ototoxicity [80]. Cisplatin (Platinol), a widely used anticancer drug, is cochleotoxic. Some studies suggest that some level of hearing toxicity occurs in 65–70% of people exposed to Cisplatin at a total dose greater than 200 mg/m^2[81]. Total deafness has been reported. Furthermore, the ototoxicity of Cisplatin is synergistic with gentamicin (Garamycin). Other cancer agents with reported ototoxicity include carboplatin (Paraplatin), dichloromethotrexate (DCM), and vincristine (Oncovin) [82]. Also, medications such as furosemide (Lasix), vancomycin (Vancocin), and metronidazole (Flagyl) are toxic in some instances, especially when used in conjunction with gentamicin.

Sensory deficits such as hearing also affect the ability to give adequate informed consent in oncology. The ability to comprehend speech frequently diminishes with age due to impaired hearing and central auditory processing disorders [83]. This becomes a substantial problem in a busy and noisy cancer clinic setting. Consonant sounds tend to be the most difficult since much of the sound is concentrated in higher frequencies, where hearing loss due to presbycusis most commonly occurs.

Nutritional Status

Poor nutritional status is an independent predictor of functional dependency and survival in the elderly population. Weight loss is a common finding in older persons [84]. There are many causes for unintentional weight loss, including acute infections, depression, drugs (including chemotherapeutic agents, laxative abuse, thyroid medications, and amphetamines), conditions that prevent food consumption (e.g., painful mouth sores, newly applied orthodontic appliances, loss of teeth), loss of appetite, malignancy, smoking, and AIDS. It is important to differentiate weight loss due to malignancy from weight loss due to other reversible causes.

In the presence of cancer, the prevalence of malnutrition is higher [85]. Malnutrition and unintentional weight loss are associated with increased toxicity of chemotherapy, lower response rates, decreased performance status [86], and poorer survival [87, 88]. However, in attempting to optimize patient outcomes, reversible factors that affect nutritional status should be addressed. These factors include depression, smoking and alcohol use, dysphasia, mucositis, changes in taste and smell, difficulty chewing, inability to shop or cook, and medication side effects. The mini-nutritional assessment is an easy tool to utilize in the outpatient setting and can help detect the risk of malnutrition while albumin and BMI are still in the normal range [73].

Incontinence

Incontinence is often mistaken to be a part of normal aging, and its impact on a patient's quality of life is underappreciated. The prevalence of incontinence in the elderly varies considerably. In the community, incontinence ranges from 15-30%, but in nursing home settings, as many as 50–60% of patients may have incontinence [89].

Metastatic disease to the brain or spinal cord can interfere with nerve pathways needed for normal micturation and cause incontinence [90, 91]. Furthermore, incontinence is sometimes an early sign of underlying urinary tract infection, which may lead to sepsis in older cancer patients. The treatment of cancer may also precipitate or worsen incontinence. Fluids and diuretics are often given in conjunction with chemotherapy and can worsen the symptoms of incontinence, making mild symptoms moderate or severe, and therefore adversely affect quality of life [92]. The history and physical examination are essential in distinguishing transient from chronic causes of incontinence.

Sleep Disorders

Sleep disturbance is a common problem among both the elderly and cancer patients. Approximately 50% of all older persons report a sleep complaint, 30% of which is of a chronic nature. Studies of insomnia in cancer patients have shown that 30–50% of newly diagnosed or recently treated patients have sleep difficulties, with many reporting insomnia lasting several years post-therapy [93]. The consequences of insomnia include worsening of cancer-related fatigue and functional impairment comprising both cognitive and psychomotor impairment [93]. Unfortunately, unlike aspects of cancer such as depression, nausea, and pain, sleep receives little attention from oncologists. There is a misperception that sleep difficulties are always due to depression or anxiety. Although it is true that psychiatric disorders are often associated with sleep disturbance, cancer is often a precipitating factor for insomnia since both the diagnosis and treatment are a series of stressful events.

Several cancer therapies increase the risk of developing insomnia. For example, patients with postchemotherapy nausea and vomiting report a high rate of insomnia, which may be secondary to the effects of certain antiemetic medications known to cause insomnia such as dexamethasone (Decadron), prochlorperazine (Compazine), metoclopramine (Reglan), and granisetron (Kytril) [87, 88]. Furthermore, drugs such as tamoxifen can cause side effects that interfere with sleep in breast cancer patients, such as hot flashes, a symptom shared by prostate cancer patients with androgen deprivation therapy [94]. Cancer pain is also a common cause of insomnia, with one study showing that 37% of cancer patients with pain report difficulty initiating sleep [95].

Assess Social Issues

Living Conditions

The physical environment can play a big role in the day-to-day function and health of older patients. Mismatches between a patient's capabilities and environmental demands can result in disability. The prevalence of environmental hazards in the homes of older persons is high. Some studies on falls suggest that between 35–45% of falls are attributed to home hazards, such as poor lighting, inadequate bathroom grab rails and stairway banisters, exposed electrical cords, clutter on the floor, and throw rugs [96]. Home assessment can help, performed by visiting physicians, nurse, or social workers using a home safety checklist provided by the National Safety Council. Home assessment can also provide other valuable information on nutritional adequacy, sanitary conditions, medication use and misuse, social interactions, and elder abuse and neglect.

Caregiver Support

Social support is another important yet often neglected topic in the health care of the elderly. There are many potential sources of support, including family, friends, caregivers, neighbors, other patients, and volunteers from agencies. Caregiver support is essential for several aspects of the cancer patient's treatment, including transportation, timely management of fever, bleeding, and other emergencies during chemotherapy, as well as emotional and psychological assistance. Involving families through education and counseling can help support the elderly cancer patient and prevent or slow functional deterioration [97]. For very frail older patients, the availability of assistance from family and friends is the determining factor for whether a functionally dependent older person remains at home or is institutionalized [7]. Often, there is one caregiver that assumes most of the responsibilities for the older cancer patient. Community-based services aimed at reducing this burden may help in maintaining social support over a longer period of time. Social isolation or the lack of social ties is an independent predictor of mortality in the geriatric population [98].

Religion

Older adults commonly turn to spirituality and religion when they meet difficult life-changing events and experience personal losses. Several studies have been conducted on spirituality and health. One study found religiosity positively associated with health-enhancing attitudes and behaviors and inversely associated with health-compromising behaviors and adverse health-related outcomes [99]. Oncologists need to be aware that religion may be more important as a person ages and that formal instruments to assess its importance are being developed.

Strategy

The key components of the geriatric assessment can be divided into steps [73]:

1. data gathering,
2. discussion among the team,
3. development of the treatment plan,
4. implementation of the treatment plan,
5. monitoring response to the treatment plan, and
6. revising the treatment plan.

No current model that includes these elements has been proven to be the most effective with respect to outcomes and cost. This remains to be determined, and research in this area is still underway. Future research needs to be dedicated to developing assessment strategies that can be performed with the available resources in busy community oncology practices as well as traditional academic centers while still retaining predictive value for both treatment toxicity and overall survival.

Conclusion

In addition to benefiting the management of older cancer patients, the routine usage of a geriatric assessment by oncologists can provide a common language in the management of older cancer patients, which is essential both for the retrospective evaluation of equality of care as well as for the prospective assessment of outcomes in clinical trials.

Therefore, the recognition of the importance of the performing a CGA in elderly cancer patients may be regarded as the introduction of "geriatric thinking" into the oncology setting [21]. Optimal training of future medical oncologists should include a better understanding of these clinical and research problems of managing the older population.

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Cancer Screening in Older Adults

Louise C. Walter

Introduction

This chapter focuses on the special issues that need to be considered when making decisions to screen older persons for cancer. Specifically, while there is substantial evidence that screening for colorectal, breast, and cervical cancer reduces cancer mortality among persons in their 50s and 60s [1–6], few screening trials included persons over age 70. Therefore, clinicians must assess whether to extrapolate results from screening trials to their older patients. To determine the appropriateness of this extrapolation, clinicians need to know whether there are differences in the behavior of cancers in older people that change the benefit of early detection and treatment; whether there are differences in the accuracy of screening tests in older people that make the tests more or less likely to miss cancer; and whether there are differences among older individuals that alter the likelihood of receiving benefit versus harm from cancer screening [7]. The need to individualize cancer screening decisions is especially important for older persons, because individuals become increasingly unique in

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their particular combination of health, life expectancy, and values with advancing age.

Like many medical decisions, individualized cancer screening decisions are best made by using quantitative estimates of life expectancy and screening outcomes to anchor decisions, tempered by qualitative consideration of how an older person values the potential benefits and harms of screening [8]. This chapter reviews evidence from clinical trials that included older persons as well as indirect evidence about the effects of advancing age on the potential benefits and harms of screening. The main benefit of screening is the reduction in cancer mortality experienced by a few people who have early-stage disease detected and treated, which would have been lethal in their remaining lifetime. The harms of screening, which may affect anyone, include complications from screening tests or workup of false-positive test results, detection and treatment of clinically inconsequential disease, which never would have produced symptoms during a person's lifetime, and psychological distress. How age affects these benefits and harms is complex because some aspects of aging favor screening (e.g., increased absolute risk of dying of cancer) while other aspects disfavor screening (e.g., life expectancy decreases) [8]. Understanding how various factors influence the potential benefits and harms of common cancer screening tests in older adults allows for individualized patient-centered screening decisions rather than a one-size-fits-all approach based solely on age.

Estimates of Life Expectancy

A common step to individualizing cancer screening decisions is to estimate an older person's life expectancy, because life expectancy affects the likelihood of receiving benefit versus harm from screening. For example, finding an asymptomatic cancer in a person who will die of something else before the cancer would become symptomatic does not benefit the person and may cause significant harm. In estimating the life expectancy of an

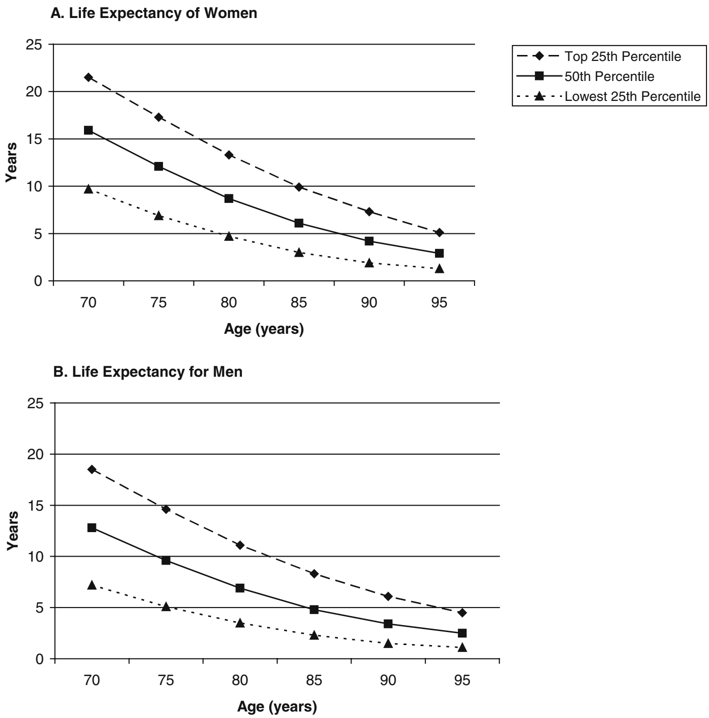

Fig. 1 Upper, middle, and lower quartiles of life expectancy for older women and men
Source: National Center for Health Statistics [9]. Walter LC, Lewis CL, Barton MB [7].

individual, it is useful to have a general idea of the distribution of life expectancies at various ages. For example, when estimating the life expectancy of an 80-year-old woman, it is useful to know that approximately 25% of 80-year-old women will live more than 13 years, 50% will live at least 9 years, and 25% will live less than 5 years [7, 8]. Figure 1 presents the upper, middle, and lower quartiles of life expectancy for the U.S. population according to age and sex and illustrates that there is substantial variability in how long people of similar ages live [9].

While it is impossible to predict the exact life expectancy of an individual, it is possible to make reasonable estimates of whether a person is likely to live substantially longer or shorter than an average person in his or her age cohort. There are many factors clinicians can use to estimate whether an older person is typical of someone at the middle of his or her age-sex cohort or is more like someone in the upper or lower quartiles. For example, the number and severity of comorbid conditions and functional impairments are much stronger predictors of mortality in older people than chronological age. Older persons with congestive heart failure, end-stage renal disease, oxygen-dependent chronic obstructive lung disease, severe dementia, or functional dependencies in several activities of daily living would fall into the lowest quartile of life expectancy [8–10]. Older persons without significant comorbid conditions or with excellent functional status are likely to be in the upper quartile of life expectancy. Such estimates, while not perfect, allow for better estimations of the potential benefits and harms of screening than focusing on age alone.

Benefits and Harms of Common Cancer Screening Tests

Colorectal Cancer Screening

Evidence of Benefit. For colorectal cancer screening, fecal occult blood testing has the strongest evidence of benefit in elderly persons because three randomized trials, including more than 40,000 persons aged 70–80 years, demonstrated that screening every one to two years reduced colorectal cancer incidence and death [11, 12]. For example, two European trials of biennial unhydrated fecal occult blood testing found that screening reduced colorectal cancer mortality for persons aged 45–75 years by 15–18% over 8–13 years [13, 14]. A trial in the United States demonstrated that annual rehydrated fecal occult blood testing also reduced the incidence of colorectal cancer for persons aged 50–80 years by 20% (95% CI, 10–30%) after 18 years of follow-up [15]. Biennial screening decreased incidence by 17% (95% CI, 6–27%). The screening's efficacy was independent of advancing age, although no subgroup analyses of older persons have been published.

Additional recommended tests for colorectal cancer screening include flexible sigmoidoscopy, colonoscopy, and double-contrast barium enema. The efficacy of sigmoidoscopy is supported by several well-designed case-control studies [11, 12]. The study by Selby et al., which included patients aged 45–91 years, found that rigid sigmoidoscopy was associated with a 59% reduction in mortality from cancer that was within reach of the sigmoidoscope [adjusted odds ratio (OR) = 0.41; 95% CI, 0.25–0.69] [16]. This protective effect did not differ according to age at diagnosis and is estimated to last between 6–10 years. Colonoscopy also has a long-lasting protective effect. A case-control study, in which almost half of the patients were over age 70, found that those who died of colorectal cancer were less likely to have had a colonoscopy in the prior 10 years (OR = 0.43; 95% CI, 0.30–0.63) [17]. No trials have examined the effectiveness of barium enema in reducing the incidence of or death from colorectal cancer.

CT colonography, also referred to as virtual colonoscopy, is another screening method that was introduced in the mid-1990s. Most guidelines do not include it as one of the recommended screening tests at this point because there is insufficient evidence for its effectiveness in improving health outcomes. However, recent American Cancer Society guidelines suggest CT colonography may be comparable to colonoscopy for identifying cancer and polyps of a significant size when using state-of-the-art techniques [18]. This methodology requires the same bowel preparation as colonoscopy, and colonoscopy is required if the result is positive. Therefore, patients may need to complete two full bowel preparations, which is not ideal for elderly patients.

Evidence of Harm. All screening tests have false-positive results. For example, approximately 86–98% of trial participants who had a positive fecal occult blood test result did not have colorectal cancer after workup but were exposed to the potential complications of colonoscopy [13–15]. Colonoscopy is also the standard workup for polyps detected by sigmoidoscopy, barium enema, or CT colonography. In a large prospective cohort study, which included 600 veterans aged 70–75 years, major complications occurred in 3 per 1,000 screening colonoscopies [19]. Major complications included perforation, bleeding, stroke, myocardial infarction, Fournier gangrene, and thrombophlebitis. Flexible sigmoidoscopy has fewer complications than colonoscopy, with perforations occurring in less than 0.1 per 1,000 examinations, and serious complications are estimated to occur in 0.04 per 1,000 barium enemas [12].

Screening may also lead to polypectomy or surgery to treat inconsequential disease that never would have caused symptoms during a patient's lifetime. In fact, very few adenomatous polyps (<10%) are destined to progress to cancer over 10 years [20]. While the U.K. trial reported that fecal occult blood testing rarely led to surgery for inconsequential disease [21], autopsy studies suggest the potential for more sensitive tests to detect inconsequential disease may be substantial. Approximately 10–33% of older persons have polyps, and 2–3% have incidental colorectal cancer discovered on autopsy [12]. It is unknown what percentage of these inconsequential lesions would have been detected if these persons had undergone screening during their lifetime.

Lastly, all colorectal cancer screening tests may cause psychological distress, which may range from the alarm of false-positive results to the stress and discomfort of the bowel preparation [22]. The severity and duration of distress varies, although the greatest anxiety for many persons occurs while waiting to undergo workup after a positive test result.

Factors Affecting the Benefits and Harms of Screening in Older Adults: Randomized trials of fecal occult blood testing provide direct evidence for the efficacy of colorectal cancer screening in older persons. However, these trials do not address the benefit of screening persons over age 80 or how other factors may change the benefit-to-harm ratio of screening. Instead, clinicians must consider additional evidence to determine whether screening is likely to be beneficial in their older patients (Table 1).

Table 1 Questions to consider when deciding whether to extrapolate results of cancer screening trials to an older patient

Questions	Colorectal cancer	Breast cancer	Cervical cancer	Prostate cancer
Are there differences in the behavior of cancers in older people that reduce the benefit of early detection/treatment?	No	Yes—higher proportion of slow-growing cancers	No	Uncertain
Are there differences in the accuracy of screening tests in older people?	Yes—flexible sigmoidoscopy less sensitive No—fecal occult blood tests and colonoscopy	Yes—clinical breast exam may be less sensitive No—mammography *more* sensitive	Yes—Pap smear may be less sensitive	Yes—Prostate-specific antigen (PSA) may be less specific
Are there differences in individual characteristics of older people that:				
Reduce the likelihood of benefit from screening?	Yes—limited life expectancy; serious comorbidity	Yes—limited life expectancy; serious comorbidity	Yes—limited life expectancy; history of normal Pap smears; no cervix	Yes—limited life expectancy; serious comorbidity; benign prostatic hypertrophy

(continued)

Table 1 (continued)

Questions	Colorectal cancer	Breast cancer	Cervical cancer	Prostate cancer
Increase the likelihood of benefit from screening?	Yes—older age; inflammatory bowel disease; history of multiple or large colorectal adenomas; lack of prior screening	Yes—older age; family history of breast cancer; longer estrogen exposure (endogenous or exogenous); lack of prior screening	Yes—lack of regular Pap screening	Unknown—no proven benefit in any age group

Source: Walter LC, Lewis CL, Barton MB [7].

Indirect evidence suggests screening may continue to benefit persons over age 80 years. For example, advancing age does not cause colorectal cancer to become more indolent or less responsive to surgery or chemotherapy [23]. Localized colorectal cancer in older persons responds to treatment and is associated with less morbidity and better survival than advanced disease.

Advancing age does increase the absolute risk of advanced neoplasia in the right colon (5.6% for persons over age 65 compared to 0.8% for persons aged 50–54 years), decreasing the sensitivity of sigmoidoscopy, which only examines the left half of the colon [24]. Therefore, screening strategies that evaluate the entire colon are recommended for older persons. Fecal occult blood testing can detect curable cancers throughout the colon. However, its sensitivity is low in all age groups (30–50%) [25]. Colonoscopy is the most sensitive and specific test, although it can be technically more difficult in older persons [12].

Individual patient characteristics are the most important factors affecting the likelihood of screening benefit versus harm. In addition to advancing age, inflammatory bowel disease and a history of multiple or large colorectal adenomas increase the absolute risk of developing and dying from colorectal cancer, which increases the chance to benefit from screening [18]. On the other hand, the chance to benefit is decreased for patients with serious comorbidity or a history of normal screening examinations [11]. For example, cardiopulmonary disease and poor functional status increase the risk of complications from colonoscopy and increase mortality from surgeries to treat colorectal cancer. The long natural history of the adenoma-carcinoma sequence and trials demonstrating that cancer mortality does not begin to decrease until five years after the start of screening also suggest that patients who have a life expectancy less than five years are more likely to be harmed from screening than to benefit [8].

Recommendations. Most guidelines do not recommend using upper-age cutoffs to decide when to stop colorectal cancer screening (Table 2). Rather, most guidelines recommend discontinuing screening if an older person has factors that

Table 2 Guideline recommendations for cancer screening in the elderly

Cancer site	Test	Frequency	USPSTF guideline*	ACS guideline[†]	AGS guideline[‡]
Colorectal	Fecal occult Blood test or Sigmoidoscopy or Colonoscopy or Double-contrast Barium enema	Annual Every 5 years Every 10 years Every 5 years	Screen all adults ≥50 years. Discontinuing screening is reasonable in persons whose age (> 85 years) and comorbid conditions limit life expectancy.	Screen all adults ≥50 years. Discontinuing screening is reasonable in persons with severe comorbidity that would preclude treatment.	Screen all adults ≥50 years. Persons too frail to undergo colonoscopy and persons with short life expectancy (3–5 years) should not be screened.
Breast	Mammography with or without Clinical breast exam	Every 1–2 years Annually	Screen all women ≥40 years. Women with comorbid conditions that limit life expectancy are unlikely to benefit from screening.	Screen all women ≥40 years, continuing for as long as a woman is in good health and would be a candidate for treatment.	Screening should continue for older women who have a life expectancy ≥4 years.
Cervical	Pap smear	Every 1–3 years	Discontinue screening in women who have had a total hysterectomy and in women >65 years who are not at high	Immunocompetent women >70 years who have had at least three normal Pap smears in a row and no abnormal	It is acceptable to stop screening women >70 who have had at least two normal Pap smears since age 60 and women who

Table 2 (continued)

Cancer site	Test	Frequency	USPSTF guideline*	ACS guideline†	AGS guideline‡
			risk for cervical cancer and have had adequate recent normal Pap smears.	results within 10 years may elect to stop. Screening may be stopped in women who have had a total hysterectomy and women with severe comorbid illness.	have a short life expectancy or would be unable to tolerate treatment.
Prostate	Prostate-specific antigen (PSA)	Annual	Evidence insufficient to recommend for or against screening. Men with a life expectancy <10 years are unlikely to benefit even under favorable assumptions.	Offer screening to men ≥ 50 years who have a life expectancy ≥ 10 years and discuss benefits and harms of testing.	No recommendation.

* USPSTF = United States Preventive Services Task Force.
† ACS = American Cancer Society.
‡ AGS = American Geriatrics Society.

considerably decrease the benefit-to-harm ratio of screening (e.g., life expectancy less than five years or conditions that increase the risk of colonoscopy).

Breast Cancer Screening

Evidence of Benefit. While there have been eight randomized trials of mammography, the Swedish Two-County Study was the only trial that included women over age 70 [26]. However, they were only invited to two rounds of screening, and subgroup analyses did not show a significant reduction in breast cancer mortality for women aged 70–74 years. When analyses included women aged 40–74 years, this seven-year trial continued to show a significant 32% reduction in breast cancer mortality in the screened group after 20 years of follow-up. Other breast cancer screening tests include clinical breast examination and breast self-examination. However, there are no data from randomized trials to show that these tests, without accompanying mammography, reduce breast cancer mortality in any age group [27].

Evidence of Harm. In the Swedish Two-County Study, 88% of women with a positive mammogram during the first round of screening did not have cancer. More recent data from Medicare claims suggest 77–86 per 1,000 women older than 70 years who undergo screening mammography will have a positive result, and approximately 86% of these will be false-positives [28]. These women are exposed to follow-up testing, which usually involves diagnostic mammography and biopsy. Clinical breast examinations and breast self-examinations, both less specific than mammography, can also lead to follow-up testing for false-positive results. In a large U.S. series of clinical breast examinations, 3.9% of examinations performed on asymptomatic women were abnormal, but 97% of these women did not have cancer after further evaluation [29].

Screening may also lead to surgery, radiation, or treatment with hormonal agents after detecting inconsequential disease that never would have come to clinical attention had the person not been screened. For example, approximately 1 in 1,000 mammograms performed in women aged 70–84 years will detect ductal carcinoma in situ (DCIS), a noninvasive form of breast cancer with an uncertain natural history [30]. Whether the majority or minority of untreated DCIS lesions will progress to invasive cancer and over what time interval are controversial, so most women undergo surgery. Women who have surgery for DCIS that would never have caused symptoms have suffered harm from screening. Autopsy studies suggest the risk of detecting inconsequential DCIS is substantial. In a series of autopsy studies, the median prevalence of DCIS at death was 9% among women not known to have breast cancer, whereas incidental invasive breast cancer was found in 1.3% [31].

Lastly, many women experience psychological distress after a positive screening test, which may persist even after normal follow-up examinations [32]. Undergoing screening mammography and follow-up procedures may be especially burdensome or frightening to frail elderly women with cognitive or functional impairments [33].

Factors Affecting the Benefits and Harms of Screening in Older Adults. While randomized trials have proven the efficacy of screening mammography for women aged 50–69 years, the trials do not provide direct evidence for or against screening women older than age 70 [34]. Therefore, clinicians must consider indirect evidence to determine whether mammography is likely to be beneficial in their older female patients (Table 1).

Breast cancer is a heterogeneous disease with considerable variation in aggressive potential at all ages [35]. However, older women have a greater frequency of cancers, with histologies and tumor markers indicative of reduced aggressiveness. Therefore, while mammography trials suggest that a reduction in breast cancer mortality begins to emerge after five years of screening in women aged 50–69 years, this lag time to benefit could be longer for older women [26]. However, the treatment of localized breast cancer in older women is associated with less morbidity and better survival than that of advanced disease [36].

Advancing age also leads to a decrease in the radiographically dense fibroglandular tissue of the breast, which increases the accuracy of mammography for detecting cancers, some of which would have progressed to advanced disease. The sensitivity of mammography for detecting cancer is estimated at 73% for women aged 60–69 years and 86% for women aged 80–89 years [37]. The specificity is estimated at 94% for women aged 70 years or more compared to 91% for women in their 40s, so the risk of false-positive results decreases with advancing age. Less data are available on the accuracy of clinical breast examination, but two series suggest its sensitivity falls after age 50 [29, 38]. For example, one study found an inverted U-shaped association between age and the sensitivity of clinical breast examination (e.g., 40–49: 26%; 50–59: 48%; 60–69: 36%; 70–79: 33%; and $\geq$80: 18%). These differences were significant for the oldest and youngest age groups compared to age 50–59 years. However, the reason for this decreased sensitivity in elderly women is unknown.

Individual patient characteristics also influence the likelihood of benefit or harm from screening. Advancing age, a family history of breast cancer, a longer duration of estrogen exposure, and a lack of previous mammograms all increase the risk of dying from breast cancer, which increases the chance to benefit from screening [4, 34]. Conversely, benefit is unlikely among women with serious comorbidity. Several studies have shown that detecting breast cancer at an early stage does not improve the survival of women with multiple comorbid illnesses (Charlson Comorbidity Index $\geq$2) [39]. In addition, based on the lag time between screening and survival benefit, older women who have a life expectancy less than five years are more likely to be harmed from screening than to benefit [8, 33].

Recommendations. There is no evidence that the benefit of screening mammography ceases at a specific age, so most guidelines recommend continuing screening mammography with or without clinical breast examination in women over age 70. Decisions to stop screening should be based on whether a woman has comorbidity that limits her life expectancy to less than five years (Table 2).

Cervical Cancer Screening

Evidence of Benefit. No randomized trial of cervical cancer screening has been conducted in any age group. However, multiple observational studies provide good evidence that cytologic screening using Papanicolaou (Pap) smears reduces the incidence and mortality from invasive cervical cancer in women less than age 65 [2, 5]. For example, a large number of case-control studies have consistently demonstrated Pap screening is associated with 60–90% reductions in the incidence of invasive cervical cancer, but few studies have included older women. Data suggesting that screening efficacy increases when Pap smears are performed more frequently also come from studies of younger women. In a study involving 1.8 million women aged 20–64 years, the incidence of invasive cervical cancer was reduced 64% when the interval between Pap smears was 10 years, 84% at 5 years, 91% at 3 years, and 93% at 1 year [40].

Evidence of Harm. A cohort study of 2,561 postmenopausal women aged 44–79 (mean age: 67 years) found that within two years of a normal Pap smear, 110 women had an abnormal Pap smear and all but one were false-positive [41]. To identify the one woman with mild to moderate cervical dysplasia, clinicians performed 5,019 Pap smears, 33 colposcopies, 8 endometrial biopsies, 35 endocervical curettages, 30 cervical/vaginal biopsies, 4 dilation-and-curettage procedures, and 9 cone biopsies/loop electrosurgical excision procedures, which all have attendant risks. An analysis of Medicare claims estimated that 39 per 1,000 older women who are screened will require at least one follow-up procedure within eight months [42].

Pap screening may also cause harm by detecting inconsequential disease. While cervical cancer typically develops 10–30 years after infection with oncogenic types of the human papilloma virus, the majority of infections cause only low-grade cervical lesions that regress without treatment [43]. Most women undergo treatment when these lesions are detected by screening because of the inability to identify which lesions will progress. Women who undergo treatment for screen-detected lesions that would have naturally regressed have been harmed by screening.

In addition, women who have abnormal Pap smear results frequently report high anxiety, partner discord, and low self-esteem [44]. This psychological distress may persist even after a normal follow-up examination.

Factors Affecting the Benefits and Harms of Screening in Older Adults. While cervical cancer screening has been shown to be efficacious in younger women, there is a paucity of data concerning the benefits of cervical cancer screening in women over age 70. Therefore, clinicians must weigh indirect evidence when deciding whether to generalize the benefits of Pap smear screening to older women (Table 1).

Cervical cancer in older women is not more aggressive than in younger women, based on the incidence of interval cancers that arise between screening tests [5, 45]. Localized cancer in elderly women also responds well to treatment and is associated with reduced morbidity and better survival than advanced disease [46].

However, anatomic changes associated with advancing age may decrease the accuracy of Pap screening. For younger women, Pap smear sensitivity ranges from 30–87% and specificity ranges from 86–100% [47]. The sensitivity of Pap smears is assumed to be less in older women because the target region for detecting cervical cancer, the squamo-columnar junction, moves higher into the cervical canal, making sampling more difficult. Specificity also may be decreased because atrophic changes that occur after menopause increase the vulnerability to inflammation, which can mimic neoplasia. More research is needed to definitively determine whether older women have more false-positive and false-negative results. In addition, the benefit of testing for human papilloma virus as an adjunct to Pap smear screening has not been evaluated in prospective studies, and evidence regarding its sensitivity and specificity is limited.

Therefore, individual patient characteristics are the driving forces for estimating screening benefit and harm. The main factors that decrease the benefit of Pap screening are a history of normal Pap smears, a limited life expectancy, or a hysterectomy [5, 6]. Older women who have no evidence of recent cervical abnormalities and have been screened regularly are at extremely low risk for developing cervical cancer (lifetime risk is less than 0.8%), and these women are therefore unlikely to benefit from screening [48]. The vast majority of older women who die of cervical cancer have not been regularly screened. Also, given the long preinvasive phase of cervical dysplasia, older women with serious comorbidity who have a life expectancy less than 5–10 years are more likely to suffer harm from screening than to benefit [8]. Lastly, older women who have undergone total hysterectomy (cervix removed) for a benign indication are not at risk for cervical cancer and should not be screened [48].

Recommendations. Most guidelines recommend that Pap smears be performed in women over age 70 who have not been regularly screened. Older women with repeatedly normal Pap smears may stop screening at age 65 or 70, as can women at any age who have a short life expectancy or who no longer have a cervix (Table 2).

Prostate Cancer Screening

Evidence of Benefit. To date, randomized controlled trials of prostate cancer screening have not demonstrated whether screening is beneficial in any age group. In addition, results of case-control studies of the effectiveness of screening for prostate cancer with prostate-specific antigen (PSA) or digital rectal exam have been conflicting. Until randomized trials of PSA screening are completed, the benefit of prostate cancer screening will remain uncertain for all men.

Evidence of Harm. False-positives are a concern with PSA screening. In the Prostate Cancer Prevention Trial, which included a substantial number of men aged 70 years and older, the false-positive rate for PSA > 4 ng/ml was approximately 6%, while it detected only 21% of prostate cancer cases [49]. In addition, the false-negative rate of prostate biopsy may be as high as 10–15%, so many elderly men with an elevated PSA and a negative biopsy will undergo repeated biopsies to rule out prostate cancer.

In addition, the major harms of prostate cancer screening are a result of the treatment of inconsequential prostate cancer that would never have come to clinical attention if not for screening. The large discrepancy between prostate cancer diagnoses and deaths in older men indicates than many cancers detected by screening are clinically inconsequential [50]. However, uncertainty about which prostate cancers identified by screening are clinically significant leads many men to undergo surgery, radiation, or treatment with hormonal agents. Men who undergo treatment for inconsequential prostate cancer have been harmed by screening, and these harms may be substantial. The major harms of treatment include urinary incontinence and erectile dysfunction, which are more common with surgery, and bowel dysfunction, which is more common with radiation. Men who receive androgen deprivation therapy also may suffer harm, such as fractures and constitutional symptoms [51].

In addition, men with an elevated PSA result frequently report having thought and worried about prostate cancer despite receiving a negative prostate biopsy result. Thus, screening may cause detrimental consequences on mental health [52].

Factors Affecting the Benefits and Harms of Screening in Older Adults. Unlike colorectal, breast, or cervical cancer screening, there is no convincing evidence that prostate cancer screening is efficacious in any age group. Two large randomized trials of PSA screening, which do not include men over age 75 years, have been ongoing for more than 10 years and have yet to definitively demonstrate a clinically significant survival advantage for men assigned to the screening group [53]. In addition, even if trials ultimately show that PSA screening has some efficacy in men younger than age 75 years, questions will remain about whether such findings should be extrapolated to older men.

It is uncertain whether there are differences in the aggressiveness of prostate cancer with advancing age that may change the benefit of early detection. In addition, there is professional disagreement about the value of prostate cancer treatment in older men. Results of a 10-year randomized controlled trial comparing radical prostatectomy versus watchful waiting in men with localized prostate cancer found that the reduction in prostate cancer mortality was limited to men in the treatment group who were younger than 65 [54]. Advancing age is also associated with higher treatment-related morbidity [55].

PSA screening is less accurate in older men. False-positive results are associated with benign prostatic hypertrophy, prostatitis, and advanced age. While raising the PSA biopsy threshold from >4.0 ng/ml to 6.5 ng/ml for men aged 70 years and older improves specificity, it decreases sensitivity [56]. Therefore, age-specific reference ranges are controversial and are not recommended by the FDA or PSA assay manufacturers. While other adjustments have been suggested to define an abnormal result (e.g., PSA density, PSA velocity, free PSA), these are not routinely used in clinical practice.

In addition, natural history studies and computer-simulation models suggest that men with a life expectancy less than 10 years will not benefit from PSA screening even under optimistic assumptions of screening efficacy [57]. Therefore, elderly men with comorbidity or functional impairments associated with low 10-year survival should not be screened.

Recommendations. Guidelines recommend that all men considering PSA screening should be educated about its uncertain benefits and potential harms. In addition, all guidelines agree that PSA screening should not be recommended to men who have a life expectancy less than 10 years. Therefore, screening should not be recommended to the majority of men over age 75 years and those with serious comorbidity (Table 2).

Integrate Patient Values and Preferences

Cancer screening decisions in older persons require weighing the potential benefits and harms for each individual rather than relying on arbitrary age cutoffs. Given the heterogeneity in life expectancy at older ages, we may find ourselves recommending efficacious cancer screening tests, such as colorectal cancer screening, to a healthy, vigorous 85-year-old while discouraging screening in an unhealthy, frail 75-year-old [58]. In addition, because the point at which the harms outweigh the benefits is subjective, it is important to talk with older patients about how much the potential benefits and harms of screening matter to them and whether they would agree to follow-up testing or treatment if required [7, 8]. Older patients who would decline follow-up or treatment should not be screened. In addition, for older patients who are bothered by the discomfort and risks of screening tests, the decrease in quality of life in the present may outweigh the small chance of future benefit.

In summary, the approach to making informed cancer screening decisions is similar to that for many other medical decisions in which the potential benefits and harms of testing are considered and patient preferences are understood. By encouraging informed individualized decisions, screening may be more appropriately targeted to older persons for whom the potential benefits outweigh the potential harms.

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Physiological Consequences of Aging

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Life expectancy has increased considerably over the past several decades, and this most certainly relates to public health measures, sanitation, advances in medical treatment, and lately, disease prevention strategies. Measured within an individual, one finds evidence for aging in almost all physiological systems. These changes alter the resting dynamic of older individuals and result in increased vulnerability, even to minor stressors [1], and amplifying risk for disease. For example, almost 50% of those aged 65 years and older have three or more comorbid conditions; among these, atherosclerosis, musculoskeletal dysfunction, and diabetes are the most common. Furthermore, the depletion of physiological reserve, coupled with the accumulation of various stressors, contributes to the clinical picture of "frailty." Physicians attending older people with cancer have begun to appreciate the inherent heterogeneity in geriatric populations and the importance of functional assessment. Whereas one 80-year-old might tolerate intensive chemotherapy well, another might succumb to serious drug-related complications. Deriving a method of assessing the overall physiological capacity has become a central goal of geriatric oncology. If successful, such an evaluation

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would allow practitioners to gauge treatments accordingly and promote a disability-free life expectancy for older individuals in general, and for older cancer patients in particular.

Physiological Changes with Age (Table 1)

Cardiovascular System

Several important changes occur in the cardiovascular system (CVS) in the elderly. These include an alteration in response to autonomic stimuli [2], a decrease in baroreceptor sensitivity and heart rate variability, and an increase in plasma norepinephrine levels, all of which indicate an increase in sympathetic activity and a decline in parasympathetic activity [3, 4]. Furthermore, there is an increase in arterial wall thickness, aortic lumen diameter, and vessel stiffness resulting from age-associated changes in collagen and elastin fibers, and lipid accumulation [5]. The net effect of these changes is an average 40% increase in systolic pressure, a 100% increase in pulse pressure [6], and a variable but common decrease in left ventricular diastolic filling with age [7, 8].

Renal Function

With age comes a progressive loss in the glomerular filtration rate (GFR) of approximately 1 ml/min/year after the age of 50 years [9–12]. Older people also exhibit an impaired response to protein load and higher basal renal artery resistance. These changes correspond to microscopically demonstrable glomerular and small vessel pathology [13–15]. Aging is also associated with lower plasma renin and aldosterone levels [16, 17] and decreased tubular concentrating ability [18, 19]. These changes predispose to hypertension, fluid and electrolyte imbalance, impaired

Table 1 Overview of major physiological changes with age

Organ systems	Changes	Effects
Cardiovascular	Increased sympathetic activity, arterial wall thickness, norepinephrine levels, decreased parasympathetic activity	Higher systolic pressures, wide pulse pressures Vasomotor instability
Renal	Decrease in GFR, low plasma renin- aldosterone levels, decreased concentrating ability, and reduced erythropoietin production	Predisposition to develop hypertension, fluid and electrolyte abnormalities, impaired handling of drugs, and a greater prevalence of CKD and anemia
Gastrointestinal	Decreased sphincter pressures, bile and fatty acids synthetic and absorptive capacity, altered hepatic enzyme function, intestinal architecture, and microbial flora	Increased risk for reflux, susceptibility to infection, alteration in hepatic metabolism of drugs
Musculoskeletal	Change in body composition with decrease in lean body and appendicular skeletal mass and increase in fat mass	Increased risk of falls, osteoporosis, diabetes, and frailty
Endocrine	Decrease in testosterone and dehydroepiandrosterone, IGF-1, and GH, altered cortisol circadian rhythm, changes in glucose metabolism	Increase in cardiovascular disease, osteoporosis, anemia, sarcopenia and impaired glucose tolerance
Immune/ inflammatory	Increase in memory B and T cells and decrease in naïve cells, change to a proinflammatory cytokine-secreting cells, increase in IL-6, TNF α, D-dimer, fibrinogen	Possible role in increase in cancers seen with age: role in frailty- and age-related diseases

Table 1 (continued)

Organ systems	Changes	Effects
Hematopoietic	Mildly reduced stem cell proliferative capacity	Mild anemia and neutropenia are common in the elderly and cytopenias are more pronounced after chemotherapy, radiation, or other marrow stressor

drug handling, and a greater risk for chronic kidney disease (CKD) [20] as well as an increased risk for osteoporosis [21] and a diminished overall functional capacity [20]. Age-acquired renal function impairment is also associated with a reduced production of erythropoietin, which is considered a major contributing factor to the commonly observed but often unexplained anemia of advanced age [22–24].

As important as this decline in renal function is with age, it remains very difficult to accurately assess. The currently available formulas to calculate GFR are likely to underestimate creatinine clearance in the elderly, and serum creatinine alone is also not reliable [10, 19, 25]. Serum levels of cystatin C, a cysteine protease inhibitor that is metabolized entirely by the kidneys and excreted freely, is a novel marker of kidney dysfunction [26]. Higher levels of cystatin C are associated with an increased risk of adverse outcomes, and lower levels identify elderly individuals at a reduced risk of death [27]. Curiously, although cystatin C levels in general correlate with other measures of creatinine clearance, the association with mortality was apparent in elderly patients with normal creatinine clearance (above 60 ml/min) as determined by the MDRD equation [26].

Gastrointestinal Function

Gastrointestinal function remains generally intact throughout the life span although symptoms are quite common in the elderly. There is an age-associated decline in gastrointestinal motility, sphincter pressures [28], and absorptive capacity, all of which may relate to changes in the intestinal architecture [29, 30]. Alterations in gut flora are also seen with age, increasing susceptibility to infections [31]. The rate and amount of pancreatic enzyme secretion decrease steadily from the third decade of life [32], and altered dynamics of hepatic circulation have been described [33]. Furthermore, certain liver enzyme pathways, including cytochrome P450 and those involved in bile acid synthesis, are altered by age [34], and this has important implications with regard to cancer treatment.

Cognition

There is a gradual age-associated change in certain aspects of cognitive function [35] primarily affecting memory, spatial ability, and tasks relating to executive function [36]. This may reach a point of clinical importance in somewhere between 9–30% [37–39] of otherwise healthy elderly people. Childhood intelligence [40] and level of education both influence the development of age-associated cognitive impairment [41]. Imaging studies show that changes in brain volume [42] and white matter damage [43] correlate with this age-related cognitive decline. However, it is not known if these imaging findings predict the development of the more serious types of dementia, including Alzheimer's disease [44].

Musculoskeletal System

Changes in body composition typically occur with age. There is a progressive loss of total bone mineral density after the age of

40 years, with greater declines in women than men [45, 46]. There are an age-associated decrease in fat-free mass and a corresponding increase in fat mass that become evident in advanced years [47] and are most pronounced in males over the age of 80 years. In general, weight loss is typically in lean mass, whereas weight gain is due to increased fat in older adults [48]. Consequently, there are an increase in the body mass index and an increase in central adiposity in elderly subjects [49]. It is estimated that men lose about 500 g and women about 200 g of fat-free mass per year, although the variability is quite remarkable in this regard [50].

Appendicular skeletal muscle, which is an important component of fat-free mass, also declines in the elderly, with losses ranging from 0.8–1.6 kg/decade in men and 0.4–0.6 kg/decade in women [51]. This loss of skeletal muscle mass, termed "sarcopenia," may occur in up to 50% of elderly males over 80 years of age [51–53]. Sarcopenia is often associated with a relative or absolute increase in adipose tissue [54], a condition now termed "sarcopenic obesity." The effects of these age-associated changes in body composition have deleterious consequences, including impaired physical function and performance and also impaired glucose and cholesterol metabolism. Lower muscle mass results in impaired strength [55], reduced mobility, and increased falls.

The increases in central adiposity (waist circumference $>$102 cm), body mass index (BMI), and fat mass also relate to impaired mobility [56], loss of physical function [47, 56–58], and increased risk of mortality [59]. Adipose tissue infiltration in the muscle also contributes to loss of muscle strength and declining physical performance [60, 61] as well as deterioration in glucose and cholesterol metabolism [62, 63].

The identification of sarcopenia is hampered by the lack of a standardized method to diagnose it. Currently, dual-energy x-ray absorptionometry (DEXA) is frequently used to measure total appendicular skeletal mass, and sarcopenia is estimated after adjusting for height. Recently, some have suggested that this may underestimate sarcopenia in obese individuals and that adjustment for body mass is more reliable [56]. Changes in chondrocytes, collagen structure, and articular surfaces of bone increase the risk for osteoarthritis [64], a major cause of morbidity in the elderly.

Endocrine Function

In both men and women, there are profound and well-characterized changes in the levels of certain hormones, which may have adverse consequences and even accelerate aging. For example, in women, a gradual decline in estradiol and an increase in follicular stimulating hormone (FSH) in the years preceding menopause [65] are followed by dramatic changes in these same hormones at menopause [66]. Menopausal hormonal alterations are associated with shifts in the lipid profile and accelerated blood loss, both of which have implications in the acquisition of age-associated diseases [67, 68]. That menopausal loss of estrogen may contribute to "aging" is exemplified by its relationship to certain proinflammatory cytokines. Estrogen bound to its receptor inhibits nuclear factor kappa B (NFκB) activation and, thus, downstream inflammatory pathways [69, 70]. The gradual rise in inflammatory mediators after menopause correlates with several features of aging and the development of frailty (see below).

Aging is also associated with a decline in sex steroids in men, a process that has been termed "andropause." Although more gradual than the hormonal changes of menopause, there are a notable decline in free and total testosterone levels and a corresponding increase in sex hormone binding globulin, FSH, and LH [71]. Also of note is the demonstrable fall in adrenal sex steroids, including dehydroepiandrosterone (DHEA) [72]. Studies have shown that lower testosterone levels are associated with an increased risk of fractures [73] and an increase in metabolic disorders, peripheral arterial disease [74], anemia [75], and cardiovascular disease, all of which cause mortality [74, 76]. Androgen deprivation in the treatment of prostate cancer is associated with an increased incidence of diabetes and cardiovascular disease as well as adverse cardiovascular outcomes [77]. Low levels of DHEA are associated with lower physical performance and depression [78].

Declines in growth hormone and insulin-like growth factor-1 (IGF-1) by more than 50% with age, referred to as "somatopause," result in reduced protein synthesis and possibly contribute to changing body composition [79]. Low levels of IGF-1 may also be directly related to impairment of cognitive functions in the elderly [80]. In contrast, serum cortisol levels increase with age and correspondingly prolong the duration of the stress response [81, 82]. Elevated cortisol levels have been associated with aging body composition, lower cognitive performance, bone loss, and an increased risk of metabolic disorders in the elderly [83–85].

Alterations in glucose metabolism, including decreased insulin release [86], decreased glucose uptake [87], and decreased beta cell sensitivity [88], occur commonly with age and account for a steady decline in glucose tolerance from the third decade of life onward [89].

Hematopoietic and Immune Function

With aging comes a gradual replacement of hematopoietic tissue within the bone marrow and a corresponding increase in adipose tissue [90]. Marrow erythroid and myeloid progenitor cells have less proliferative capacity, but under steady-state circumstances, these changes are insufficient to account for clinically important peripheral blood alterations [91–93]. Thus, when anemia, neutropenia, or thrombocytopenia occurs, the cause should not be attributed to aging per se, and a specific etiology should be sought.

Similarly, changes in immune function with age, termed "immune senescence," result in only mild to moderate dysfunction, and for those found to be more profoundly immune-deficient, other mechanisms are likely to be causative. That stated, there are both qualitative and quantitative changes that occur with advancing age in the absence of disease, and in sum they may render an individual more susceptible to certain pathogens, such as herpes zoster and tuberculosis, and less responsive to weak immunogens, such as the influenza vaccine.

Despite the rather modest clinical consequences of aging on immune function, an abundance of descriptive literature has shed light on both immune function in general and the biology of aging. Typical changes include an increase in “memory” and a decrease in “naïve” T and B components of the overall lymphocyte population [94–96]. Also well characterized is the gradual involution of the thymus gland from its peak in the second decade and throughout the remainder of the life span [90]. Furthermore, there are defective cytokine production by CD4 lymphocytes and a shift to a proinflammatory cytokine profile [97, 98], a change that has become increasingly recognized as potentially important in the pathogenesis of age-related diseases and frailty.

Inflammation, Coagulation, and Aging

The age-associated increase in inflammatory cytokines has been implicated in the pathogenesis of many age-related diseases and with the development of “frailty” [99] (see below). IL-6 is the prototype in this regard. In young adults, the expression of IL-6 is tightly regulated and serum levels are usually nonmeasurable or very low in the absence of inflammatory conditions. Animal studies reveal an increased production of IL-6 [100, 101] from peripheral mononuclear cells and lymphoid cells upon stimulation with lipopolysaccharide or other mitogens. Similarly, in humans, serum IL-6 levels increase significantly with age [102–106]. Other inflammatory proteins, including tumor necrosis factor-alpha (TNFα) and C-reactive protein

(CRP), are also seen at higher levels in the elderly [107–109]. Visceral adipose tissue from older mice expresses greater levels of both IL-6 and TNFα mRNA than younger mice [110]. Thus, some of the age-associated rise in IL-6 may be the consequence of those metabolic shifts mentioned above.

Presumably on the basis of chronic inflammatory stimuli, there is an age-associated activation of coagulation [111] and fibrinolytic [112] pathways that favor thrombus formation. Fibrinogen levels are typically high, with more than 80% of those aged 65 years and older having levels above 320 mg/dl [113]. Similarly, an analysis of D-dimer levels in the Established Population for Epidemiological Studies in the Elderly (EPESE), which included 1,727 community elderly, revealed an age-associated increase, and this correlated with declining overall physical function [114]. Furthermore, when combining D-dimer and IL-6 levels, it was discovered that those individuals who had elevations of both were at the greatest risk for mortality over a four-year interval [115]. In the Cardiovascular Health Study (CHS), which included relatively healthy elderly, higher fibrinogen and Factor VIII levels were associated with a greater risk for cardiovascular disease and mortality, even after adjustment for other cardiovascular risk factors [111, 116]. Summarizing what has now become a robust literature, it is apparent that higher IL-6, TNFα, D-dimer, and C-reactive protein (CRP) have each been associated with negative physiological consequences, including reduced lower muscle mass and strength [117, 118], cognitive decline [119], insulin resistance [120], subclinical and clinical cardiovascular disease [121, 122], renal insufficiency [123], loss of bone mineral density [124], depression [125], anemia [126], dementia [127], and mortality [118]. As a result, there is now a general consensus that activated inflammatory mediators contribute, at least in part, to the physiology of aging, and to the extent that these pathways are dysregulated, important functional outcomes are impaired.

Frailty

From a functional perspective, people age at different rates. A subset will fall into a pattern of advanced decline with profound functional impairment and poor outcome, a syndrome that is now recognized as "frailty." For an operational framework, frailty has been described as "a physiological syndrome characterized by decreased reserve and diminished resistance to stressors resulting from cumulative decline across multiple physiological systems and causing vulnerability to adverse outcomes" [128]. With aging there is a gradual decline in reserve, and when deficits occur, compensatory mechanisms are called upon to return an individual to his or her functional steady state. Almost all of those age-associated changes that occur in the absence of disease (i.e., physiological aging) are exaggerated in frail individuals [121, 129].

Although some will become frail without a diagnosed medical illness, obesity and the presence of comorbidities are certainly risk factors [130]. Nonetheless, certain features of frailty may be preventable or modifiable. Accordingly, instruments have been developed to quantify the degree of global impairment [131, 132], and clinicians are becoming increasing comfortable with these assessments. One common measure, the "frailty index," includes a history of weight loss, low grip strength, exhaustion, slow gait speed, and low physical activity [131] as factors used to derive the index. Those who meet criteria for frailty are at great risk for developing vascular disease [133], insulin resistance [134], anemia [135], institutionalization, and mortality [131, 132].

Inflammatory Cytokines and Cancer

It has long been recognized that inflammatory cytokines contribute the constitutional symptoms that accompany certain malignancies, including night sweats, fever, weight loss, and fatigue [136]. Recently, inflammatory and coagulant factors have also been investigated as possible biomarkers in various cancers. For example, high levels of plasma D-dimers were known to predict lymph node status and vascular invasion in early breast cancer, and progression and overall survival in both metastatic breast cancer and colorectal cancer [137, 138]. Similarly, IL-6 levels correlate with disease progression and/or survival in patients with multiple myeloma [139], non-small cell lung cancer [140], prostate cancer [141], and CRP (as well as IL-6) with renal cancer [142, 143]. To date, there remains no study examining the effect of the age-associated presence of inflammatory mediators and the subsequent development or clinical course of cancer. Although cancer is clearly more prevalent in the elderly, there is the curious observation that its prevalence may be less common among the frail when compared with nonfrail individuals of the same age [144].

Summary

Although aging should not be considered a disease, physiological changes occur over time that render an individual susceptible to disease and/or to adverse consequences of therapy. Physicians are becoming increasingly aware of the importance of accounting for age-associated physiological changes when developing treatment strategies, and this is particularly important in the management of older patients with cancer. In this regard, there has yet to be established a single reliable biomarker or clinical assessment tool that will serve this purpose. Well-informed physicians may do well for their patients by applying sound judgment based upon an awareness of the effects of aging, but in order to advance the field of geriatric oncology, a uniform appraisal that incorporates key biochemical markers and a standardized clinical assessment will be essential to providing evidence-based advances in patient management.

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Assessment and Impact of Comorbidity in Older Adults with Cancer

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Assessment of Comorbidity

Cancer is increasing with age. Almost 60% of cancers and two thirds of cancer deaths occur beyond the age of 65 years in developed countries [1]. Due to the aging of the population, this proportion is expected to increase in the future. Older patients present with increased concomitant diseases. In a geriatric series, people 65 years of age and older suffer on average from three different diseases, and, similarly, older cancer patients present a high level of comorbidity [2–5]. Furthermore, comorbidity does not appear to correlate closely with either tumor stage or functional status. Therefore, comorbidity should be assessed independently [3].

Contrary to functional status, comorbidity is a multidimensional variable. Many validated tools are available to measure it, and each has specific characteristics and differences regarding its ease of use and validity in measuring comorbidity. Among them, oncology authors most frequently use in different settings the Charlson Index [6], the Cumulative Illness Rate Scale [7] with the Geriatric module (CIRS-G) [8], the Index of

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Coexisting Diseases (ICED) [9], the Kaplan-Feinstein Index [10], and the Adult Comorbidity Evaluation 27 (ACE-27) [11], with Charlson being the most widely used [12]. In the transplant setting, the Sorror Index is also used [13].

The Charlson is simple and highly suitable for vast cohort studies but may underdetect significant problems resulting in nonlethal endpoints. In contrast, the CIRS gives a very accurate profile of comorbidity prevalence but may overdetect minor problems that may confound its prognostic ability, although head-to-head studies with the Charlson have demonstrated no such effect on the correlation with mortality. The CIRS is the most detailed but, along with the ICED, is the most complicated to rate of the indexes presented. In addition, the Kaplan-Feinstein Index and its later development, the ACE-27, have shown results that are reproducible in a way similar to the Charlson and offer a more detailed grading of some comorbidities than the Charlson while remaining simple to use. A good measurement and understanding of comorbidity, as well as its interaction with other health problems of the older cancer patient, will be the key to future progress in geriatric oncology, notably when it comes to expanding cooperative study results to the general population of older cancer patients. Assessing comorbidity with the use of institutional lists of diseases should be avoided since there are a number of validated tools. This will allow the use of a common "language" for clinical trials and interpretation of the results in relation to comorbidity.

The Charlson Comorbidity Index

The Charlson Comorbidity Index [6] is based on the one-year mortality of patients admitted to a medical hospital service. The relative risk of death associated with several conditions was assessed. Any comorbidity that implied a relative risk of death greater than 1.2 is used in the scale and weighted, which leads to a scale with 19 diseases weighted from one to six points.

The total score is calculated. It can then be collapsed into four ordinal categories: 0, 1–2, 3–4, and >5 points. The index was validated in a cohort of breast cancer patients, with the 10-year mortality rate as an endpoint. In the validation cohort, the Charlson was adjusted for age using the following formula: Each decade of age, starting at 50 years of age, was counted as an extra point. It is valid in predicting mortality risk over a period of a few weeks to 10 years in conditions ranging from breast cancer to spine surgery, and it has also been validated in older cancer patients [3]. Its performance in predicting mortality is in the range of that of the CIRS and the Kaplan-Feinstein scale [6, 14]. Potential limitations in oncology include the fact that the index ignores several comorbidities that may be relevant in designing the treatment of cancer patients, such as hematopoietic disorders other than malignancies, polyneuropathy, or moderate renal dysfunction. The Charlson is very easy to complete, especially if the criteria for rating comorbidities are preprinted. The rating criteria are well defined in the appendix of the original paper [6] and are fairly easy to memorize for a frequent user. Its ease of use is without a doubt part of its success. The Charlson has been adapted to databases via the ICD-9 codes; therefore, it could also be used in epidemiological studies (see below). The Charlson can also be extracted fairly easily from a CIRS-G score, given a few precautions.

The Cumulative Illness Rating Scale

The Cumulative Illness Rating Scale (CIRS) was first designed by Linn and colleagues in 1968 [7]. It is aimed at a comprehensive recording of all the comorbid diseases of a patient. Its principle is to class comorbidities by organ system affected, and rate them according to their severity from 0 to 4, in a way similar to the Common Toxicity Criteria grading (none, mild, moderate, severe, extremely severe/life-threatening). Within each category, if two diseases are present, the disease with the higher severity is counted. The scale can then be summarized as a total number of categories involved, total score, mean score, or number of grade 3 or 4 diseases. Linn and colleagues did not define precise diseases/rating associations, and relied on the physician's judgment. Later authors have added slight modifications to the list of organ systems or, in trying to enhance interrater reliability, have designed a rating manual [8]. As a result, the CIRS has 13 (or 14 in recent versions) organ system subdivisions. These are cardiac, vascular (in recent versions, subdivided either between vascular and haematopoietic (CIRS-G [15]), or vascular and hypertension [16, 17]), respiratory, eyes, ears, nose, throat, and larynx (EENT), upper GI, lower GI, liver, renal, other genitourinary (GU), musculoskeletal/integuments, neurological, endocrine/metabolic, and psychiatric. An adaptation that is particularly interesting for geriatric oncologists is the CIRS-Geriatric (CIRS-G) designed by Miller and colleagues, with a multidisciplinary rating manual aimed at a geriatric population (and therefore detailing several geriatric problems in the list) [8].

The Index of Coexistent Diseases

The Index of Coexistent Diseases (ICED) was developed by Greenfield and colleagues in 1987 to address issues of intensity of care [9]. It consists of two subscales: physical and functional. In the ICED's present version, the physical subscale rates comorbidities from 0 to 4 in severity (the same principle as the CIRS) and regroups them in 14 categories: organic heart disease, ischemic heart disease, primary arrhythmias and conduction problems, congestive heart failure, hypertension, cerebral vascular accident, peripheral vascular disease, diabetes mellitus, respiratory problems, malignancies, hepatobiliary disease, renal disease, arthritis, and gastrointestinal disease. The diseases are graded according to a manual. The functional subscale contains 12 domains of functional impairment, rated 0–2. Each scale is then summarized by the highest score obtained, and both scores are lumped together to form an overall severity score ranging from 0 to 3.

The ICED can be used to extract some functional information from medical records. It can be very interesting for studies where a distinction between functional status data and comorbidity is not necessary, and where a global "host cofactor" measurement is sought. Its structure still allows the extraction of pure comorbidity information afterward.

The Kaplan-Feinstein Index

The Kaplan-Feinstein Index was developed in 1974 [10]. It consists of a list of conditions grouped in 12 categories (hypertension, cardiac, cerebral or psychic, respiratory, renal, hepatic, gastrointestinal, peripheral vascular, malignancy, locomotor impairment, alcoholism, and miscellaneous) and rated 0–3 according to severity. The severity criteria are well defined. The number and severity of diseases are then summed in an overall comorbidity grade from 0 to 3.

The index has been used in many studies in various settings and correlates with mortality in patients with several medical conditions, including breast and prostate cancer patients [10, 18–20]. It has also been integrated in predictive scores of cancer outcome for prostate and head and neck tumors [19, 21].

The rating instructions are simpler than those of the CIRS and the ICED and are closer to the simplicity of the Charlson. The Kaplan-Feinstein data are not directly translatable in other comorbidity scales.

The Adult Comorbidity Evaluation 27 Index

The Adult Comorbidity Evaluation 27 (ACE-27) is a validated comorbidity index for cancer patients, developed from Piccirillo and colleagues at the Barnes-Jewish Hospital, Washington University School of Medicine [11]. It consists of a list of 27 specific diseases and conditions that can be extracted from the medical records. The instrument was developed through modifications and additions of comorbid ailments to the Kaplan-Feinstein Comorbidity Index. The ACE-27 grades comorbid conditions into one of three levels of severity according to the individual organ decompensation and prognostic impact. An overall comorbidity score (none, mild, moderate, or severe) is assigned based on the highest-ranked single ailment. The prognostic value of comorbidity measured by the ACE-27 was shown in a large observational prospective cohort study from the same center [22]. The level of comorbidity was an independent prognostic factor for survival for many solid tumors, and the relevance was stronger for cancer primaries with longer mean survival, such as breast and prostate cancer.

The Sorror Index

The Sorror Index was developed specifically for the bone marrow transplant setting [13]. Compared to the Charlson score, it uses more numerical definitions of the disease severity, as is readily available in the transplant setting. It collapses the total score into low-, intermediate-, and high-risk groups for nonrelapse mortality. This index has been also used to compare transplant outcomes among institutions [23].

Indexes Used in Epidemiologic Databases

Some indexes have been adapted or developed for databases. As the severity of a disease is often difficult to extract retrospectively from partial medical records or databases, databases usually use a template of ICD-9 or -10/Medicare codes instead of a direct severity rating. The index with the most adaptations is the Charlson index [24–27]. Another index was derived from the Charlson by Klabunde et al. specifically for cancer patients [28, 29]. This index weighs ICD-9 codes from inpatient and outpatient claims, with the aim of predicting noncancer deaths. Cancer-specific weighting of comorbidity is used (e.g., breast, colorectal, lung, and prostate). This might increase the precision in research focusing on one cancer type, but might create confusion in patients with multiple cancers (one in five older cancer patients).

Impact of Comorbidity

Comorbidity may influence cancer patients in many aspects, such as treatment decision, treatment tolerance, and, finally, cancer prognosis. There are only a few clinical trials that incorporate an assessment of comorbidity, and so it is difficult to define the exact role in each aspect of cancer management [30, 31].

Comorbidity and Treatment Decisions

The presence of comorbid diseases can influence treatment decisions and influence survival by leading to suboptimal care. This was shown in patients with various cancers, where less surgical treatment, radiotherapy (RT), and chemotherapy was offered to patients with comorbidity.

In a large cohort from the Netherlands, older patients and those with increased comorbidity were less likely to undergo surgical resection for non-small cell lung cancer (NSCLC) and axillary lymph node dissection for breast cancer. Comorbidity was measured retrospectively from medical records with the use of a modified Charlson Index scale [32]. Aside from age, comorbidity influenced the decision for radiotherapy treatment in patients with lung cancer, breast cancer, and non-Hodgkin's lymphoma (NHL). Patients with comorbid conditions and stage I and II NSCLC received RT as single treatment more often while patients treated with breast-conserving surgery had a lower chance of receiving adjuvant RT when they had at least one concomitant disease. Patients with aggressive NHL and comorbidity received RT in combination with chemotherapy less often. Comorbidity was measured with a modified Charlson Index score retrospectively [33].

In breast cancer patients, age and comorbidity tend to minimize treatment options and increase the risk of death from causes other than breast cancer, as was shown several years ago [34].

In a recent study using data from the SEER Registry in a sample of 1,800 women diagnosed with breast cancer in 1992, it was shown that women older than 70 years of age and those with comorbid diseases were less likely to receive what was considered the standard treatment at that time. Treatment options such as breast conservative surgery and axillary lymph node dissection were offered less often to these women. The assessment of comorbidity was done retrospectively from the medical records without using a specific tool [4].

In a relatively small cohort of patients with stage III NSCLC, age, grade 4 comorbidity assessed by CIRS, and weight loss were independent factors for offering combined modality treatment with chemotherapy and radiotherapy. Comorbidity and age were also independent factors for inferior overall survival [35].

Comorbidity and Cancer Prognosis

Comorbidity (general and specific diseases) also influences survival in cancer patients independently of the influence on treatment decision for various cancer types.

General Comorbidity

Comorbidity measured by the Adult Comorbidity Evaluation 27 (ACE-27), a validated chart-based instrument, in a large cohort of adult patients with different cancer types (prostate, respiratory tract, digestive system, gynecological, urinary system, and head and neck), was an independent prognostic factor for survival [22].

In a study from the Netherlands, comorbidity, along with older age, was also associated with increased perioperative morbidity and mortality in patients with colorectal and non-small cell lung cancer [32].

There are many data from a number of studies in both early- and advanced-stage NSCLC disease regarding comorbidity and survival with controversial results. Increased comorbidity was associated with decreased survival in most of them [36–39], while others failed to show such a relation [40, 41]. It is important that in most of these studies, comorbidity was measured using validated tools such as the Charlson score [36–41], the CIRS-G [37, 41], and the Kaplan-Feinstein Index [41]. The same negative influence of comorbidity in survival was shown in a small series of SCLC patients [42].

Large series also highlighted the same negative impact of increased comorbidity in prognosis of breast [29, 43–45], head and neck [46], and colon cancer patients [29, 47] .

In AML, comorbidity (measured with Charlson score index) was a predictor of response to treatment in elderly patients [48]. It is also a predictor of mortality in transplant patients [13, 49].

Diabetes

The role of diabetes mellitus on survival in colon cancer was studied in a large intergroup randomized trial of stage II and III disease patients who received adjuvant treatment. In that study, diabetes mellitus was an independent factor for worst time to progression (TTP), disease-free survival (DFS), and overall survival (OS) [50].

In contrast with the above study, another study showed that diabetes mellitus was not associated with colon cancer death, but with death from other causes [51].

Obesity

Obese women (BMI $>$ 30 Kg/m^2) had a higher mortality risk and a nonsignificant increase in disease recurrence for colon cancer. This was not observed for the men in the study [52]. Furthermore, obese patients with rectal cancer were less likely to undergo a sphincter preservation surgery and had more local relapses after postoperative chemoradiotherapy in an intergroup trial reported by the same author [53].

Obese women (BMI $>$ 30) with ovarian cancer have a shorter time to recurrence and survival [54]. A large number of reports suggest that obesity is associated with poorer outcomes in women with breast cancer [55–64]. This observation was confirmed prospectively in a recently published study [65]. In that study, BMI and, even stronger, fasting insulin levels were significantly related with poorer DFS and OS in women with early-stage breast cancer. There was a strong correlation between BMI and fasting insulin levels as well.

There is also evidence that hyperinsulinemia and other components of the metabolic syndrome are related to a worse prognosis in prostate cancer. Obesity is related with more aggressive histology, faster PSA progression, and, most important, earlier death [66].

Rheumatoid Arthritis

It has been well known for many years that patients with rheumatoid arthritis have an increased risk of developing NHL. A retrospective study showed that these patients have better NHL-related treatment outcomes and a lower risk of relapse. However, that was not translated to better survival due to an increased risk of death from causes other than lymphoma [67].

Depression

The negative role of depression in survival was shown in a study of ovarian cancer. Depression in presentation was an independent prognostic factor for overall survival in elderly patients treated with the carboplatin plus cyclophosphamide combination [68].

Comorbidity and Treatment Tolerance

Another important role of comorbidity in elderly cancer patients is the influence on treatment tolerance. Data from subgroup analysis of many clinical trials indicate that toxicity was similar or slightly increased for older patients in comparison with younger patients, but only a few studies that measured comorbidity are available. In an elderly-specific study from Italy, comorbidity measured with Charlson Index influences both survival and treatment tolerance in patients with advanced NSCLC [40].

In a large Norwegian phase III study with carboplatin-based doublets in advanced NSCLC presented recently, comorbidity of elderly patients, assessed from medical records using the CIRS-G instrument, was associated with a higher incidence of neutropenic infections and thrombocytopenia, while there was no correlation with overall survival, even for patients over 75 years of age [69].

Conclusion

Cancer is a disease of older age, and with the aging of the population, the percentage of elderly patients with cancer will continue to increase. Older cancer patients have more comorbid diseases that complicate the oncologic approach of their disease. There are data showing that comorbidity influences both treatment decision and treatment tolerance and finally survival of elderly cancer patients. There is a great need for further research on the role of comorbidity in patients with cancer in order to better define the best treatment for these patients; that can be accomplished by incorporating an assessment of comorbidity in randomized trials. Several validated tools are available for measuring comorbidity. Their use should be preferred instead of general lists of diseases in order to better reproduce and compare the data among the different studies. The various tools have different characteristics; there is no clear general advantage of using one against the others. This is a field for further research.

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Geriatric Syndromes Defined and Explained for Oncology Practice

Miriam B. Rodin

Introduction

This chapter addresses three goals. The first is to explain the concept of geriatric syndromes. The second goal is to provide guidance so that geriatric syndromes can be anticipated and recognized in oncology practice. The third is to offer suggestions for managing and preventing selected geriatric complications of cancer treatment. As such, this chapter is not intended to be a pocket guide to geriatrics. It is intended to raise awareness of geriatric syndromes to trigger appropriate geriatric referral as an adjunct to cancer treatment.

The reason why it is important for oncologists to recognize and appreciate geriatric syndromes is that most solid tumors and many hematologic malignancies are diseases of old people. There are projected to be about 40 million people over age 65 in the United States in 2010. That number is expected to double by 2050 [1, 2]. The most common cancers are the solid tumors that occur most frequently in older people. As shown in Table 1, more than half of all new cases in 10 of the 15 most common adult malignancies are diagnosed in Medicare-age patients; and more than half of all cancer deaths occur in

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Table 1 Proportion of incident tumors by site and site-specific mortality among patients aged $\geq$ 65 years, 2000–2004 [3]

Site	Incidence percent	Mortality percent
Colon and rectum	70.2	74.8
Pancreas	69.2	72.8
Prostate	63.8	90.9
Bladder	72.2	84.4
Stomach	65.5	70.6
Lung	67.8	71.1
All sites	55.8	70.2
Leukemias	54.3	71.3
Kidney	50.9	66.3
Corpus uteri	45.3	73.1
Non-Hodgkin's lymphoma	54.3	73.4
Head and neck	44.7	58.0
Breast	42.3	58.0
Ovary	47.0	66.0
Brain	34.7	48.2

14 of 15 of these most prevalent sites [3]. Therefore, the diagnosis, treatment, and outcomes of cancer will involve the management of age-associated noncancer comorbidities, increased vulnerabilities, and syndromes of aging.

What Is a Geriatric Syndrome?

The term "geriatric syndrome" has, in the opinion of some authorities, undergone semantic drift to the point that the significance of the core concept has been lost [4]. In general, in medicine, the term "syndrome" is used to describe signs and symptoms that characterize the typical presentation of a disease of known or unknown causation. Even without knowing the etiology, physicians can understand the pathologic changes in organ function and provide supportive care. Geriatricians have emphasized the probability that common diseases or conditions may have atypical presentations, such as pneumonia presenting as a fall and myocardial infarction presenting as delirium. So when physicians speak of geriatric syndromes, they are referring to signs and symptoms that are unusual in the young, but not necessarily pathognomic of any single underlying condition in the elderly. In general, in medicine, the presenting signs and symptoms cluster to form a pattern that narrows the search for the underlying disease. In geriatric syndromes, several different underlying diseases may have the same clinical presentation; and the same underlying problem may present itself in several different ways [4]. The organ showing the syndrome may not be the one experiencing the acute pathology. Or worse, the underlying problem may not be confined to one organ.

Table 2 shows a schematic representation of how diseases and syndromes may be described. The clinical approach to diseases can be confirmatory, where a disease looks like Disease x and physicians order the confirmatory test. Alternatively, the clinician may recognize a disease entity with unknown causation or poorly understood pathophysiology and provide successful "empiric therapy." Compared to these scenarios, the clinical presentation of a geriatric syndrome often points away from the failing organ, does not localize to any particular organ system, or may represent the failure of minimally compromised organs to function together.

The unifying concept behind aging is loss of homeostatic reserve. Young and healthy humans have more than enough organ reserve to carry them through a physiologic challenge such running a marathon, falling into icy cold water, or undergoing cancer chemotherapy [5]. Furthermore, their organ functions are smoothly integrated and follow precise diurnal cycles. Blood pressure, pulse, and respiration have wide ranges of values in response to environmental demand. The serum glucose never wavers, because the young can pump out as much insulin as needed, and their cells take it up with undiminished avidity. The hallmarks of aging are loss of variability, loss of integrated cycling, loss of signal transduction efficiency, and thus loss of homeostatic reserve. Therefore, for an old person finely balanced within a narrow band of demand, even small perturbations can result in failure of the whole organism [6].

A task force of leading geriatricians undertook a systematic evaluation of the literature on geriatric syndromes, confirming that they are highly prevalent among the elderly, characterized

Table 2 A schematic representation of the relationship among pathophysiology, etiology, and clinical approach to diseases, classical syndromes, and geriatric syndromes

Disease vs. syndrome	Etiology or exposure	Pathophysiology (organ malfunction)	Presenting signs and symptoms	Clinical approach
Disease	Known	Known	Common and uncommon presentations	Confirmatory focused investigation
Syndrome 1	Unknown	Known	Defined by the clinical presentation	Diagnosis of exclusion
Syndrome 2	Known	Unknown	Defined by the clinical presentation and known exposure	Supportive therapy
Syndrome 3	Unknown	Multiorgan Involvement	Defined by clinical course	Supportive therapy, diagnosis of exclusion
Geriatric syndrome	Multiple risk factors	Multiorgan, often with apparently minimal compromise	Defined by the clinical presentation	Broad investigation to identify etiology

*Source:*Adapted from Inouye et al.'s [7] adaptation of the Olde Rikkert [4] schematization.

by impairments affecting more than one organ system, and associated with substantial morbidity and poor outcomes for medical care [7]. Furthermore, experienced geriatricians also recognize that geriatric syndromes tend to cluster; patients who present with one geriatric syndrome are likely to manifest others as well. The expert panel focused its analysis on identifying the common risk factors of five well-studied, highly prevalent geriatric syndromes: pressure ulcers, incontinence, falls, functional decline, and delirium [7].

The five syndromes shared four common baseline risk factors: older age, cognitive impairment, functional impairment, and impaired mobility. However, except for age, each risk factor is itself multifactorial and may involve some component of the other. The principal value of identifying these risk factors is that they are easily and reliably measured, have a range of severity, and may be remediable by targeting rehabilitation therapies to the individual or by modifying the environment to decrease the performance demand on the patient.

Waiting to Exhale: Anticipating Geriatric Syndromes

What does this mean for oncologists? Routine comprehensive geriatric assessment (CGA) has been urged on clinical oncologists [8, 9]. The screening tools proposed by expert panels include a variety of functional measures both self-reported and directly observed. The value of CGA data for prognostication and for improving outcomes has yet to be shown in the specific application to cancer treatment. All have been shown to be robust predictors of medical outcomes in the community and in medical populations. In oncology, decisions about treatment, home monitoring for adverse treatment-related events, and quality-of-life outcomes all involve having accurate predictions of risk for unplanned hospitalization in specific individuals.

A semistructured Medline search on the term "geriatric syndrome" yielded a list of over two dozen items that included age-associated diseases, risk factors for disease-related outcomes, sentinel events, "conditions," physical findings, and symptoms. The list included dementia, delirium, depression, dysphagia, sensory impairment, pressure ulcers, and osteoporosis; falls, abuse, neglect, self-neglect (Diogenes syndrome), polypharmacy, adverse drug events, and iatrogenesis; frailty, fatigue, immobility, deconditioning, malnutrition, weakness, functional decline, functional dependence, cognitive impairment, confusion, and insomnia; incontinence, weight loss, dizziness, anorexia, and constipation.

Table 3 presents an extensive list of conditions that have been called geriatric syndromes. Yet as shown in Table 2, they may be usefully classified as symptoms of known age-associated diseases in order to focus the clinical approach. The following discussion examines four common geriatric syndromes because of their specific relevance to cancer treatment. These are weight loss, falls, cognitive impairment, and polypharmacy.

Weight Loss, Cancer Cachexia, and Sarcopenia of Aging Are Not the Same Thing, but Does It Matter?

Weight loss and nutritional deficiencies are common to cancer and to aging. For elderly cancer patients, the correct diagnosis of weight loss and therapeutic interventions are going to be complex. Any unintended weight loss in the elderly should trigger an appropriate investigation because weight loss by itself is a risk factor for functional decline and reduced life expectancy [10–12]. In the absence of obvious disease such as end-stage COPD or CHF, or an inflammatory process such as osteomyelitis, rheumatoid arthritis, or TB, cancer is a likely diagnosis in old people with rapid weight loss. Specifically, rapid weight loss is associated with certain of the solid tumors [13, 14] more so than the hematological malignancies. Weight loss as the presenting sign of cancer nearly always indicates advanced disease [15–17]. Weight loss, in the absence of an easily imaged tumor, may be due to another cause entirely that would clearly complicate the treatment of localized cancer [18].

Table 3 Classification and differential diagnosis of common geriatric "conditions"

Classification	Diagnosis	Differential diagnosis
Geriatric syndromes	Decubitus ulcers	Immobility after acute hospitalization vs. end of life
	Delirium	Drugs, endocrine, low blood pressure, infection, respiratory, immobilization and pain, urinary tract infection/retention, metabolic and electrolyte disorders
	Falls	Multifactorial; see risk factors
	Frailty	Primary age-related vs. comorbidity-related
	Incontinence	Multifactorial; see risk factors
Risk factors	Cardiovascular diseases	Duration and severity
	Functional decline	Rapidity of decline
	Low body weight	Rapidity of weight loss
	Muscle weakness	Environmental demand exceeds capacity
	Nursing home residence	Patient care demand exceeds capacity of home care
	Orthostatic hypotension	Drugs, neuropathy, cardiac function
	Polypharmacy	Appropriate vs. inappropriate
	Slow gait	Primary frailty, cardiopulmonary, orthopedic, central neurologic disease, neuropathy, vascular

Table 3 (continued)

Classification	Diagnosis	Differential diagnosis
Age-associated diseases	Osteoarthritis	Joint replacement, palliative therapy
	Cancer	Curative vs. palliative therapy
	Dementia	Behavioral management, caregiver education, drugs
	Depression	Effective drug therapy, ECT
	Osteoporosis	Hormone deficiency, drug therapy
	Sensory deficits	Cataracts, macular degeneration, neuropathy, retinopathy, presbyopia, presbycusis
Symptoms	Anorexia	Therapy depends on cause
	Constipation	Age-associated slowing of colonic transit time, drugs
	Dizziness	Vertigo vs. syncope vs. presyncope vs. central disequilibrium vs. drug effects, can be chronic
	Dysphagia	Oral phase: dementia, delirium vs. pharyngeal phase stroke, prolonged intubation, Parkinson's and related diseases
	Fatigue	Effective therapy depends on cause
	Insomnia	Age-related decreased REM, Stage 4 sleep vs. other causes: drugs, dementia, depression, OSA
	Nocturia	Diuretics, venous pooling, loss of diurnal ADH cycle, (detrusor instability)
	Weakness	Multifactorial

ECT: Electroconvulsive therapy; REM: Rapid Eye Movement
OSA: Obstructive Sleep Apnea; ADH: Andiuretic Hormone

Weight loss is one of five criteria defining frailty, an age-associated syndrome characterized by loss of muscle strength, loss of muscle mass (sarcopenia), neuromuscular slowing, subjective fatigue, and declining activity levels [19]. Although frailty and cancer share some features, the frailty phenotype and the phenotype of advanced cancer are physiologically and prognostically distinct [20]. It is important to distinguish the two because the search for an occult or nonexistent cancer imposes a heavy diagnostic burden on frail patients. Furthermore, preexisting frailty is associated with various poor prognostic outcomes, but survival may be quite long compared to cancer. Several studies have shown that the association of wasting, or cachexia, with survival in advanced cancer is stronger and more predictable than the association with muscle wasting of aging, or sarcopenia [21–23]. For the increasing numbers of elderly presenting with both frailty and cancer, the treatment will necessarily involve modifications of treatment and supportive protocols as well as a careful history of usual weight, appetite changes, and the trajectory of weight loss.

Cancer-associated weight loss is always an adverse prognostic factor [17]. The differential diagnosis of unintended weight loss itself has subtypes [21]. To paraphrase, weight loss can be attributed to three general causes. Starvation results from poor intake due to anorexia, dysgeusia, dysphagia, odynophagia, depression, nausea and vomiting, and oropharyngeal dysfunction. Disturbances of digestion include malabsorption, fluid losses, constipation, obstruction, and autonomic dysfunction. Wasting may be due to a pathology of intermediary metabolism, which includes failures of anabolic metabolism such as sarcopenia of aging, hypercatabolism, as seen in cancer, and inflammatory wasting. Mixed processes occur in specific disease-related wasting as in end-stage heart, lung, liver, renal disease, and HIV [12]. With regard to the last group, weight loss and cachexia can be classified empirically by whether improved nutrient intake affects weight loss/gain and whether anorexia is a prominent component of decreased intake [21, 24, 25]. In cancer cachexia the contribution of anorexia seems to vary by tumor type, and the specific expertise of the oncologist is required to determine whether wasting and weakness are due to the cancer or to another process [16].

Effective nutritional interventions for the elderly often differ from general advice to take supplements or eat a balanced diet. Aside from the physiology of aging, the social and functional milieu of the aged demands special attention to dietary recommendations. For example, cardiac diets are widely urged on the elderly but may even be harmful to elderly at nutritional risk at baseline or due to cancer and cancer treatment. There are functional eating problems as well [21]. Elderly who are independent may become dependent on others for transportation, shopping, and cooking during cancer treatment. Specific interview questions or standardized screenings devised for the elderly, such as the Short Nutritional Assessment Questionnaire (SNAQ), may be needed to elicit these data [26, 27]. An elderly woman with a long history of "eating lightly" and early satiety due to COPD may not report a change in appetite unless the question is asked in various ways. The sweet taste of supplements is not always acceptable to some elderly.

Falls, Function, and Fractures

Falls are a sentinel event among the elderly. It is so important and such a well-documented prognostic measure that Medicare selected documentation of fall history as a Pay-For-Performance quality indicator [28]. It has been shown in many observational studies that standardized assessments of walking can predict the risk for falls [29]. Falls are sentinel events for an elderly person's ability to live safely alone at home and to avoid injury. The three components of walking are gait, speed, and dynamic balance. These components demonstrate whether the patient has the muscle strength for a low-demand task, since walking should be energy-efficient, and allows a global clinical assessment of integrated neurological function. This is quite a different approach from isolated muscle group and single neurological pathway testing that are taught in medical school physical examination courses. Mobility problems, such as the new onset of ataxia, may signify metastatic disease, but a preexisting unsteady gait is not likely to improve during cancer treatment. A fall even without a fracture can be devastating.

Recognizing the risk of fractures for patients receiving hormone deprivation therapy for breast and prostate cancer has changed practice to consider using preventive bisphosphonate therapy [30–33]. The quality of bone, however, is not the only risk factor. The likelihood of falls is the other. The Tinetti Gait and Balance Scale [34] permits a rapid, reproducible assessment of fall risk linked to mobility. A different rapid assessment tool, the Short Physical Performance Battery (SPPB), includes part of the Tinetti Scale and measures gait speed, also shown to be a strong predictor of fall risk [35, 36]. Both are freely available with scoring instructions.

Bylow et al. examined the usefulness of these tools for falls assessment for a small group of men receiving androgen deprivation therapy (ADT) for advanced prostate cancer [37]. They were asked about functional impairment and history of falls and observed for gait. Deficits were noted in all three component areas of this assessment. More than one in five (22%) reported recent falls, and 10% reported more than one fall over the previous three months. This is double the 11% of patients who reported falls in a general outpatient geriatrics population. Supporting this finding, 52% of the men reported impairment in their self-perceived physical health, 24% reported difficulty stooping, crouching, or kneeling, and 32% reported difficulty walking a quarter of a mile. In these data, age, activities of daily living (ADL) deficit, and independent activities of daily living (IADL) deficit were all associated with an abnormal physical performance as measured by the SPPB. ADL deficit and the use of a cane or walker were associated with an increased risk of falls in this sample. At three months' follow-up, 20% of men had worsening of SPPB scores (defined as a decrement of 2 or more points out of 12). Of those with a history of falls, over half experienced additional falls. Of those with no history of falls, 12% experienced a new fall over those three months. Therefore, men with prostate cancer on ADT constitute a population at high risk for falls with injury. Usual cancer care of the elderly should include screening for falls whether by asking a single question [38] or by using well-validated screening tools such as the SPPB and the Tinetti Gait and Balance Scale.

Delirium, Dementia, and Decisional Capacity

Abundant research has shown that physicians, contrary to their own opinions, are not very good at determining decisional capacity [39–41]. When dementia is severe, it appears that cancer patients with diagnosed dementia receive appropriately less treatment [42]. Many patients with mild dementia may not appear to be impaired. Clearly, it is not the oncologist's job to diagnose dementia, but it is necessary to recognize decisional incapacity when treatment decisions involve assumptions of variable risk to benefit [43]. That being said, patients with evident cognitive impairment can still have decisional capacity about their care [44, 45]. The prevalence of cognitive impairment among oncology patients appears to be considerably underestimated [46]. Dementia is characterized by insidious onset over months to years. The course is progressive, and until new treatment modalities become available, it is relentless [47]. Thus, a patient with cancer and dementia has two potentially terminal diseases.

Delirium is a disturbance of cognition and attention characterized by an acute or subacute onset over a few days or even hours that fluctuates over the course of the day [48]. It is characterized by distractibility, inability to be redirected, disorganized thoughts, and incoherent speech. It may manifest itself as agitation or as a hypoactive, lethargic state.

It is important to recognize delirium early [49]. The underlying cause of delirium is essentially loss of brain reserve. In other words, in the presence of infection, fever, hypoxia, anemia, neurotoxic drugs, sedating drugs, electrolyte imbalances, rapid fluid shifts, pain, sleep deprivation, and any combination of these common nosocomial exposures, an elderly brain may be unable to maintain ordinary alertness [50]. If the inciting causes cannot be corrected rapidly, prolonged delirium leads to prolonged hospitalization and increased risk for further adverse events [48]. The seriousness of delirium has stimulated many institutions to have organized delirium services, or Acute Care of the Elderly units [51, 52]. These units aim to prevent delirium when possible by managing environmental and pharmacological intoxicants and by having dedicated staff expert in managing the syndrome.

For oncologists, it is important to anticipate and recognize delirium [49]. Cognitive impairment at baseline is the single greatest risk factor for delirium [50]. Three delirium rating scales are commonly used in oncology settings. The most widely used is the Confusion Assessment Method (CAM) [53]. The CAM is a five-item observational scale that takes less than 5 minutes for an experienced observer to complete. It has the further advantage of being easily integrated into a hospital nursing routine. The Memorial (Sloan Kettering) Delirium Assessment Scale (MDAS) was developed specifically for diagnosing delirium on cancer wards. It has been widely used in research [54]. The Delirium Rating Scale (DRS) has also been used extensively, including in cancer wards [55]. A comparison of the properties of the three scales indicates some variability between the MDAS and DRS based on changes in diagnostic criteria between the American Psychiatric Association's Diagnostic and Statistical Manual (DSM) versions III and IV [56].

Polypharmacy: The Good, the Bad, and the Ugly

As people age, they accumulate chronic disease diagnoses and multiple comorbidities. For prognostic purposes, it appears that for an individual, the specific disease or disability is very important [29]. On a population level, however, it appears that it matters less what the specific problem is than the sheer number of problems that have accumulated [57]. The number and rate at which deficits accumulate have powerful predictive value for individual mortality and institutionalization [57]. The common comorbidities in Western populations tend to cluster around cardiovascular risk factors, high blood pressure, high cholesterol, smoking, obesity, and the variable outcomes of myocardial infarction, congestive heart failure, diabetes, renal insufficiency, stroke, and so forth. Thus, much of standard medical care involves multiple drugs to modify multiple risk factors [58].

There is considerable evidence that managing blood pressure, hyperglycemia, and lipids is beneficial and can rarely be accomplished with one or two drugs. When considering other common comorbidities, including arthritis pain, osteoporosis, COPD, and psychiatric illness, polypharmacy is more often the rule than the exception. Surveys indicate that 40% of those over age 65 are taking five or more prescription drugs, and 12% are taking at least 10 [59]. In geriatrics, there has generally been a skeptical view of benefit and a concern for harm due to the use of many drugs. This is partly because trials conducted to obtain indications either have been flawed or have excluded elderly with multiple comorbidities, or both. Furthermore, the association among the number of drugs and the risk of adverse drug effects, harmful interactions, and the potential for drug errors has been shown to increase with the number of prescriptions.

Balanced against this, studies of prescribing patterns have repeatedly shown that elderly patients receive "inappropriate," "substandard," or "non-guideline-adherent" drug therapy for a variety reasons that may result in poorer disease management. This has been shown in cardiovascular diseases [60–64] as well as in cancer treatment. The reasons are multiple. Clinicians correctly recognize that clinical trial results are difficult to generalize to their elderly patients and hold back, it turns out wisely, with treating to population-defined goals. That is, although for the population of adult diabetics, tight glycemic control may be beneficial, for the elderly, it may be detrimental [65]. Achieving consensus blood pressure targets of 130/80 and lower may lower risk for middle-aged patients, but aggressive blood pressure lowering has been shown to be harmful to very old people [66]. Nonetheless, numerous studies support rational polypharmacy for common chronic diseases and show that management with multiple drugs does result in better outcomes [64].

The idea of disease management teams comes quite naturally to oncologists. So for the oncologist, treating the cancer requires having all the other diseases optimally managed. The first problem is to prioritize disease-specific goals and to recognize when "optimal" ought to be supplanted by "good enough." In addition, it is important to think through quantitatively which disease or geriatric impairment (cognition, frailty, or falls) is most likely to cause death, hospitalization, institutionalization, and distress. The risk of adverse drug interactions increases with the number of drugs. However, the literature is quite sparse in identifying specific clinically significant drug-drug interactions [67]. Drugs can increase or decrease the metabolism, binding, uptake, and direct effect of other drugs in both specific and nonspecific ways. But in reality, since the genomics of the metabolism of the commonly used drugs are unknown, it is difficult to absolutely predict specific drug interactions beyond the common problems with warfarin-antibiotic interactions and with insulin [68].

The disease management program (DMP) model of care, however, may not suit an elder with five different disease management programs to follow. Furthermore, the narrow focus and dedicated mission of disease-specific teams may make it difficult to provide balanced care and a coherent set of instructions to a complex patient. In the context of cancer treatment, it is appropriate to be vigilant about suspecting drug interactions when unexpected events happen. It is prudent to closely monitor drugs with a narrow therapeutic window, or to avoid them entirely if possible. It is also advisable to work closely with consultants to optimize the management of comorbidities and improve the tolerance to cancer treatment [69].

There are two other important aspects of polypharmacy in the elderly cancer patient. The first is not unique to the elderly.

The physician's choice of therapy may be constrained by the cost to the patient and limitations on Medicare Part D insurance formularies. Whether these formularies become more or less restrictive remains to be seen. Participation in Phase II, III, and IV clinical trials may offset some costs for patients with limited income. And clinical trials properly focused on the elderly should be advocated and advanced, especially through community-based trial networks.

Finally, and with reference to the earlier discussion of dementia, delirium, and decisional capacity, with comorbidity comes polypharmacy. Complex and variable regimens, especially those that require substantial patient self-management, may result in mistakes. Patients and family helpers make mistakes of both over- and underuse of medications. Doctors make mistakes by not keeping a meticulously up-to-date record of current medications [30]. For doctors to make fewer mistakes requires several specific actions. First, patients should be requested to bring all of their medications, prescriptions, over-the-counters, and neutraceutical "natural" remedies and dietary supplements to office visits. The contents should be verified, catalogued, and identified. Many "natural" remedies have been shown to be biologically active [70]. The purity of the substances can be assured if the manufacturer submits samples for United States Pharmacopoeia verification, the "USP" seal on the label. While this does not constitute FDA approval of the therapeutic claim, it does attest to the identity of contents. Furthermore, both the USP and Memorial Sloan Kettering Cancer Center support extensive online reference resources for neutraceutical supplements [71–73].

Second, despite its limitations, an important component of geriatric prescribing is to be familiar with the updated Beers Criteria for prescribing in the elderly [74]. In brief, these criteria identify a number of drugs with questionable efficacy, long half-lives for which shorter-half-life alternatives are available and effective, and drugs with other toxicities, such as anticholinergic activity, that are commonly problematic for elderly. It is neither absolute nor inclusive, especially as new drugs are added almost daily to the market. Rather, the general principles of geriatric prescribing should be adhered to, and violations of these principles should be noted by oncologists, who may legitimately question standing prescriptions for obsolete drugs, long-half-life drugs, unnecessary drugs, redundant drugs, and drugs at doses too high for safety in the elderly [75].

Summary

This chapter discusses the meaning and significance of geriatric syndromes for practicing oncologists. The critical point is that the occurrence of geriatric syndromes in the setting of cancer treatment represents a sentinel event that warns of loss of reserve, of resiliency, to the stress of serious illness. Loss of homeostatic reserve places elderly patients at high risk for poor outcomes, including not only death, or treatment failure, but excess hospitalization, institutionalization, and poor quality of remaining life. Four syndromes were selected for a more detailed review. Weight loss, frailty, and cachexia have different causes and different significance for cancer and for aging. Oncologists should pay close attention to the trajectory of weight and appetite, as changes may or may not be due to the cancer. Falls, walking problems, and fractures represent a second syndrome complex to be monitored. The risk for falls and the consequences of falls with injuries are quite high in some cancer populations, and the new occurrence of falls should prompt a further inquiry and consultation. Dementia, delirium, and decisional capacity affect all aspects of oncology care for the elderly, from the initial disclosure of diagnosis to determining the prognosis in a progressive dementia with possibly stable neoplastic disease. The emergence of delirium should be regarded as a high priority for intervention and consultation. Finally, polypharmacy is a fact of life with the elderly. This is neither absolutely bad, nor necessarily good. It does place an extra burden of vigilance on the oncologist to work collaboratively with primary care specialists for the management of comorbid diseases and patient safety.

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Family Caregivers

Betty R. Ferrell and Polly Mazanec

Introduction

Caregiving an elder with cancer has the potential to be rewarding and meaningful but is often described as burdensome and overwhelming because caregiver needs are frequently unmet. As the provision of care has transitioned from the hospital to outpatient settings, family caregivers have taken responsibility for the day-to-day care of their ill loved ones at home [1–4]. Despite the fact that caring for a loved one at home is technologically more complex than in the past, managed care and other reimbursement restrictions on hospital and home care services have forced family caregivers to provide care to family members with little support. Because patients are living longer with chronic illnesses such as cancer, caregiving burdens have increased not only in intensity, but also in duration.

According to the Family Caregiving Alliance [5], over 80% of all home-based care is provided by family and friends who are informal caregivers, rather than by formal, paid caregivers. It is estimated that family caregivers save the health-care system $306 billion a year by providing care themselves rather than using paid home care staff, and this number continues to rise [5].

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Although there is a huge cost savings to the health-care system, the burdens associated with caregiving may result in substantial costs to the caregiver. These costs include not only the financial burden as a result of lost wages or costs of medications and equipment, but also the cost to the caregiver's physical and psychological well-being as a result of the care demands.

Family Caregivers

Who are the family caregivers of elders with cancer? Throughout this chapter, family is defined as the individual(s) considered to be family to the patient, regardless of blood relationship [6]. Family members are informal caregivers, defined as unpaid persons who help someone with physical care or coping with disease. This differs from formal caregiving, which refers to paid unlicensed or licensed caregivers.

Family caregivers can provide direct and/or indirect caregiving. Direct caregiving comprises "activities and experiences involved in providing help and assistance to relatives or friends who are unable to provide for themselves" [7]. The tasks associated with direct caregiving are complex, including physical hands-on care, help with daily and weekly household chores, transportation, and meal preparation. Indirect caregiving involves management of care, delegating and other supervisory activities, arranging medical appointments, and managing financial affairs and can be very time-intensive.

Caregivers may be considered as primary or secondary caregivers. A primary caregiver is the individual responsible for the majority of direct caregiving tasks, including emotional support [8]. Secondary caregivers, or backup caregivers, provide support to the primary caregiver, sharing some of the tasks of direct and indirect caregiving. Although primary caregivers may have the burdens associated with providing hands-on physical care that secondary caregivers do not have, it has been reported that the provision of emotional support is more burdensome than physical care [3, 9].

Most informal caregiving is done by spouses (80%) and adult children (20%). Most caregivers are female (65%). Eight out of 10 family caregivers are 50 years of age or older, and the average age of those caregiving family members aged 50 and older is 75. In the National Caregiving Alliance Study of 1,247 caregivers, the number of those caregiving cancer patients was as great as those caregiving elderly family members with heart disease and was greater than the number of those caring for elderly family members with Alzheimer's disease [10].

Much is known about the spouse or local adult child caregiver of an elder with cancer who lives within the same community. Because of today's changing and global world, family members frequently live far away from each other, and this reality adds a new dimension to caregiving referred to as long-distant caregiving, or distant caregiving. Distant caregiving is the experience of providing instrumental and emotional support to an ill loved one who lives far away [11]. More than seven million Americans are distant caregivers, and the number is rising. In generations past, family members often lived in close proximity and were available to help when caregiving needs arose. Now many adult children are struggling with the demands of distant caregiving with limited or no support. Research in progress is being conducted to identify the effects of distance on the caregiving experience of adult sons and daughters of parents with advanced cancer and will lay the foundation for future intervention studies for this new and growing population of caregivers of elders [11].

"Nuclear" or "traditional" families comprise 52% of families in the United States. Those families who are not considered "traditional," such as single-parent families, gay and lesbian families, and families with second marriages, have unique needs with regard to taking on the caregiver role of an elder with cancer. It may be that the caregiver has been estranged from the family, and roles and relationships add additional stress and burden on the caregiver. Additional responsibilities associated with families of second marriages may increase the demands of juggling multiple roles and relationships while caregiving.

Impact of Cancer on Family Caregivers

A total of 1,437,180 new cancer cases and 565,650 deaths from cancer are projected in the United States for 2008 [12]. Over half of all cancers occur in those who are age 65 and older, and the incidence rate for all sites is tripled for those between 60–79 compared to those between 40–59 [13]. Cancer is the leading cause of death in those aged 60–79 [12].

A diagnosis of cancer is a major life stressor for the patient and the family [14, 15]. The diagnosis poses a threat of losing a family member and of subsequent disruption of the family system. With the advent of many new treatments, even patients with advanced cancer are living longer. The patients and their families are struggling with the prolonged and difficult course of a debilitating, chronic illness. While patients are forced to deal with the diagnosis of cancer and the related symptoms, as well as the side effects associated with its treatments, family members must confront the stressors associated with having a family member with a life-limiting disease [14, 15].

Family caregivers of patients with cancer are faced with the challenges associated with a cancer diagnosis. Dealing with advanced-stage cancer, as compared to limited-stage disease, has been associated with higher levels of emotional distress in family caregivers. The emotional burdens associated with the inevitability of death and the worries about uncontrolled pain and symptoms can be overwhelming. Research has shown that distressed family caregivers of loved ones with cancer have poorer physical and psychological health than those who are not distressed [16–18].

Factors Contributing to Caregiver Burden

Demographic characteristics of caregivers have been linked to caregiver burden (Table 1). There is empirical support for the relationship among care demands, sociodemographic variables, resources, and caregiving burden [19, 20]. Caregivers

Table 1 Demographic factors associated with caregiving burden

Factors	Caregiver considerations
Age	• Increasing age makes it physically more challenging to provide care to spouse. • Adult children experience greater depressive symptomatology than older spouses.
Gender	• Females have more depressive symptomatology than males. • Females are expected to juggle multiple roles—adult child caregiver, spouse, mother, employee, etc. • Burden often falls to daughters/daughters-in-law because of role socialization.
Race	• More African-Americans die from cancer than Caucasians, increasing burden on African-American caregivers. • African-Americans are more likely to insist on providing care at home rather than nursing home or hospice, often with few resources.
Socioeconomic status	• Patients with lower socioeconomic status (SES) are more likely to die from cancer than those with higher SES. • Fewer resources are available for help. • The cost of caregiving can be a financial burden, including lost wages.

who have fewer socioeconomic resources are at risk for more distress than those with greater financial resources because the options available to assist them with caregiving are limited. Those who are caregivers from vulnerable populations such as elderly in rural areas, minorities, or caregivers with disabilities suffer from additional stressors and need help from the health-care team to meet the demands of caregiving.

Older caregivers, who may themselves have limited physical functioning, social isolation, and fixed resources, are at risk for caregiver burden. Many caregivers of elders have comorbidities themselves, with limited physical capacity to provide tasks associated with caregiving [14]. In addition, they may be socially isolated, having already had many friends and siblings die before them, and this isolation may contribute to psychological distress. In a small sample of 50 cancer patients and their caregivers, Ferrario et al. [21] reported that caregivers over the age of 50 had higher depression scores than those who were younger. Fletcher et al. [22] found that family caregivers who were older, with higher levels of depression, morning fatigue, and pain, had significantly poorer functional status.

However, other studies have demonstrated that younger caregivers may, in fact, experience greater burden than older caregivers, especially when juggling multiple roles [23, 24]. Younger caregivers were more likely to report more exhaustion and fatigue with care demands than older caregivers [8]. Adult children of elderly parents with cancer are often "sandwiched" between the responsibilities of caregiving parents and the responsibilities to their spouses and children [25]. Competing care demands can result in missed work days and limited productivity, a lack of time for leisure activities and rest, and overwhelming burden [14].

Gender may also be an important factor in caregiver burden. Seventy percent of primary local caregivers are women [26]. In a study of 135 family caregivers and their ill family member, female caregivers were found to be more anxious, were more worried about recurrence and test results, and had greater uncertainty about the future than male caregivers [19]. Given et al. [24] found that female caregivers of patients with cancer had more depressive symptomatology than males. However, psychiatric morbidity may be buffered by personality characteristics, coping resources, and social support. In the American Cancer Society's Quality of Life Survey for Caregivers, male caregivers were more likely than female caregivers to appraise the experience as positive, and adult daughters were more likely to appraise the experience as stressful when compared to adult sons [27].

Benefits of Caregiving

Despite the often-cited focus on burdens of caregiving, family caregivers who are well prepared and supported during the illness experience often report significant benefits of caregiving

[28]. In geriatric oncology, family caregivers are most often elderly spouses or adult children, and the ability to meet the physical and emotional needs of a loved one with cancer represents an opportunity of great meaning and personal satisfaction.

Health-care professionals should recognize that caregiving experiences can be opportunities to express thanks, to pay back care after a life of receiving care and support, and a time of affirmation of relationships. Importantly, the experiences of caregiving in cancer often become the memories of the bereaved after the death of a patient. Regardless of the outcomes of care or length of survival, cancer caregiving for older adults can be a positive, life-affirming experience.

Burdens of Family Caregiving

Health-care policies in the United States mandate earlier discharge of patients from the hospital following surgery and other treatments. This shift in the provision of oncology care has resulted in an increase of informal caregiving in the home as a primary source of patient care. Thus, family-centered care has become a basic tenet of quality oncology care. There is a growing recognition that patients and family caregivers exist within a social system that is intimately impacted by diagnosis, treatment, survivorship, and palliative care [29]. The caregiving role in cancer is associated with physical and psychological burden for informal caregivers, and this is even more important in geriatric oncology since patients are known to have comorbidities that may increase the need for care [30, 31]. Caregiver burden has been defined as the distress that caregivers feel as a result of providing care, and this distress is different from depression, anxiety, and other emotional responses.

Montgomery and colleagues described three dimensions of caregiver burden. Objective burden is defined as the perceived infringement or disruption of tangible aspects of a caregiver's life [32]. Subjective demand burden is defined as the extent to which the caregiver perceives care responsibilities to be overly demanding. Finally, subjective stress burden is the emotional impact of caregiving responsibilities on the caregiver. Other factors that affect caregiver burden are described as patient characteristics, caregiver characteristics, and characteristics of the care situation [30]. Patient characteristics include diagnosis, treatment, advanced stages of disease, and increased number of care tasks [30, 31].

Caregivers of patients receiving palliative care have been shown to have significantly higher burden than caregivers of patients receiving curative treatments [32]. Caregiver characteristics include age, distressed relationships, lack of social support, perceived loss of control, optimism, feelings of inadequacy, guilt, and perceived unmet needs of the patient [30, 33–37]. Characteristics of the care environment that are associated with caregiver burden include socioeconomic status and type of care tasks, such as intimate/personal care of the body and care that is intense and on a rigid schedule [30, 35]. The perceived burden in caregiving is high among caregivers of seriously ill patients, with 55% of these caregivers reporting at least one severe burden, which results in major life changes and the inability to function normally [38].

The shifting role of cancer caregivers has changed dramatically in the past decades from promoting convalescence to providing highly complex hands-on care and emotional support in the home care setting [33]. Caregivers play many important roles in the care of cancer patients. They frequently step into their new role without a complete understanding of the complexity of their responsibilities and how the new role will alter their own lives [34]. The tasks placed on cancer caregivers may intensify over time and at specific intervals such as during transitions of care. They are expected to become experts in symptom management at home and are responsible for keeping records, dispensing medications, and performing procedures generally requiring nursing expertise, such as injections, catheter care, and management of infusion devices [31]. Caregivers also function as home health aides and companions. Responsibilities for this role include emotional support, communication, personal care, meals, and arranging transportation. Finally, caregivers are often given legal and medical responsibilities, and these include treatment decision making, goals of care, advance directives, finances, managing home care assistants, facilitating transitions of care, and preparing for the patient's death [31].

The expectations and tasks given to cancer caregivers are multifaceted, but the current health-care system does little to support the fulfillment of the caregiving role. Family caregivers assist with cancer demands such as nutrition needs related to cachexia or nausea as well as to significant functional decline of patients. Family caregivers assume major responsibilities for care postoperatively, and caregiving often entails intense emotional burdens in dealing with patient depression and anxiety, which are common patient problems.

The cancer experience can profoundly affect the caregiver's overall well-being. Most caregivers are novices in providing care for cancer patients from diagnosis through the terminal phase of the disease. Together with the patient, caregivers also experience the disease trajectory with unique challenges across all phases of disease. While caregiving can be viewed as a positive experience and an expression of a dedicated relationship, the physical, psychological, social, and spiritual effects of cancer caregiving may negatively impact the quality of life (QOL) and overall outcomes for cancer caregivers. Figure 1 illustrates the dimensions of QOL for family caregivers.

The current literature provides some preliminary insights into the physical burden of cancer caregiving. As the patient experiences increasing disease- and treatment-related symptoms, the caregiver also experiences symptoms related to the burden of caregiving [39]. Research indicates that as the patient's disease progresses, the physical well-being of caregivers decreases [2]. The physical demands of caregiving are generally related to the patient's medical situation and often require 24 hour-per-day demands. Thus, common symptoms in caregivers resulting from the provision of care include sleep disruption and fatigue [40]. There is an emerging body of literature that suggests that higher caregiver burden is

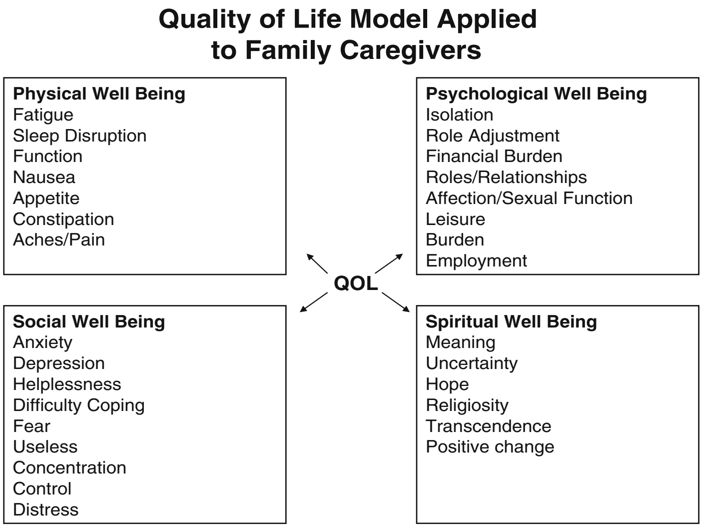

Fig. 1 Quality-of-life model applied to family caregivers
Source: Betty Ferrell, PhD, FAAN, and Marcia Grant, DNSc, FAAN, City of Hope.

associated with increased mortality risk for caregivers [4]. It has been reported that caregivers who reported higher burden during a four-year follow-up had a 63% greater mortality risk than caregivers who were not providing care [41].

The overall QOL of cancer caregivers has been explored in the literature. In a study with 51 dyads of women with lung cancer and their family members, Sarna and colleagues found that predictors of lower QOL in family members include older age, comorbidities, education level, and alcohol consumption [42]. In general, family members in this cohort had poorer emotional QOL than general population norms. The health status for these family members was also severely compromised, with 59% reporting at least one comorbid condition. In a study that compared the symptom experience of advanced cancer patients and caregivers, Sherman and colleagues found no statistically significant differences in total symptom scores between patient and caregiver [43]. This finding supports the current literature, which suggests that symptom distress in cancer caregivers is just as severe as that experienced by cancer patients [44, 45]. QOL studies with caregivers of cancer survivors found that caregiver esteem and perceived stress were strong predictors of caregiver QOL [45]. In a study of 246 cancer survivors and caregivers, survivor QOL was found to be higher than caregiver QOL [46].

Researchers have explored the impact of cancer on spousal and children's well-being. The large portion of this research was conducted by Lewis and colleagues in women with breast cancer. Results suggest that distress is high in spouses and children, parenting is less effective, the quality of spousal communication is poor, modifications in coping behaviors rarely occur spontaneously, and families struggle to maintain core functions and roles [47–50].

Of the four domains of QOL, the psychological effects of caregiving have been explored most extensively, and findings suggest that this domain is an important predictor of caregiver QOL [51]. In general, the psychological demands of caregiving relate to anxiety, depression, and psychological distress. Caregivers have been shown to exhibit their own emotional responses to the patient's diagnosis, prognosis, and treatment. In long-term cancer survivors, studies have shown that caregivers appraised the cancer experience as more stressful than their surviving loved ones [52]. Research has shown that caregivers of cancer patients receiving palliative care are at risk of developing psychological distress. A caregiver's psychological distress is strongly associated with terminal disease progress and patient's declined functioning. Psychological distress was not found to be significantly different between patient and caregivers [53–57].

In a secondary analysis of data from 618 caregivers, Doorenbos and colleagues found that caregiver depressive symptomatology differed based on patient survival status, and caregivers experienced greater burden at the end-of-life [58]. Miaskowski and colleagues found that the presence of pain in patients adversely affects the level of depression and anxiety in caregivers

[59]. In a study using structural equation modeling to identify personality correlates of depressive symptoms in 120 spouses of lung cancer patients, Kim and colleagues found that neuroticism and self-efficacy were associated with greater caregiver depressive symptoms [60]. Other predictors of caregiver depression reported in the literature include perceived caregiving burden, marital dissatisfaction, education level, and lifestyle interference [61].

The social demands of caregiving are primarily related to relationships and financial factors. Marital relationships can be strained, and research has found that depression in both patient and spouse negatively affected marital relationships. Communication has also been found to create strain in social relationships. Conflicting styles of communication may impede patient and caregiver coping. Family communication patterns, roles, and coping methods are crucial components of family functioning, and difficulties in these components can be exacerbated by cancer and increase caregiver burden. In a qualitative study with 12 lung cancer caregivers, Badr and Taylor found that couples coping with lung cancer experience a wide variety of social constraints, such as denial, avoidance, and conflict, that may compromise open communication and spousal support [62]. Specifically, the study found that patients and spouses reported difficulty in discussing tobacco use, cancer-related symptoms, prognosis, and spousal emotional response to cancer.

The Clinical Practice Guidelines for Quality Palliative Care established by the National Consensus Project (NCP) recommend that routine patient and family meetings be conducted with the interdisciplinary care team to facilitate communication and develop an individualized plan of care [63]. These guidelines refer to the importance of family caregivers in palliative care, and the social well-being domain focuses on family issues. The guidelines also suggest that palliative care applies to patients and families throughout the course of serious illness not only in end-of-life care.

Spiritual well-being has been increasingly recognized as an important factor in cancer patients and caregivers. Research suggests that similar to cancer patients, caregivers also derive meaning in their cancer experience [31]. Mellon and colleagues found that cancer was a transformative experience for caregivers of long-term cancer survivors [64]. As a result of cancer, caregivers were able to reprioritize their lives, and studies have shown that finding meaning resulted in more positive adjustments to the illness. Other studies have found that caregiver QOL is predicted by the derived meaning of the illness [65]. Sherman and colleagues found that spiritual well-being was similar in patients with advanced cancer and their caregivers [66]. This finding suggests that the suffering of terminally ill patients and their families are interrelated, because the suffering of one amplifies the distress of the other. In a study with 20 inoperable lung cancer patients and their caregivers, Murray and colleagues found that regardless of religious beliefs, the need for love, meaning, purpose, and transcendence was common in this cohort [67].

Cancer caregivers frequently report unmet needs in all of the QOL domains described previously. In a recent literature review, Shelby and colleagues found that 60–90% of patients and caregivers were found to have a need for assistance in at least one area [68]. Needs most often reported by caregivers include assistance with personal adjustment to the loved one's illness (38–70%), psychosocial support (30–60%), transportation (31–58%), financial assistance (50–52%), home care (10–42%), and medical information (3–29%) [68].

Strategies to Strengthen Benefits and Decrease Burdens of Caregivers

Many of the tasks placed on cancer caregivers presuppose that certain skill sets are already acquired. Such skills include proficiency with insurance reimbursements, ability to follow medical instructions, ability to anticipate medication refills ahead of time, caring for high-tech devices such as catheters and home infusions, managing payment requests, and navigating the complex health-care system. Physical care in cancer may include lifting patients, assisting with ambulation, managing nutrition due to weight loss, and managing treatments for pain and dyspnea. Unfortunately, caregivers are automatically assumed to be capable of performing these complex tasks at home, with little support and virtually no appraisal of acquired skill sets.

Given the astronomical amount of responsibilities, tasks, and expectations that are placed on cancer caregivers, it is important to understand that these caregivers must be prepared adequately for their responsibilities as a method of diminishing burden. The current literature supports this concept. Scherbring explored preparedness in 59 caregivers of cancer patients following discharge and found that perceived preparedness was significantly associated with caregiver burden [69]. In a study with 87 caregivers of cancer patients receiving treatment, Schumacher and colleagues found that mutuality in the dyad relationship and preparedness for caregiving role were significant moderators of perceived caregiving demands and caregiver outcomes [70].

Self-Care for Cancer Caregivers

Much of the health-related research in family caregivers has focused on health-related problems as a result of caregiving duties. Few researchers have explored caregiver health within a health promotion and self-care paradigm. However, there is increasing recognition that the ability of family members to care for patients is dependent on caring for themselves. Examples of health-promoting self-care include getting enough rest, eating nutritiously, exercising, seeking psychological counseling or spiritual support, maintaining routine health checks, and seeking attention to the caregivers' own chronic illnesses and health conditions [71]. Changes in caregiver health behaviors include eating less nutritiously, increasing use of sleep and over-the-counter medications, and engaging in risky behaviors such as alcohol consumption [72]. Reasons for caregiver neglect of self-care include not having time to worry about his or her own health, high levels of perceived burden, and high demands of care tasks. Demographic characteristics such as age and gender have been shown to predict self-care utilization. Sisk found that female caregivers utilized more self-care strategies, while younger adult children participated in fewer self-care activities, which may reflect the difficulty in balancing the needs of caring for a loved one and their own career, family needs, and lifestyles [73].

Given the benefits of health maintenance, engaging in self-care behaviors should logically reduce caregiver burden. The emerging literature in this research area supports this hypothesis. Acton explored the effect of health-promoting self-care behavior on caregiver stress and well-being, and findings suggest that caregivers who practiced more self-care behaviors were better protected from stress, and the effects of stress on well-being were reduced [71]. Lu and Wykle described the relationship between self-care behavior responses to physical and psychological symptoms in caregivers. Results indicate that one third of caregivers elected to take no action to deal with their symptoms, despite high depressive mood and more symptom severity [72]. Caregivers often have little time to attend to their coexisting health needs. This is not surprising since family caregivers perform the essential work of professionals and often with no "days off" or vacation from caregiving responsibilities.

While there is increased recognition of caregiver self-care, few studies have tested such strategies in cancer caregivers. Many of the self-care strategies recommended for nurses and other professionals such as meditation, relaxation, and exercise are applicable to family caregivers. Consistent with the literature recommendations, self-care strategies must be goal-oriented and tailored to meet individual needs. These methods should also be combined with the establishment of a plan of care and follow-up evaluations.

Summary

Issues of family caregiving are critically important in geriatric oncology. The aging population, prolonged survival, complexity of cancer treatment, and outcome focus of care are all significant factors for family caregivers. Both geriatric patients and their often geriatric caregivers present unique demands and require special attention to ensure that patient needs are met and that the caregiving experience yields benefit instead of only burden.

For both patient and caregiver, the QOL domains of physical, psychological, social, and spiritual well-being are essential targets for attention. Optimum support includes skill preparation as well as self-care for the caregiver.

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Surgical Management of the Older Patient with Cancer

David M. Heimann and M. Margaret Kemeny

Introduction

In the first 50 years of the new millennium, the percentage of Americans over the age of 65 is expected to double [46] from 35 million to 70 million. Since the incidence of cancer increases exponentially with advancing age, it is expected that there will be a significant swell in the number of elderly patients diagnosed with cancer. It is projected that by the year 2030, the number of cancers in the elderly will reach 1.5 million [120] and will exceed 2.6 million by 2050 [46]. People over age 65 account for 60% of newly diagnosed malignancies and 70% of all cancer deaths [17]. The incidence of cancer is 10 times greater in the population over 65 compared to those younger, and the cancer death rate is 16 times greater in the population over 65 years of age. In 2005, cancer was the leading cause of death for Americans between the ages of 60 and 79 [71].

Surgery remains the best treatment modality to cure solid tumors regardless of age. Surgery is instrumental for diagnosis, resection with curative intent, or palliation. Since the population of the United States is not only growing but also aging, the number of elderly patients with cancers requiring surgical intervention can be expected to rise.

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Life expectancy is often underestimated for the elderly. According to the National Vital Statistics, the life expectancy of a girl born in 2004, the last year for which data are available, is 80.4 years, while it is 75.2 years for a boy [117]. The life expectancy of a 65-year-old female and a same-aged male is an additional 20 and 17.1 years, respectively, while that of a 75-year-old female and a same-aged male is 12.8 and 10.7 years, respectively. Thus, inadequate initial therapy for someone diagnosed with cancer at an older age can result in recurrence or metastases and death from cancer—outcomes that may have been preventable or avoidable with correct treatment at the outset.

Surgery is the mainstay of treatment of the tumors common in the elderly such as colorectal, breast, gastric, and pancreatic cancers. With adequate preoperative evaluation, surgical treatment for the elderly should not be different from that offered to younger groups; therefore, the standard of care should not be based on a patient's age.

Unfortunately, scientific data from randomized studies are often not readily available for older populations because they were more likely to be excluded from clinical trials. Older patients are more likely to reside in rural areas where treatment facilities are few and farther apart. For example, in 2002, 24% of Americans aged 65 or older lived in rural communities, compared to only 19% of the general population. More pronounced is the fact that between 1992 and 2002, the number of Americans aged 75 and older who lived in rural areas increased by 17% compared to an overall decrease in the rural population during that time period [46].

Studies that are available are retrospective and often display considerable bias in the patients chosen for certain treatments, especially surgical procedures. Many biases influence the selection of therapy in the elderly. Concerns stem from what is perceived as limited life expectancy, the presence of comorbid disease, decreased functional status, alterations in mental status, limitations in economic resources, and assumed inability to tolerate treatment. The influence of these biases may affect survival from cancer in the elderly.

In one study, factors that influenced survival up to 10 years after the diagnosis of cancer in patients over 65 years of age with cancers of the colon, rectum, breast, and prostate were health status (comorbidity, functional status, level of activity), socioeconomic status (income and education level), cognitive status, and availability of social support [58]. In this study, not receiving definitive therapy for the patient's cancer, with the exception of cancer of the prostate, was associated with a threefold greater death rate. Inadequate treatment remained a significant factor even after controlling for stage at diagnosis, socioeconomic factors, comorbidity, and physical functioning. Thus, withholding appropriate treatment because of age will result in inferior cancer survival in the elderly.

Traditionally, surgical procedures in particular have been viewed as carrying prohibitive risk in elderly patients. As the population ages, there has been an increased interest in the feasibility and outcome of surgical intervention in the elderly. In fact, the number of articles available upon performing a search for "neoplasm, surgery, and elderly" in Pubmed has greatly increased in number since 1990 (Fig.1). Over the past 30 years, numerous publications have shown

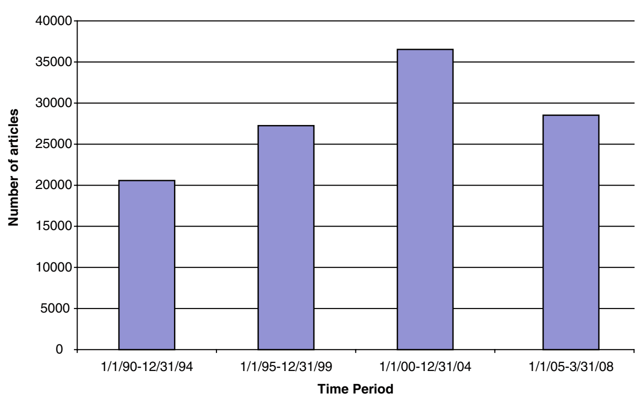

Fig. 1 Pubmed articles relating to cancer surgery in the elderly

that surgical procedures can be performed safely in the elderly [19, 54, 55, 59, 65, 83, 88, 103, 109, 117, 124]. The balance between operative risk and expected cure or palliation is important when treating any patient with cancer but even more so in the elderly. The impact of treatment on the quality of life is of prime importance. Many cancer operations are complex and require extensive dissection when attempted for cure in any patient population with significant morbidity and mortality associated with them regardless of the patient's age.

Increases in surgical morbidity and mortality are associated with advanced disease states and emergency surgery. Since there is often a delay in cancer diagnosis in elderly patients, this can lead to more advanced cancers and a greater number of emergency presentations. Early diagnosis and treatment in the elderly should be encouraged.

This chapter reviews the role of surgery in the management of older patients with the following common solid organ cancers: (1) breast; (2) colorectal; (3) pancreatic; (4) hepatocellular; (5) gastric; (6) melanoma; and (7) esophageal. Preoperative assessment of the elderly cancer patient is also discussed.

Preoperative Assessment

As the population ages, the need to develop tools that assess the operative risk factors and predict postoperative outcome for patients with cancer has become of the utmost importance. The assessment of risk involves the interaction of the underlying physiological status, including normal physiological changes of aging, in addition to those changes attributable to comorbidity, cancer, surgery, and anesthesia. Advanced age should never be used as the sole criterion to deny standard curative therapy. Normal physiological changes occur with aging in every major organ system and affect the response to surgical procedures. The reductions in the functional reserve in each organ system represent parallel decreases in the capability to maintain homeostasis in the setting of surgical stress and anesthesia [118]. There is a decrease in the distensibility of the cardiac wall and a greater dependence on preload to increase cardiac output as patients get older. Renal function decreases with age, with a gradual loss of both renal mass and glomerular filtration rate. In the liver, there is a decrease in volume, blood flow, and perfusion with an increase in age. Pulmonary function changes with alterations in compliance and a decrease in the forced expiratory volume over one second and in vital capacity.

The ability to withstand the stress of various types of treatment for cancer is dependent on the functional reserve and ability to respond to the stress. However, no one tool exists currently for surgeons to assess functional reserve for all stages of management from preoperative to postoperative care. Until one is developed, the American Society of Anesthesiologists' (ASA) general classification of Physical Status aids in determining patient risk assessment. The scale grades the mortality rate from anesthesia by assessing the physical state of the patient prior to anesthesia and surgery in order for the patient to be assigned to one of five groups.

The APACHE II system, which includes 12 variables including age and the presence or absence of severe chronic health problems, was originally devised to study patients in the intensive care unit. It is now used to study risk in the surgical setting. High APACHE II scores are associated with an increased morbidity and mortality for patients undergoing major elective surgery [56].

The Physiological and Operative Severity Score for enUmeration of Mortality and Morbidity (POSSUM) predicts both surgical morbidity and postoperative mortality in general surgery. It is similar to the APACHE score but includes EKG changes. This is advantageous, but the finding of chronic EKG changes, common in the older population, should not preclude them from definitive therapy [118]. The POSSUM data are mostly useful for the immediate postoperative period.

The Preoperative Assessment of Cancer in the Elderly score (PACE) is a questionnaire that provides a scoring method to evaluate the geriatric patient for candidacy for surgery. In a pilot study, it has been shown to be feasible, inexpensive, and rarely refused by patients [11], yet definitive results are still pending. PACE incorporates various tools to predict the outcome of cancer surgery in the elderly. The patient's performance status and instrumental activities of daily living (IADL) correlated to prolonged hospital stay. The performance status is significantly lower in patients who developed morbidities, while the IADL score helped predict postoperative complications. Comorbidities did not play a role in predicting poor surgical outcome. PACE is aimed at overcoming the selection bias associated with advanced age as well as assisting the surgeon's decision making for treatment.

Being able to assess risk preoperatively can help get the patient into the best presurgical state possible. Patients should be instructed and aided with smoking cessation, their respiratory function should be optimized with preoperative pulmonary toilet, and ways to optimize nutrition should be implemented. Also, optimizing preoperative medications such as beta-blockade should enhance cardiac function.

Abdominal cancer surgery often requires extensive dissection with possible large shifts in fluid balance. These conditions are particularly stressful for the very elderly because of decreased cardiac compliance. Intraoperative monitoring with central venous access, placement of an arterial line for continuous monitoring, and careful observation of urinary output all help to maintain a balanced cardiovascular state.

In addition to preoperative planning and intraoperative management in the elderly, there should also be optimum supervision of perioperative care by a multidisciplinary team. This team should aid in addressing those issues that contribute to morbidity and mortality in the elderly population such as pain, delirium, sepsis, poor nutrition, and rehabilitation. This team approach enables the elderly patient to obtain the full level of care that he or she, as well as all patients, require postoperatively to ensure better postoperative outcomes. Postoperative monitoring should include a telemetry unit in the early postoperative period (up to 72 hours) and close monitoring of fluid status to prevent under-resuscitation or fluid overload states. Nutritional support should be implemented as early as possible either enterally or parentally. Medications that can cause mental status changes should be avoided. Early mobilization with aggressive physical and occupational therapy is also needed in the elderly patient population.

Breast Cancer

The incidence of breast cancer rises with age. It is the most common cancer in women, with 182,460 cases predicted in 2008 [71] and the second leading cause of cancer deaths, with 40,480 in 2008 [71]. Nearly one third of breast cancers occur in women over the age of 70 years [115], and half the deaths are in women more than 65 years of age [170]. Despite this, many studies have demonstrated that breast self-examination, clinical examination by health-care providers, and screening mammography are underutilized in the elderly [89, 157, 166]. Also, many studies show significant undertreatment of the elderly in every stage of breast cancer.

A Swedish two-county trial confirmed that routine mammograms resulted in a reduction in breast cancer mortality for women between the ages of 50 and 74 years [143]. The relative risk was lower for women between the ages of 60 and 69 years (RR 0.6) than for women aged 70–74 years (RR 0.79). Thus, mammography should be performed routinely in the elderly, because the incidence of breast cancer continues to rise with age, and since the breasts become less dense with aging, the sensitivity of mammography should improve. In one series, the positive predictive value of an abnormal mammogram was greater for women over 65 years of age than for women 50–64 years old [49]. However, there may be as many as seven years of delay in seeing a benefit, which must be considered in relation to life expectancy.

There is a belief that breast cancers in the elderly may not be as aggressive as in younger women. The upper outer quadrant of the breast is still the most frequent site, and infiltrating ductal carcinoma is the most common histological type [5, 26]. In situ carcinomas do tend to be less common in the elderly [167]. Yet, in the past, this may have reflected an underutilization of mammography, since the overall incidence of in situ disease has increased dramatically in the last 20 years with the advent of routine mammography [45]. The elderly do have a higher incidence of estrogen receptor (ER)-positive and progesterone receptor (PR)-positive tumors [26, 136]. In one large series of over 10,000 women, 63% younger than the age of 50 years had ER-positive tumors, whereas 83% of those older than 50 years had ER-positive tumors [122]. In another series, which included 307,115 patients with invasive breast cancer, ER-positive tumors were seen in 87-91% of patients 65 years or older, while those younger than 65 years had ER-positive tumors 83% of the time [38, 99]. Progesterone receptor-positive tumors were also noted to be more common in the elderly patients in this series [38].

One of the greatest areas of controversy is whether breast cancer in the elderly should be managed any differently than in younger women. The fear of treatment morbidity and mortality sometimes prompts a minimalist approach in the elderly, whereas at other times, mastectomy is offered with little, if any, discussion about the possible desire for breast conservation. Likewise, reconstruction is often not readily offered to elderly patients. Randomized trials in both the United States and Europe have shown breast-conserving therapy (BCT) to be equivalent to mastectomy in terms of survival from early-stage breast cancer [5, 45, 167]. The National Institutes of Health consensus conference also found it to be the preferable method of treating early-stage disease [1]. More recently, a 20-year follow-up of the randomized study evaluating breast conservative surgery confirmed earlier findings of no decrease in disease-free or overall survival with breast-conserving surgery [51]. However, breast-conserving therapy is still underutilized for all ages and particularly in the elderly.

Hurria et al. [69] performed a retrospective study examining the factors influencing treatment patterns for women aged 75 and older with breast cancer. The goal of the study was to determine local and systemic treatment patterns for these patients. Even in this advanced-age cohort, there was a difference in treatment seen between those patients aged 75–79 and those who were older. The older patients were less likely to be offered an axillary dissection and radiation therapy compared to the younger group. Likewise, patients with increased comorbidities were significantly less likely to receive radiation therapy despite the findings of the CALGB study that radiation is beneficial, at a median follow-up of 7.9 years, in preventing locoregional disease in women aged 70 and older who have undergone partial mastectomy [67].

The study by Hurria also demonstrated that age was the greatest predictor of lesser treatment. However, there was no difference in receiving hormonal therapy, which is generally viewed as a "less" toxic treatment. Chemotherapy and axillary lymph node dissection, which are generally viewed as more "toxic" therapies, were less likely to be used in the armamentarium for patients aged 80 or older.

Other studies have also demonstrated that when breast conservation is performed, it is often done without axillary dissection or the use of postoperative radiation, as would be the standard for younger women [26, 162]. In one retrospective series, the survival of elderly women was found to be lower for those treated with less than standard procedures [162].

There are many factors that influence the use of BCT, including geographical location, race, and hospital characteristics. In one analysis of Medicare patients, geographical variations were marked in the use of BCT [111]. In another review of over 18,000 Caucasian women in three age groups—younger than 65, 65–74, and older than 74 years—the lowest rate of breast-conserving surgery was in the 65- to 74-year age group [48]. In areas of the country where BCT was common in the younger ages, it was less common in the older age group, whereas in areas where it was not commonly used in the younger group, it was more commonly used in the older group. It was postulated that disfiguring surgery was avoided in the younger group, whereas morbidity and mortality were avoided in the older group. But the morbidity and mortality for breast surgery in the elderly are very low [26]. The elderly have also been found to have a lower rate of BCT in the treatment of ductal carcinoma in situ (DCIS) [45].

With the advent of sentinel lymph node (SLN) biopsy, the fear of morbidity from an axillary dissection is decreased. SLN biopsy has been shown to be a safe procedure, with accuracies of 97% in randomized studies [84, 155]. Furthermore, the safety and feasibility have also been evaluated in the elderly [57]. In a series of 241 patients 70 years or older, the SLN was identified in all patients, with no major complications [57]. In this series, the SLN was positive for metastasis in 37% of the patients. Using the SLN technique obviates further axillary dissection in SLN-negative patients, therefore decreasing the bias of adequate staging in the elderly. In another study [66] of 104 patients between the ages of 65–95 (median 74), 29 (28%) patients had metastatic disease in at least one sentinel node. This resulted in nonsurgical treatment modification in 38% of patients. This finding has been shown in multiple other articles [39, 100]. McMahon et al. studied 730 breast cancer SLN mapping patients, 261 (36%) of whom were at least 70 years of age [100]. The overall sentinel node identification rate is statistically equivalent in the group under 70 (98.8%) versus the older group (97.1%). When controlling for primary tumor size and receptor status, the detection of SLN metastases still resulted in significantly higher rates of systemic therapy administration. Sentinel node biopsy should be offered to all women diagnosed with invasive breast cancer without palpable axillary disease regardless of age. Lumpectomy with SLN biopsy, which is now considered the standard of care, can be done as an outpatient procedure with intravenous sedation and local anesthesia with limited, if any, morbidity. This is the ideal situation for the elderly population, and there should be no reason they should be denied this definitive treatment.

Axillary dissections are primarily done for local control of disease in the setting when there is a positive sentinel node. The value in preventing distant disease is more controversial, and the procedure does carry risks, such as lymphedema. But in the past, axillary dissections were often omitted in the elderly patient [36]. Even when node dissections are performed, fewer nodes are removed in the elderly [33]. The risk for the development of local recurrence in the axilla is another consideration. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial, 18% of women with clinically negative axillae who did not have an axillary dissection went on to develop delayed axillary disease [52].

Radiation therapy to the breast after BCT for invasive cancer is considered standard therapy. Yet radiation is omitted in many elderly patients. In one series, even in areas where BCT was used frequently, only 41% of women over the age of 75 years had radiation, in contrast to 90% of women younger than 65 years and 86% of women between the ages of 65 and 74 years [48]. In another report, when surgical therapy was more aggressive and included axillary dissection in the elderly, the use of radiation was also more frequent [26]. Concerns have been expressed about whether the elderly will tolerate radiation, whether they will have difficulty completing therapy because of physical restraints in getting to radiation facilities, and whether long-term outcomes are the same as in younger patients. However, studies have provided evidence to refute these concerns [119, 142].

Disturbingly, local recurrence rates for breast cancer have been reported as high as 35% in the elderly when radiation is not given [125]. A randomized study from the CALGB compared 647 women over the age of 70 with stage I estrogen-positive breast cancer that were randomized to receive either lumpectomy plus tamoxifen or lumpectomy followed by tamoxifen and radiation therapy. The group given radiation had a significantly lower risk of locoregional recurrence (1% vs. 7%; $p < 0.001$) at a median follow-up of 7.9 years [67].

A recent advance in the treatment of breast cancer with radiation has been the addition of accelerated partial breast irradiation (APBI) such as MammoSite. In a study of 1,440 patients, 1,255 of whom had invasive breast cancer, treated with APBI, 23 patients developed an ipsilateral breast tumor recurrence with a median follow-up of 30.1 months [156]. Cosmetic results were considered good to excellent in 94% of patients at two-year follow-up. This treatment might be especially beneficial to elderly patients since the full treatment can be accomplished in five days as opposed to the five to six weeks required for standard radiation therapy.

In the elderly patient who undergoes a modified radical mastectomy, very rarely is breast reconstruction performed or even offered. In one study, the single greatest predictor for a surgeon to recommend breast reconstruction was age under 50 [104]. Yet experience with breast reconstruction in patients older than 60 demonstrates that it is safe, provides good long-standing results, and has acceptable complication rates when compared to younger patients. Age alone should not be a determining factor in selecting women for breast reconstruction.

For the few elderly women with breast cancer who have significant coexisting medical problems that preclude any form of surgical therapy and who have a limited life expectancy, it is not unreasonable to treat patients with hormonal therapy alone. Two prospective randomized trials compared tamoxifen alone to surgery and found good initial response rates for tamoxifen, although local control rates were worse than with surgery [16, 125].

Breast cancer treatment in the elderly should not be different from that in the younger groups. Breast-conserving surgery has been shown to be safe and effective in treating breast cancer with low morbidity and mortality. Sentinel node biopsy may eliminate the need for axillary node dissection in a number of elderly patients. Pharmacotherapy has improved, side effects have been reduced, and the rate of breast cancer in patients at risk has continued to decrease. All these modalities decrease morbidity and are just as applicable to the elderly as they are to the younger patient with breast cancer.

Colorectal Cancer

Colorectal cancer ranks third in the incidence of all cancers in both men and women. Over 148,810 cases of colorectal cancer were estimated in 2008, with 49,960 expected deaths [71]. The incidence of colorectal cancer increases with age, with 90% of patients being diagnosed after age 55 [145]. The probability of a male aged 70 or older developing colorectal cancer is 1 in 21 (4.8%), and for a female in the same age group, it is 1 in 23 (4.3%). This is a three- to fourfold increase compared to a person aged 60–69 [71]. Right-sided colon cancer is two times more common in elderly patients compared to younger cohorts (33% vs. 16%, respectively), which may account for the later presentation seen in the elderly [10].

Symptoms at presentation are reported to be similar in elderly compared to younger patients [76]. The tumor location in some studies was not significantly different for younger versus older patients [8], but in several other reports there was a difference, with more right-sided lesions and fewer rectal lesions [18, 76, 77, 107]. Patients with right-sided lesions are more likely to present later due to fewer signs and symptoms compared to left-sided or rectal cancers. Some studies showed that a higher percentage of women over age 70 were diagnosed with colorectal cancer compared to those under 67 [18, 145]. In a recent review by the United Kingdom National Bowel Cancer Project examining the epidemiology and surgical risk of colorectal cancer in the elderly, there was a significant decrease in the number of patients above age 75 (81%) undergoing surgery compared to those younger than 75 (88%, $p < 0.001$) [145]. Elderly patients are also more likely to undergo emergency surgical procedures compared to younger populations. In one study from the British Colorectal Cancer Collaborative Group (CCCG), the incidence of undergoing an emergency operation statistically increased from 11% for patients younger than 65 to 29% ($p < 0.0001$) for those 85 or older [34]. The same study also revealed that even within the elderly population, there is a difference in both stage presentation and likelihood of undergoing curative surgery, with the “older-of-the-old” presenting with more advanced disease and less likely to undergo curative surgery. These findings have also been demonstrated in earlier studies [76].

Because of data from a number of studies that demonstrate improved survival when at least 12 lymph nodes are examined in resection specimens for colon cancer, this number is now considered the gold standard. Lymph node involvement is the most important prognostic factor in patients with nonmetastatic colon cancer. The importance of this as well as the adequacy of the number of lymph nodes removed in elderly patients were recently examined [18]. As age increased, the number of nodes removed decreased, which might reflect a lesser operation performed. The study revealed a benefit in resecting at least 12 lymph nodes irrespective of patient age.

Surgical resection of the colon or rectum remains the mainstay of curative therapy for colorectal cancer. It is required in many cases even in the presence of disseminated disease to avoid or treat the inevitable complications of obstruction and bleeding. A number of retrospective series have looked at the influence of advanced age on the risk of surgical resection of colorectal cancer [23, 53]. The risk of perioperative complications is generally reported to be higher in the elderly than in younger patients. In a meta-analysis, the cardiovascular complications were statistically significantly increased ($p < 0.001$) in one series from 0.8% in patients under 65 years old to 4% in patients over the age of 75 years [34]. Pneumonia and respiratory failure were seen in 5% of patients under 65 years of age compared to 15% in those at least age 85 ($p < 0.001$). Anastomotic leak rates in the meta-analysis were not statistically different in young versus elderly patients. This finding was also seen in a Veterans Affairs' study of surgery for colorectal cancer in patients older than 80 [90] as well as in a study by Araujo [8], which revealed no difference in anastomotic leak rate with regard to patient age.

Heriot et al. [64] recently examined the postoperative mortality rate for 2,533 elderly (age 80 and older) patients diagnosed with colorectal cancer in the U.K. The 30-day overall mortality rate was 15.6%, but increased to 27.5% for those at least age 95. Multivariate analysis for this group of very elderly patients revealed the following independent risk factors for 30-day mortality: age; operative urgency; ASA grade; resection versus no resection; metastatic disease. In a recent review by Tan, 30-day mortality was significantly lower for patients under 75 (4%) compared to older (11%) patients. In a VA study comparing colorectal patients aged 80 and older with younger matched controls, the 30-day mortality rate was higher but not statistically significant ($p = 0.10$). The overall one-, three-, and five-year survival, however, was 71%, 48%, and 31%, respectively, compared to 92%, 79%, and 71% in the control group [90].

Emergency operations are clearly associated with an increased mortality rate [70]. Elderly patients presenting with malignant large-bowel obstructions are a high-risk cohort, with increased postoperative complications and mortality [64]. Mortality rates are also high for palliative operations such as creation of a colostomy [59, 64, 140]. For example, in a review by Heriot, approximately 25% of patients who underwent either a palliative stoma or a Hartmann procedure had a 30-day postoperative mortality. These procedures are often done as an emergency in an end-stage patient—two factors known to contribute to an increased risk [59, 140]. Patients presenting as emergencies also tend to have more advanced-stage disease [161]. With the increase in mortality associated with an emergency operation and advanced-stage disease, it seems advisable to intervene earlier on an elective basis to avoid problems such as bleeding, perforation, and obstruction.

The role for laparoscopic-assisted colon resection has been shown to have similar outcomes compared to open procedures in stage II and III disease. Less postoperative pain, better pulmonary function, and less stress response seem particularly pertinent to the elderly population, where there is the potential for increased risk of morbidity associated with an open colectomy. Eight studies in the literature have compared open to laparoscopic colectomy in the elderly population, and all have concluded that laparoscopic resection was a safe option in this cohort [31]. Chautard et al. studied 536 laparoscopic colorectal procedures performed by one surgeon in 506 patients from June 1997 to August 2006. Of the 506 patients, 75 were age 70 or older and were matched with 103 younger patients with regards to risk factors and procedure performed. Only 40% of the colectomies were performed for cancer, but these patients were matched with regard to tumor stage to their younger counterparts. Conversion to an open procedure was comparable in both groups, and there were no mortalities in either group. Morbidity was not significantly different in either group. Chautard concluded that laparoscopic colectomy could be safely performed in the elderly population with similar post-operative outcomes as seen in a younger patient cohort despite the higher incidence of cardiorespiratory comorbidities pre-operatively, but the sample size over age 70 was small.

The quality of life, although more difficult to measure, is an important outcome for any planned treatment. Creating a stoma must be viewed with caution, as it may be difficult for some elderly patients to manage not only physically but also psychologically. One series examined the posthospital course of patients over 80 years old who underwent surgery for a gastrointestinal tumor [103]. Thirty-one percent of patients went home following surgery, 51% convalesced in a specialized home or medical recovery center, 10% went to a nursing home or specialized institution, and 4% required nursing assistance at home or went to a family member's home. Overall, 83% eventually returned to their homes without any change in their social environment. Using a survey, a Canadian study also explored the impact of surgery for colorectal cancer on quality of life and functional status in the elderly population (above 80). Those elderly patients who were selected to undergo a surgical procedure had a quality of life preoperatively that was comparable to the younger control population. Also, survivors of over five years had a quality of life comparable to their preoperative level. Stoma care, however, was a greater concern in the elderly population [97].

In a retrospective review of 50,042 patients with stage III colon cancer, Greene et al. revealed that patients at least age 70 have a lower survival rate than younger patients in the same stage subset [60]. The reason for this inferior survival may have been the reduced use of adjuvant chemotherapy in this age group. In a recent study comparing patients aged 75 and older to those under 75, cancer-related survival was comparable despite an increase in operative mortality compared to the younger population [8]. A recent Swiss study investigating surgery for rectal cancer in patients aged 80 and older concluded that, whenever possible, treatment with curative intent be employed in patients with rectal cancer regardless of age. The five-year overall survival was 67%, yet the majority of deaths that occurred within five years after surgery were not related to the cancer [6]. Another series indicated that although the physical status and operative mortality were worse in the elderly undergoing surgery for colorectal cancer, for those elderly who were fit for surgery, who underwent curative resection, and who survived over 30 days, the five-year survival was as good as in younger patients by multivariate analysis [9, 77]. Age alone should not be a contraindication for colectomy, and whenever possible the full curative treatment including adjuvant chemotherapy should be utilized when indicated.

Liver Metastasis for Colorectal Cancer

The liver is the most common site of metastasis for colorectal cancer. Liver resection remains the optimal treatment for patients with three or fewer colorectal liver metastases. Liver resection can lead to a 21–48% five-year survival in selected patients [67, 131, 126, 152, 141, 113]. The safety for performing liver resections has greatly improved in recent years owing to improvements in techniques of resection and intraoperative and postoperative care. Liver resections are now being performed with mortality rates of less than 5% [40, 68, 113, 126, 141].

Liver resections can also be performed safely in elderly patients. A number of series have looked at morbidity and mortality rates for older individuals. Fong et al. reviewed liver resections for colorectal metastases in 128 patients over 70 years old [54]. For patients over 70 years old, the perioperative mortality rate and the morbidity rate were the same as for patients younger than age 70. Most of the complications in the elderly were cardiopulmonary. In a multivariate analysis, three factors were found to be important in predicting complications. These were male sex, resection of at least one lobe of the liver, and an operating time of greater than four hours. The median hospital stay for patients aged 70 years and older was only one day longer than for patients less than 70 years old.

In a series of 61 patients older than 70 years, the morbidity was 41% and the mortality was 0% for first-time resections. The mortality increased for a repeat liver resection up to 7% [173]. Factors associated with poor long-term survival in a multivariate analysis were extrahepatic disease, high CEA level (> 200), and the presence of at least three liver lesions. The five-year survival rate of 36% was similar to those of younger patients after the first liver resection for patients without the presence of risk factors.

A recent Japanese study looked at 212 consecutive patients who underwent hepatic resection of colorectal liver metastases. The patients were divided into two groups: age 70 and older versus those under 70. The older patients (age 70 and older) were more likely to have severe cardiopulmonary disease and respiratory insufficiency. Similar rates of postoperative complications and mortality rates (0% in the elderly group vs. 0.49% in the younger group) were seen. The authors concluded that age should not be regarded as a medical contraindication for surgery in this setting [25].

These findings were also seen in a recent Italian review. The study compared surgical treatment of colorectal liver metastases in patients aged 70 and older versus those under 70. There was no statistical difference in overall morbidity, in-hospital mortality, or five-year survival. This group likewise concluded that age alone should not be a contraindication to surgery [98].

Long-term survival following liver resection for colorectal metastases is not influenced by age. No statistically significant difference in survival was found between elderly patients or younger patients in multiple reports [130]. Thus, an elderly patient with colorectal metastatic disease limited to the liver should do the same after liver resection as a younger patient unless he or she has prohibitive comorbidities.

Hepatocellular Cancer

In the United States, liver and intrahepatic bile duct cancer accounted for an estimated 21,370 cases in 2008 [71], with an estimated 18,410 deaths. Hepatic resection is the treatment of choice for patients with hepatocellular cancer (HCC) who do not have advanced cirrhosis. Treatment with major liver resections has resulted in a substantial decrease in mortality over the past 30 years, from 20% in the 1970s to less than 5% today [4]. This is due to a better understanding of liver anatomy and improved techniques for surgical resection. This has also led to a broadening of the indications for hepatic resection.

The extensive experience with resection of colorectal liver metastases demonstrates that liver resections can be performed safely in the elderly. Many patients with HCC, unlike those with metastatic colorectal cancer, have underlying cirrhosis, making surgical resection more challenging and dangerous. The functional reserve problems that are encountered with liver resection in the elderly are compounded by the presence of cirrhosis.

Comparative studies of the outcome of hepatic resection for HCC in the elderly versus the young patient are infrequent in the English literature [4] (Table 1). Many of these have been included in larger studies of hepatic resections for a wide

Table 1 Hepatic resection for HCC in the elderly

Reference	Number of patients	Age	Number with hepatic failure (%)	Number of perioperative deaths (%)	Five-year survival rate (%)
[47]	37	>65	1 (2.7)	2 (5)	18.1
[150]	32	>70	2 (6.3)	4 (12.5)	17.6
[144]	39	>70	4 (10)	5	51.6
[62]	103	>70		5 (4.9)	51
[32]	26	>65			60
[129]	34	>70			39.6
[4]	14	>75	0 (0)	0 (0)	

multitude of reasons ranging from benign disease to HCC to colorectal metastasis.

The morbidity and mortality associated with resection for hepatocellular carcinoma in the elderly have been comparable when compared to the younger cohort of patients [41, 62, 144] (Table 1). With the exception of one series, the mortality rates are similar to those for younger patients [169]. In one study of 103 elderly patients, 70 years or older, with hepatocellular carcinoma, the resectability rate was 84% in the elderly, compared to 88% in the younger group [62]. The morbidity and mortality were comparable between the elderly and younger patients, 28.2% vs. 23.3 % and 9.7% vs. 6.0%, respectively. In the Milan study, the surgical complication rate for patients older than 75 undergoing resection for HCC was 0% compared to 38.5% in younger patients ($p = 0.005$) [4]. The median stay in the older patients was 7.5 days, which was less than the younger patients' median stay of 9 days ($p = 0.18$).

The presence and severity of cirrhosis as judged by Child's criteria influence the rate of operative morbidity and mortality. Regardless of their age, patients with advanced cirrhosis may not be candidates for major hepatic resection [41, 62, 109].

The overall five-year survival has been reported to be comparable with the younger patients', ranging from 24.3 to 60% [62]. Hepatic resection for HCC is safe to perform in elderly patients as long as it is preceded by an accurate selection, including a significant workup of cardiopulmonary disease as discussed earlier.

Pancreatic Cancer

Over two thirds of patients with pancreatic cancer are over the age of 65 years at diagnosis [112, 3, 135]. In the United States, pancreatic cancer accounted for an estimated 37,680 cases in 2008 [71], with an estimated 34,290 deaths, making it the fourth most common cause of cancer-related deaths. The overall survival of patients with pancreatic cancer is dismal, with a five-year survival of 5%, up from 3% in 1986 [71]. This is attributed in part to the fact that the majority of patients with pancreatic cancer are diagnosed late in the course of the disease, when surgical resection is no longer feasible, as only 9–15% of patients are amenable to surgical resection [112, 135]. Also, there remains a bias against surgery for pancreatic cancer, so that even potentially surgically curable patients may not be referred to surgery. Even when resection is possible, the five-year survival is still only 20%.

A pancreaticoduodenectomy (PD), with or without sparing the pylorus, is the operation of choice for the most common lesions, which are located in the head of the pancreas. This is also the case for periampullary, duodenal, and distal common bile duct neoplasms. Until the early 1980s, pancreatic resection was associated with an extremely high complication rate and also a mortality rate as high as 26%. When weighed against the relatively small survival impact seen with successful surgery, many viewed the procedure as an unreasonable option for treatment [43, 35]. The role of this operation in elderly patients was fraught with even more concern due to the high morbidity and mortality risks. However, in more recent years, the morbidity and mortality rates associated with the Whipple operation have decreased significantly at specialty centers [27, 101, 160]. Mortality rates between 0-5% are more now the standard at high-volume centers [27, 101, 147]. In selected elderly patients, mortality rates for surgery are acceptable and even comparable to the younger group [54, 63, 93, 159]. The major causes of morbidity after pancreatic resection are related to complications associated with pancreatic fistula, anastomotic breakdown, and sepsis [83, 147, 160, 172].

One review of 138 patients over 70 years old who underwent pancreatic resection for malignancy reported an operative mortality rate of 6% and a morbidity rate of over 40% [54]. No significant differences were found in the length of hospital stay, the rate of intensive care unit admission, and morbidity or mortality rates between patients younger than 70 years old and those older than 70 years. A univariate analysis revealed that a history of cardiopulmonary disease, an abnormal preoperative electrocardiogram, or an abnormal chest radiograph were predictors of complications. However, the multivariate analysis found that the only factor that was a significant predictor of complications was a blood loss of more than 2 liters. The median survival was 18 months, and the five-year survival was 21%.

In an Italian study, 88 consecutive patients (70 patients with adenocarcinoma) who had a major pancreatic resection were evaluated in two groups: younger than 70 (53 patients), and at least 70 years old (35 patients) [28]. Survival and length of stay were not statistically different, but the presence of COPD was associated with a significantly higher mortality rate (30%, $p = 0.018$) compared to elderly patients without COPD (0%).

In another Italian study, 166 patients underwent curative PD for pancreatic adenocarcinoma over an 11-year period. The patients were divided into those older than 70 and those under 70. There was a trend ($p = 0.09$) toward a difference in the postoperative death rate between the two groups. This trend was related to the significantly higher operative mortality rate in elderly patients undergoing reoperation for surgical complications, mostly secondary to pancreatic-jejunal anastomotic leaks. Despite this, the pancreatic fistula rate and the overall complication rate were similar between the two groups [24].

Several other smaller series of pancreatic resections have also reported mortality rates in patients over 70 years old to be 5–14%, with morbidity rates of 14–48% ([37, 73, 139, 159].

The Johns Hopkins group has reported a series on 37 patients who were over the age of 70 years [27]. No significant differences were found between the length of stay and the rate of complications in patients over 70 years old compared to younger patients. However, the patients were admittedly carefully selected prior to the operation, as evidenced by no differences in the preoperative medical risk factors between patients under and over the age of 70 years. Another study from Hopkins evaluating the PD procedure in octogenarians showed that they had a longer postoperative length of stay and complication rate compared to younger patients. The mortality rate, however, was similar between the two groups [138].

Although long-term survival rates for resection are still low, they are not different in the elderly [101, 147]. One series reported a five-year survival rate for pancreatic cancer of 17% and 38% for periampullary tumors in patients over the age of 70 years and 19% for pancreatic cancer and 45% for periampullary tumors in patients younger than 70 years old [63]. The Hopkins group reported a five-year survival rate for pancreatic cancer of 19% in patients over the age of 80 years and 27% in patients under 80 years old (*p* value not significant) [138]. Despite limited long-term survival, resection remains superior to bypass or laparotomy alone. In a review of over 3,000 patients from the 1970s, mean survivals of 12.7 months for resection, 5.7 months for bypass, and 2.6 months for laparotomy alone were reported [164]. In the same review of over 2,000 patients from the 1980s, the mean survival increased significantly in resected patients to 17 months, whereas bypass (6.6 months) and laparotomy alone (3.1 months) were no different.

Still, the majority of patients with pancreatic cancer cannot be resected. In the past, surgery was needed in nearly 50% of patients for palliation of the two common complications that occur in the natural course of the disease, biliary and gastric obstruction [164]. Pain often also requires palliation. The mean survival of patients after bypass is considerably lower than for resection, at 4.0–11.3 months [164]. The operative mortality rate for biliary bypass ranges from 4–33%, with a mean of 19% [129]. The elderly may not tolerate bypass procedures as well as younger patients. A VA study did indicate a higher 30-day morbidity and mortality rate and a lower median survival rate after bypass procedures, which was statistically significant for patients over 70 years old [160]. However, VA patients may have unique characteristics that put them at higher risk. Each patient must be judged on an individual basis, taking into consideration the overall status of the patient and the expected benefit.

Currently, biliary obstruction can be effectively managed with stents placed either endoscopically or percutaneously transhepatically, as shown in several randomized series [7, 22, 42, 134]. Mortality rates are lower for stent placement than for surgical bypass and hospital stays are shorter. Although early complication rates are lower, long-term complication rates such as recurrent jaundice and cholangitis are more common than with surgical bypass but are acceptable in light of the high surgical morbidity and mortality for bypass procedures.

Gastric outlet obstruction, although a far less common presenting symptom, usually requires operative bypass for relief. The overall value of this procedure may be questioned because survival after bypass is often limited and does not always result in palliation [165]. More recently, endoscopically placed stents have been utilized as a surgical alternative.

Gastric Cancer

Gastric cancer rates have been declining over the past 75 years in the United States [78], but the prognosis has not improved, with five-year survival being 20–40% [121]. There were an estimated approximately 21,500 new cases in the United States in 2008 and 10,880 deaths [78]. Most of these were adenocarcinomas (86%), with 9% gastric lymphomas and 5% GIST/neuroendocrine tumors. Despite the fact that the incidence of the disease has fallen in the past 75 years, the number of patients diagnosed at or above age 75 is actually increasing [121]. Gastric cancer is generally seen in the elderly, with nearly 50% of males diagnosed with gastric cancer in the United States and 60% of females over the age of 70 years [175]. Surgery is the only curative modality currently available for gastric cancer, and in noncurative situations, palliative surgery is often needed for bleeding and obstruction. Surgery is the most powerful tool to improve prognosis, but the problem is the delay in diagnosis that leads to advanced disease at the time of exploration.

In Asia, where gastric cancer is much more common, many investigators have examined the characteristics of gastric cancer in the elderly. Symptoms at presentation and the location of disease in the stomach are similar in younger and older patients [15, 81]. One series reports no difference in histological type, whereas another reports a higher incidence of intestinal-type histology in the elderly [15, 81, 168]. The macroscopic pattern according to the Borrman criteria appears to be more localized in the elderly, but the occurrence of synchronous multiple primaries is greater and ranges from 7.7-13.2% [15, 81, 95]. The incidence of angiolymphatic invasion has been reported to be higher in the elderly. Two Japanese studies showed no difference with age in the incidence of lymph node metastases and stage at diagnosis, and 60% of all patients treated had T3 and T4 disease at the time of exploration [15, 81].

Curative surgery for gastric cancer requires either subtotal or total gastrectomy depending on the location of the tumor. The exact extent of lymph node dissection necessary remains a controversial subject. The removal of perigastric nodes is termed a Dl resection, whereas the removal of more extensive regional lymph nodes outside the perigastric region is termed a D2 resection. There is no agreement about whether to perform a D1 or D2 resection, especially when comparing the Western versus Asian literature. In the Western literature, studies have not shown a benefit to a more extensive lymph node dissection and have shown higher complication rates after D2 regional node dissections [21]. In a large prospective randomized trial from the Netherlands, with an average patient age in the mid-60s, the rate of surgical complications was doubled after D2 resections [21]. The rate of nonsurgical complications (with the exception of pulmonary complications, which were also doubled in the D2 group) such as cardiac, urinary tract, and thromboembolic was similar in both groups.

There have been a number of reports on the morbidity and mortality rates of gastric resections in the elderly (Table 2). Although preoperative risk factors are increased in the elderly with gastric cancer, particularly of a cardiac and pulmonary nature, the majority of complications and deaths are caused by infections, anastomotic leaks, and pulmonary problems, which are the same as in younger patients [19, 21, 116].

Table 2 Gastric resections in the elderly

Reference	Country	Age	Number of patients	Morbidity (%)	Mortality (%)
[158]	Norway	≥80	106	34	15
[21]	the Netherlands	>70	231		
		D1 dissection	128	30	7
		D2 dissection	103	45	18
[148]	Japan	70–79	341	22	5.3
		≥80[b]	43	23	5
[133][a]	USA	>70	310	47.1	7.1
[168]	Taiwan	≥65	433	21.7	5.1
[128]	USA	≥70	24	33.3	8.33
[102]	Japan	≥70	30[c]	13.3	0
		≥70	16[d]	25	0
[86]	Japan	≥75	117	29	0.85
[61]	Germany	>75	48	48	8
[114]	Italy	≥75	249	29	3

[a] 85% > D1 resection.
[b] Limited surgical procedures only 10-year.
[c] All laparoscopic-assisted gastrectomies.
[d] All open gastrectomies.

A recent Italian study reviewing 1,118 gastric resections for gastric cancer over a 15-year period had similar findings to that of the Japanese study. The study revealed that the overall postoperative surgical complication rate was 20% in the elderly group (age 75 and above) versus 17% in the younger. The postoperative mortality rate for both groups was 3%. Multivariate analysis revealed that age was not a risk factor for either postoperative morbidity or mortality [114].

The role of laparoscopy for gastric cancer has increased greatly over the past decade. Mochiki and colleagues investigated the role of laparoscopic-assisted gastrectomy for early gastric cancer in elderly (greater than age 70) patients in Japan. Early gastric cancer is more common in Japan due to increased surveillance since the disease is more prevalent than in Western countries. Blood loss was significantly less in the elderly than in the younger patient population. Operating time was the same in both groups, and there was no difference in postoperative complication rate or mortality [102]. They concluded that laparoscopic-assisted distal gastrectomy is safe in the elderly patient population, but the long-term survivals have not been studied in a comparative fashion.

An important element in deciding about surgical treatment in the elderly is the impact on the quality of life. In a small series of patients over the age of 70 years undergoing total gastrectomy, 70% of patients returned to "normal life" after one year, although the regaining of body weight was slower than in younger patients [82].

The five-year survival for curatively resected patients with gastric cancer is similar for younger and older patients (Table 3). In a recent Japanese study, the overall survival was significantly

Table 3 Gastric cancer survival after curative resection in young versus elderly patients

Reference	Number of patients	Age	Five-year survival (%)	Cancer-specific survival (%)
[19]	57	<70	14.5	
	24	≥70	19.4	
[15]	232	<70	49.4[b]	
		>70	48.6	
[146]	480	50–59	66.3[a]	
	578	60–69	58.3	
	341	70–79	48.6	
	432	≥80	28	
[128]	24	<70	20.8[b]	
	24	≥70	16.6	
[102]	73	<70	98.4[b,c]	
	30	≥70	95.7[c]	
[86]	625	45–65	73.6	76.3
	117	≥75	59.2	72.2
[61]	148	<60	59	63
	167	60–75	46	53
	48	>75	40	61
[114]	869	<75	54[b]	
	249	≥75	47	

[a]Survival rates are significantly different between age groups.
[b]Survival rates are not significantly different between age groups.
[c]Laparoscopic-assisted distal gastrectomy for early gastric cancer only.

different between the two groups ($p < 0.0001$), but the cause-specific survival was not statistically different ($p = 0.3447$) [86]. A U.S. study found that the five-year survival was 17% for elderly patients (>70) compared to 21% for younger patients ($p = 0.45$). Surgical resection for gastric cancer should be offered to patients irrespective of age, as this offers the only chance for cure.

A smaller percentage of patients with gastric neoplasms are diagnosed with gastric lymphoma, which, like gastric adenocarcinoma, is a disease of the elderly. The treatment has changed greatly in the past 20 years from surgical to medical management. This shift toward medical management of this problem was due to the significant morbidity and mortality associated with the operative interventions in this setting. Today patients with mucosal-associated lymphoid tissue (MALT) lymphomas are treated with a "triple therapy" consisting of antibiotics. More advanced lymphomas may require chemotherapy and radiation. Surgery is now reserved for the patients with obstruction or bleeding who cannot be treated with these nonsurgical modalities.

Melanoma

The overall incidence of melanoma in the United States is increasing, and surgery continues to be the mainstay of therapy. In 2008, 62,480 new cases of cutaneous melanoma were expected, with estimated deaths of 11,200 [71]. The cumulative lifetime risk of developing melanoma in the United States in 1980 was 1/250, compared to 1/68 in 2002 [91]. The incidence of melanoma in the older population is increasing, while the incidence in the younger populations appears to be leveling off or even declining [30]. In 1985, 21.2% of cases occurred in patients over 70 years of age [149], and in 1990, this number increased to 27.2% of cases. Nearly 50% of all melanoma deaths in the United States are in white men older than age 50 [30]. Many studies have shown that men diagnosed with melanoma have a worse prognosis than women. However, in one study with over 12,000 patients, a multivariate analysis showed age to be independently important in the prognosis, especially in women [75].

The characteristics of melanoma appear to be slightly different in the elderly. Although the extremities are the most common location for melanomas in females, head and neck melanomas become more frequent with advancing age [146, 75]. In men, truncal melanomas are most common, but again head and neck melanomas become more frequent and surpass truncal melanomas after the age of 70 [146, 75]. Older patients have been reported to have worse prognostic indicators, with an increased incidence of ulceration, thicker melanomas, and deeper levels of invasion [12, 96, 108]. A study of more than 17,000 patients showed that for each 10-year increase in age, there was a decrease in both the 5- and 10-year survival rates [13]. This was corroborated in another study of 488 patients with nonmetastatic melanoma, where the 10-year survival rate was 84% for patients younger than 60 compared to 57% for those 60 or older [132]. Whether this represents a delay in the diagnosis or a worse malignant potential of these lesions in the elderly population is unknown.

The treatment for malignant melanoma is surgical excision with adequate margins; there is no evidence to suggest that the treatment for the elderly should be any different. Controversies over the width of margins and the need for regional lymph node dissection have been addressed in a number of randomized trials. These studies have shown that the necessary width of margins of resection is determined by the thickness of the primary melanoma. For lesions less than 1 mm thick, a 1-cm margin is adequate [153, 154]. For lesions greater than 1 mm thick, a margin of 2 cm is advised based on the results of the Intergroup Melanoma Surgery Trial [14, 74].

Although age has not been used as a criterion for determining the margins of resection, one large retrospective series did report age to be a significant independent factor in the risk for local recurrence [150]. Patients over 60 years old were found to have a local recurrence rate of 7.8%, patients between the ages of 30–59 had a local recurrence rate of 2.5%, and patients under 30 years old had a local recurrence rate of 1.2% at a median follow-up of eight years. Another study reported a 12.1% local recurrence rate for patients over the age of 70 with thin melanomas (<0.76 mm) [137]. Although an analysis was not performed for potential factors affecting this high recurrence rate, it might be explained by the higher incidence of head and neck melanomas in the elderly, with its attendant higher rate of local recurrence. In the prospective randomized trial evaluating margins, no difference was found in the rate of local recurrence for age over 50 years old versus under 50 years old [74]. However, a higher rate of local recurrence was demonstrated for head and neck lesions.

The dissection of regional lymph nodes for melanoma treatment is routine for patients with clinically positive nodes; however, the value of elective node dissection (ELND) for patients with clinically negative lymph nodes has long been debated. Since regional node dissections carry significant long-term complications, it would be advantageous to avoid them in patients with known negative lymph nodes. The use of the sentinel lymph node (SLN) biopsy technique, introduced by Morton in 1992, has allowed an accurate evaluation of the lymph node basin without a complete dissection. However, complete dissections are still necessary for positive sentinel nodes and for palpable nodal disease. Patients are now routinely getting SLN biopsies for any lesion greater than 1 mm in thickness.

SLN biopsies can be done using one of two techniques or combining both. The original technique used a blue dye injected intradermally at the site of the primary melanoma. The regional node basin was then explored surgically for the identification of a "blue node," which was removed. These were termed the sentinel lymph nodes. If these nodes were positive for tumor on permanent section, then a full node dissection would be performed at a separate time. If negative, then no dissection was done. Initial experience with this technique showed the blue dye method was able to identify the sentinel lymph node in 82% of patients [105]. The false-negative rate of the technique in identifying the presence of metastatic disease was 1% [105]. Because of technical difficulties with the blue dye, radiolymphoscintigraphy using technetium-labeled sulfur colloid has been utilized to locate the sentinel node [85]. Utilizing both techniques has allowed the sentinel node to now be harvested with 98% accuracy [92].

Morton [106] reported the findings of 1,269 patients with intermediate-thickness melanomas (1.2–3.5 mm) randomly assigned to wide local excision with or without SLN biopsy. As expected, disease-free survival was significantly higher ($p = 0.009$) in the patients undergoing SLN biopsy compared to the observation group at five years since potentially positive lymph nodes were not removed from this group. The overall rate of death from melanoma and melanoma-specific survival, however, was similar for both groups, but for patients with positive nodal metastasis, the five-year survival rate was higher in the SLN group (72% vs. 52%). Also, the number of positive lymph nodes was lower in the SLN group (1.4 vs. 3.3), showing disease progression during observation. This study led to the conclusion that SLN biopsy has staging, prognostic, and survival value in patients with intermediate-thickness melanoma.

Adjuvant therapy for stage III melanoma remains controversial. High-dose interferon alfa-2b was approved by the U.S. Food and Drug Administration for adjuvant therapy of high-risk melanoma (stage IIb and III) in 1995 [78, 80] but is highly toxic. A pooled analysis of adjuvant high dose interferon trials showed a benefit in relapse free survival but not overall survival [79]. Currently, patients with high-risk melanoma should be offered interferon therapy or enrollment in a clinical trial.

In a large retrospective analysis of the national cancer database for melanoma (comprising a total of 84,836 cases), factors associated with decreased survival included more advanced stage at diagnosis, nodular or acral lentiginous histology, increased age, male gender, nonwhite race, and lower income. Five-year survival was worse stage for stage in patients 60 years or older. For early disease, the five-year survival was 81.4% for patients older than 60 versus 90.5% for those under 60 years.

For late disease, the five-year survival was 32% for the older patients versus 40.5% for the younger ones [29].

Because surgical treatment of melanoma can be done with low risk, in fact under local anesthesia if necessary, no one should be denied it because of age or poor performance status. Treatment of melanoma for elderly patients should be as aggressive as in younger patients.

Esophageal Cancer

The incidence of esophageal cancer is rising in the United States, with an estimated 16,470 Americans diagnosed in 2008 versus 13,100 in 2002 [71, 72]. Most of this increase is associated with an increase in the number of cases of adenocarcinoma. The death rate remains high, with 14,280 deaths in 2008 versus 12,600 in 2002 [71, 72]. Most cases (79%) are diagnosed in men between the fifth and seventh decades of life. The five-year survival rate has tripled from 6% in the mid-1970s to 18% as of 2003 [71].

Although controversies exist on the treatment for primary esophageal cancer, with the increase in adenocarcinoma and distal esophageal lesions, surgery has become more common as a first-line therapy. Morbidity and mortality for esophagectomy have improved but are still significant. Some reports state that mortality rates are strongly related to age and preoperative performance status [121, 2, 50]. In more recent reports, morbidity and mortality rates are similar for elderly and younger patients mostly as a result of advances in perioperative management [20, 44, 123].

An Italian group studied the effects of advanced age on the outcomes from esophagectomy for esophageal cancer at a high-volume center [127]. The patients, who underwent surgery between 1992 and 2005, were divided between those under 70 (580 patients) and those 70 and above (159 patients). All patients underwent a laparotomy with a right thoracotomy, with some patients requiring a left cervical incision for a tumor in the upper third of the esophagus. Preoperative cardiac and pulmonary risk factors were more common in the elderly group. The 30-day mortality rate and overall morbidity rate were the same for both groups, at 1.9% and 49%, respectively. The overall five-year survival rate was 33.6% for the younger patients and 35.4% for the older group ($p = 0.257$). In the elderly, survival rates were the same for patients aged 70–74 versus those who were older.

A recent report from China showed similar findings when comparing esophagectomy for esophageal cancer in elderly patients versus younger ones. Again, the elderly population was more likely to have comorbid conditions, including hypertension, respiratory dysfunction, and diabetes. The morbidity and mortality rates were similar in both groups despite the fact that cardiopulmonary complications were encountered more frequently in the elderly group [94].

These data support the use of esophagectomy in the elderly. It has been shown that esophagectomy can be performed safely in elderly patients even with comorbid conditions, and they can be expected to have equivalent long-term survival after a curative resection.

Conclusions

Surgical intervention in the elderly should no longer be ruled out simply because of the patient's numerical age. Appropriate evaluation of the existing comorbidities and optimization are essential to successful surgical outcomes. Multiple studies have shown the safety and benefit of performing a vast range of oncologic surgeries in the elderly. As the population ages, more elderly patients will present with neoplasms, which will need surgical intervention. The data demonstrate that under optimized conditions, the elderly can do as well in terms of morbidity and mortality as their younger counterparts. If surgery is deemed to be the appropriate therapy for the particular cancer, the elderly patient should not be denied this modality because of his or her age.

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Chemotherapy for the Older Adult with Cancer

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Introduction

Cancer is a disease of aging; approximately 60% of all cancers and 70% of cancer mortality occur in persons aged 65 years and over. Aging is a highly individualized process, characterized by physiologic and psychosocial changes that can affect tolerance to treatment. Older patients are a highly heterogeneous group, with varying levels of risk for functional or physical decline and mortality. Historically, clinical trials have not reflected the general population of older cancer patients due to the low numbers of older patients included and the strict inclusion criteria for healthy, "fit" older adults [1]. Therefore, the majority of patients aged 65 years and older with cancer are treated based on data derived from clinical trials that often describe the effects of treatment on the median-age population enrolled in the studies or on the elderly with good performance status. It is difficult and often impossible to extrapolate these data for the treatment of older vulnerable patients who may suffer from severe or multiple comorbidities and varying functional health statuses [2].

Because the underlying health status of included older persons is not well defined or characterized in trials, the results of efficacy and tolerance to treatment often conflict. Some

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authors suggest no significant relationship among the age of the patient and treatment decisions, delivered dose, toxicity, or clearance rate of drugs, despite age-related physiologic changes [3]. Others consider several variables in the decision process, such as the anticipated life expectancy at a specific age, comorbid conditions, and the benefits versus risks of treatment [4]. Most authors agree that age alone should not be used to deny chemotherapy to elderly patients [5].

Although “fit” older persons derive a similar benefit to chemotherapy as their younger counterparts, complications from cytotoxic chemotherapy are more common in older patients. Age-related physiologic changes can increase the toxicity of chemotherapy. In prospective trials of chemotherapy for solid tumors and lymphoma, age is a risk factor for neutropenia and its complications. Anemia can affect quality of life. Myelosuppression, mucositis, cardiac toxicity, and neurotoxicity are all more common in older persons receiving chemotherapy [6].

The evidence suggests that comorbidities and performance status correlate directly with the outcomes and toxicity of therapy. Although the commonly used Karnofsky and Eastern Cooperative Oncology Group (ECOG) performance measures do correlate with treatment toxicity, these tools alone do not reliably predict survival in the elderly [7–9]. Geriatric assessment, a compilation of standardized tools to assess geriatric domains such as comorbidity, functional status, nutrition, physical and cognitive performance, and social support, can help define the “stage of the age.” Geriatric assessment thus can better quantify life expectancy and predict tolerance to treatment [10–12]. Geriatric assessment adds important information to the traditional performance status assessment tools utilized in oncology [13]. Unfortunately, clinical trial data that dictate evidence-based care for older patients with cancer have not generally included geriatric assessment tools. Most trials have thus utilized chronologic age and performance status as predictors of toxicity.

This chapter provides a systems-based overview of how age-related physiologic changes can influence the pharmacology of anticancer therapies. It also discusses the tolerance of specific anticancer treatments as a function of age.

Pharmacology of Cancer Therapies in Older Adults

Although aging is a heterogeneous process, certain common and characteristic age-related physiologic changes can lead to differences in the pharmacology of cancer therapies in elderly patients compared to their younger counterparts. These age-related changes can be subtle and difficult to identify. Pharmacokinetic studies of cancer chemotherapy have included only a very small number of older patients, and it is often difficult to apply these data to the clinical care of older populations. Consequently, the data that are utilized for chemotherapy dosing are inferred from clinical trials that did not specifically target older persons [14].

Pharmokinetics describes the interactions between the drug and the host in terms of absorption, distribution, metabolism, and excretion of the drug. Aging processes can affect all aspects of the pharmacokinetics and pharmacodynamics of anticancer therapies in older patients. Absorption is affected by mucosal atrophy, diminished secretion of digestive enzymes, decreased gastrointestinal motility, and altered splanchnic blood flow [15, 16]. Absorption is an important issue, as oral therapies increase in importance. In addition, factors that affect absorption can impact the efficacy of supportive care medications. In older cancer patients, nonadherence to prescribed medications is prevalent and can influence survival [17]. Nonadherence to therapies may result from both clinician and patient factors. The clinician may fail to understand the patient's cognitive, functional, or financial status. The patient may not fully understand the reasons behind certain medications and may not fully grasp the scheduling and dosing of complex treatment regimens. In addition, comorbid conditions such as depression or dementia and the use of multiple other medications may affect adherence.

The volume of distribution (Vd), which is dependent on body composition and the proportion of lean body mass, fat, and total water, is a variable affected by nutrition and hydration [18]. In the elderly, both a doubled fat content and decreased intracellular water lead to an increased volume of distribution for drugs that primarily distribute in body water and may, at the same time, increase the distribution of lipid-soluble drugs [14]. These distribution effects may lead to changes in peak concentration and prolongation of terminal half-life in older patients compared to their younger counterparts. Furthermore, comorbid conditions—most commonly renal insufficiency, heart failure, and the presence of ascites or effusion—increase the volume of distribution and require a dose adjustment of certain agents. The albumin concentration can affect protein-bound drugs. Albumin concentrations are decreased in older patients due to the decreased manufacturing ability of the liver, decreased intestinal absorption, and poor nutritional status. Therefore, protein-bound drugs such as valproic acid, naproxen, phenytoin, and others are displaced in older patients, leading to higher drug concentrations [19]. In addition, concomitant medications can further displace protein-bound drugs. Some anticancer drugs, including antimetabolites, enzymes, alkylating agents, and topoisomerase I and I/II inhibitors, are heavily bound to red blood cells, and the volume of distribution of these medications may be affected by anemia, which is more prevalent in older persons [20]. Correction of anemia may be beneficial in these patients, as it is one of the few factors that can be manipulated quickly to modify the volume of distribution [14, 20].

The liver, which is the main site of drug metabolism, is also affected by age-related processes. In older patients, metabolic clearance of a drug by the liver may be reduced because aging decreases the liver blood flow, size, and mass. The first phase of drug metabolism occurs through the liver's cytochrome P450 (CYP450) system. The CYP450 system functionally declines with age, with a decrease in enzyme activity of 20–25% in healthy older persons compared to younger persons [21]. Clinically important differences in drug metabolism could be related to genetic variability [22]. It is often difficult to quantify the effect of age on metabolism because of variations in the activity of drug-metabolizing enzymes, transport plasma proteins, and blood flow [23]. In addition, older patients have more profound individual differences due to the accumulated effects of comorbidities and a higher potential for drug-drug interactions [24].

Age-related changes in renal function can affect the elimination of anticancer therapies. These changes include reduced kidney size, decreased renal blood flow, a decreased number of functioning nephrons, and decreased renal tubular secretion. Together, these changes lead to a lowering of the glomerular filtration rate (GFR) in older persons. On average, the GFR decreases by 0.75–1.00 ml/min/yr after age 40 [25]. Although decreases in renal function in the elderly are common, approximately one third of older patients will not experience a decrease in creatinine clearance [25, 26]. Serum creatinine is the most common tool utilized to evaluate renal function (Fig. 1). While serum creatinine tends to accurately reflect the glomerular filtration rate in younger adults, it does not always accurately reflect renal function in older patients. In older patients, serum creatinine can remain in the normal range due to a lower lean body mass and a lower glomerular filtration rate, masking changes in creatinine clearance.

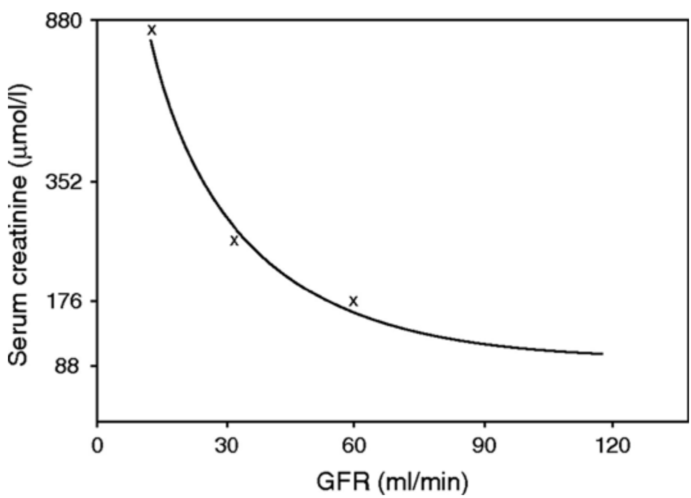

Fig. 1 Relationship between serum creatinine (SCr) and glomerular filtration rate(GFR)
Source: Launay-Vacher, V et al. Ann Oncol 2007 18:1314-1321; doi10.1093/annonc/mdd011

Chemotherapy that is primarily excreted through the kidney must be utilized with extreme caution in older patients with renal dysfunction. Guidelines for the use of potentially nephrotoxic chemotherapy agents are described later in this chapter.

Stem cell and hematopoietic reserve can be compromised in older patients. This lowered reserve can lead to serious adverse chemotherapy effects. The incidence and prevalence of myelosuppression increase with age in both men and women and are common among older patients who are more vulnerable or frail due to comorbidities and functional impairment [27]. A number of studies have reported an association between uncorrected chemotherapy-related anemia and poor patient outcomes [28–31]. Erythropoiesis-stimulating agents (ESA) have recently been shown to shorten overall survival potentially by increasing the risk of tumor progression or recurrence in some clinical studies involving breast, non-small cell lung, head and neck, lymphoid, and cervical cancers [32]. Red blood cell transfusions may prove beneficial in situations when correction of the hemoglobin level and improvement in fatigue are desired, but frequent transfusions are associated with transfusion reactions, acute heart failure, iron overload, and virus transmission. In one study of patients with esophageal cancer treated with combined chemoradiotherapy, transfusion in patients with pretreatment hemoglobin levels less than or equal to 12 g/dl was strongly associated with improved overall survival [33]. Data to suggest similar outcomes in other elderly cancer patients are lacking, so the risks and benefits of therapeutic options such as transfusion and ESA after evaluation of anemia should be carefully weighed in each case. Current guidelines advocate the correction of anemia (hemoglobin $\leq$12 g/dl) in symptomatic older patients receiving chemotherapy [34].

The risk of neutropenia from chemotherapy is also significantly higher in older patients and leads to greater complications, increased hospitalizations, and higher mortality rates [35]. Due to potential toxicity because of lower bone marrow reserve, older patients may receive less effective doses of chemotherapy, even in the adjuvant or curative setting. Primary prophylaxis with granulocytic growth factors has been advocated for older patients receiving chemotherapy [36]. One systematic review of 17 randomized controlled studies revealed a 46% decrease in the rate of febrile neutropenia and a 40% decrease in death during chemotherapy in patients who received primary prophylaxis with granulocyte colony-stimulating growth factor [37].

Patient characteristics such as sex, ethnicity, comorbid conditions, polypharmacy, frailty, and stress may overlap with and exacerbate age-related changes. In general, age itself is not a contraindication or limitation to chemotherapy, although poor performance status, functional impairment, and comorbid conditions that are frequently present in the elderly population likely influence the ability to tolerate efficacious treatment [38] (Fig. 2). Despite emerging treatment strategies, chemotherapeutic agents

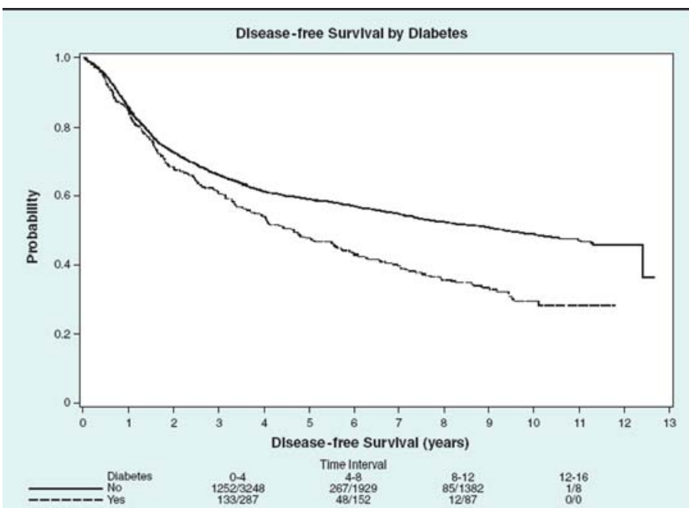

Fig. 2 Effect of diabetes on disease-free survival in an intergroup adjuvant trial in colon cancer

Source: From Meyerhardt JA, Catalano PJ, Haller DG, et al. Impact of diabetes mellities on outcomes in patients with colon concer. J Clin Oncol 2003;21:433-440. Reprinted with permission from the American Society of Clinical Oncology.

are still the most commonly utilized treatment modality. The reminder of this chapter focuses on a systems-based approach to interactions of age-related physiologic changes with chemotherapy and summarizes what is known about how age affects the pharmacology of different classes of chemotherapy.

A Systems-Based Focus on Age-Related Physiologic Effects in Older Cancer Patients

Aging is associated with a decline in physiologic reserve in organ systems. Decreases in organ function generally begin in the third decade of life [26]. Lower organ function is most apparent during times of physiologic stress, such as during a cancer diagnosis and treatment. Tolerance to cancer treatment can be affected by organ system changes due to age-related decreases in reserve. The next section highlights the major organ systems and discusses how age-related changes may affect the tolerance to and efficacy of cancer treatment. Table 1 provides a summary of age-related physiologic effects and impact on chemotherapy in older patients.

Endocrine System

The most important endocrinologic changes observed in the elderly are related to thyroid and pancreatic function. About 5% of healthy adults have thyroid abnormalities, but 20% of the population aged 65 years and over have subclinical hypothyroidism [39]. Several thyroid abnormalities are observed in the elderly. Subclinical hypothyroidism can affect quality of life and decrease functional status. Hyperthyroidism is implicated in atrial fibrillation, congestive heart failure, and osteoporosis [40]. Age-associated nonthyroidal illnesses and age-dependent decline of thyroid function are frequently encountered in the elderly, particularly after the age of 85 [41]. There is no consensus on thyroid replacement therapy in

Table 1 Impact of physiologic age-related changes on chemotherapy tolerance and efficacy

Organ system	Age-related changes	Potential effects in the elderly	Suggested interventions
Endocrine	Hypothyroidism. Hyperthyroidism.	Chemotherapy toxicity may mask thyroid abnormality.	Thyroid function monitoring. Lowering dose of steroids.
	Glucose intolerance and diabetes.	Increased risk of hyperglycemia with glucocorticoid administration.	Close blood glucose monitoring and adjustment of diabetic medications required.
Neurological	Decrease in cerebral blood flow. Cognitive decline. Peripheral and autonomic dysfunction.	Variable concentration of neurotropic agents in brain areas. Exacerbation of existing cognitive dysfunction or delirium. Progression of existing or development of new dysautonomia (orthostatic hypotension, disequilibrium, syncope, constipation, bladder, erectile dysfunction, etc.).	Dose adjustment, substitution, or discontinuation of agent recommended.
Immune	Weakening of adaptive immunity (decreased phagocytic activity, radical formation, and increase in cytokines, TNF).	Higher incidence of infectious complications.	Monitor for signs of infection; prophylactic use of granulocyte colony-stimulating factors.

Table 1 (continued)

Organ system	Age-related changes	Potential effects in the elderly	Suggested interventions
	Diminished T- and B-cell proliferation and antigen-expressing surface molecules.		
Cardiovascular	Decline in cardiac reserves, development of cardiovascular diseases with alteration of myocardial perfusion, conduction delay.	Increased risk of heart failure, dysrhythmias, blood pressure changes, and acute coronary events.	Assess ventricular function at baseline and upon onset of symptoms. Limit anthracycline use; consider cardioprotective agents (e.g., dexrazoxane).
Pulmonary	Reduction in oxygen saturation capacity, impairment of response to hypoxia. Decline in pulmonary reserves, chronic pulmonary diseases. Decrease of respiratory muscle strength with increase in work of breathing.	Limits administration of certain chemotherapeutic agents, surgical procedures, and radiation. Interferes with monitoring for pulmonary symptoms.	Emphasize smoking cessation; closely monitor for symptoms of respiratory compromise. Adequate vaccinations.
Musculoskeletal	Reduction in skeletal muscle mass, disproportional body fat distribution.	Affects volume of distribution for certain chemotherapeutic agents.	Perform assessment of musculoskeletal health at baseline, frequently monitor

Table 1 (continued)

Organ system	Age-related changes	Potential effects in the elderly	Suggested interventions
	Age-related bone loss.	Chemotherapy, glucocorticoids, and hormonal agents increase risk of osteoporosis.	for bone mineral density, and assess fracture risk.
Gastrointestinal	Age-related decline in absorption, secretion, and neuromuscular function; vascular and mucosal alterations.	Absorption of oral agents, delay in emptying.	Monitoring and prophylaxis of mucositis, dehydration, dyspepsia, diarrhea, and constipation should be considered.
	Polypharmacy with agents that depend on hepatic metabolism.	Affects liver enzymes, resulting in unpredictable biologic effect of the chemotherapeutic agents.	Potential for multidrug interaction should be eliminated if possible.
Renal	Renal function declines with age, hastened by hypertension, diabetes, atherosclerosis, and nephrotoxic drugs.	Increased sensitivity to nephrotoxic drugs, predisposition to acid-base and fluid-balance abnormalities during and after chemotherapy administration.	Dose modification of renally cleared agents should be performed. Adequate hydration and close renal function monitoring are required.

patients with subclinical hypothyroidism; however, screening is justified in women over 60 years [42]. Although no clear evidence describes how thyroid abnormalities affect chemotherapy efficacy and toxicity, monitoring of thyroid function should be considered in patients who experience adverse chemotherapy side effects that mimic hypo- or hyperthyroidism.

The prevalence of noninsulin-dependent diabetes progressively increases with age, reaching 16.5% in men and 12.8% in women at age 75–84 years [43]. Glucose intolerance or diabetes was reported in 30–40% of Framingham Study subjects over 65 years of age [44]. Awareness is growing of the interactions of preexisting diabetes and cancer care. Studies have illustrated a reduced efficacy of chemotherapy in patients who have diabetes compared to those who do not [45, 46]. Diabetes may cause an increased risk of hyperglycemia due to either chemotherapy and/or necessary premedications. For example, premedication with corticosteroids is recommended with docetaxel to prevent fluid retention. Older patients, and especially those who are diabetic, may benefit from a lower dose of steroids. Diabetics may require higher doses of their diabetic medications during treatment; other effects of acute hyperglycemia while on treatment have not been systematically studied. Recent diabetes prevention studies showed that both lifestyle changes and treatment have significantly reduced the incidence of diabetes in patients with impaired glucose tolerance, particularly in older patients [47]. More research is needed to determine whether cancer chemotherapy is less efficacious in diabetics because of hyperglycemia or another cause. In addition, more data are needed in the adjuvant setting to determine whether the use of chemotherapy and associated premedications increases the risk of developing diabetes.

Neurological System

The distribution of chemotherapy agents in the central nervous system depends on several factors. In addition to drug metabolism differences that are associated with aging, certain specific and localized physiologic alterations in the neurological system are important to consider. Studies demonstrate the steady and predictable decrease in cerebral blood flow in healthy older individuals, with most prominent changes affecting the frontal, basal temporal, parietal, and motor cortices [48]. These blood flow changes may diminish the therapeutic effect of certain agents targeting these brain areas. Decreased blood flow and aged tissue may result in greater neurotoxicity on brain tissue unaffected by disease by causing white matter atrophy, neuronal loss, and vascular changes [49]. Physiologic changes in memory and treatment-related central nervous toxicity due to chemotherapy may play a role in developing new, or exacerbating existing, cognitive decline, [50–52], which in turn could result in poor adherence to treatment and noncompliance, noted to be as high as 50% in some studies [53–55]. Delirium, a geriatric syndrome associated with an increased risk for morbidity and mortality in older adults, is not uncommon among older patients receiving chemotherapy and is more prevalent in patients with preexisting cognitive impairment [56, 57]. Functional neurologic decline and loss of myelin are evident not only in the central but also in the peripheral and autonomic nervous systems, presumably due to decreased levels of myelin proteins, including glycoprotein Po and peripheral myelin protein 22 [58]. These changes increase the risk of developing new or aggravating existing peripheral and autonomic (orthostatic hypotension, disequilibrium, syncope, constipation, ileus, bladder dysfunction, and erectile dysfunction) neuropathy with standard doses of agents such as platinum compounds, taxanes, and vinca alkaloids [59, 60].

Immune System and Homeostasis

Significant changes occur with aging in the ability to mount an effective response after infectious challenges. Studies of the immune system in elderly persons have demonstrated that a combination of intrinsic and extrinsic factors cause a deterioration in adaptive immunity. Within the innate immune system, decreased phagocyte capacity, decreased radical formation, and increased cytokine production such as interleukin-6 (IL-6) and tumor necrosis factor (TNF) are demonstrated with aging [61]. Adaptive immunity is affected by age-related decreases in T- and B-cell proliferation, repertoire degeneration of B cells, decreased numbers of naïve cells, and decreased expression of surface molecules important for antigen detection [62]. Immune system compromise is common among older frail individuals [63]. The immune system plays a large part in protecting the cancer patient against significant morbidity from infections. Both compromised immunity and compromised hematopoiesis, which occur with aging, likely lead to the higher rate of infectious complications noted in older persons who receive chemotherapy compared to their younger counterparts [64, 65].

Age-related changes in the hematopoietic system affect both plasma and cellular components. Anemia is present in 10% of the elderly and impacts performance status, cognitive function, mobility, and drug tolerance [66]. Anemia is also associated with frailty in older adults, a geriatric syndrome that signifies poor physical performance, decreased mobility, and fatigue [67]. While the majority of anemias are due to iron deficiency, including blood loss, a significant proportion can be attributed to nutritional deficiency [66]. Other important etiologies of anemia include renal insufficiency, chronic inflammation, and primary disorders of hematopoiesis that can sometimes be difficult to recognize due to a lack of sensitive and specific diagnostic tests. When anemia is suggested by screening laboratory tests, it should be further evaluated and corrected because the distribution of certain chemotherapeutic agents depends on the hematocrit. Although the clinical importance of red blood cells in the pharmacokinetics of cytotoxic agents is uncertain [20], anthracyclines, ifosfamide and its metabolites, and topoisomerase I and II inhibitors are incorporated in red blood cells, transported to tissues, and mobilized from the erythrocytes by active or passive transport mechanisms. Erythrocytes also serve as carriers for drugs such as asparaginase and mercaptopurine [20]. Bone marrow activity and cellularity decline with age, which affects their ability to respond to the increased demand of recovery from chemotherapy-induced anemia and neutropenia. The use of stimulating agents such as granulocyte colony-stimulating factors initially appeared to improve quality of life, neutrophil recovery time, and incidence of febrile neutropenia; thus, these agents were incorporated into certain chemotherapy protocols [68, 69]. Balducci et al. reported that proactive administration of Pegfilgrastim lowered the incidence of febrile neutropenia in elderly patients treated with myelosuppressive chemotherapy regimens for solid or lymphoproliferative malignancies, allowing optimal delivery of cytotoxic therapy [70].

Human aging is accompanied by systemic inflammatory conditions. Inflammation biomarkers are powerful predictors of frailty and mortality in the elderly [71, 72]. Commonly, the term "frailty" is often used to describe the general condition of older patients. Different factors, such as age, comorbid conditions, disability, and cognitive impairment, may contribute to the frailty syndrome. A number of published studies include additional criteria that can help identify which older persons are frail: weakness, insulin resistance, weight loss, increased blood-clotting activity, propensity for viral infection, sarcopenia, obesity, low testosterone level, fatigue, anemia, etc. Fried et al. defined frailty as a clinical syndrome in which three or more of the clinical criteria were present: unintentional weight loss, self-reported exhaustion, weakness, slow walking speed, and low physical activity [73]. After validation of the concept in subsequent studies, globally acceptable definitions are being added to the International Classification of Functioning, Disability and Health [74]. Generally, frail individuals have dependence in one or more activities of daily living (ADLs), three or more significant comorbidities, or one or more geriatric syndromes [75]. Frailty is a common condition among cancer patients, and cancer or its treatment may increase the risk of frailty [76]. In addition, the changing composition of plasma proteins and the coagulation cascade in the elderly and altered platelet function with diminishing endothelial adhesion [77] may predispose older patients to thromboembolic events in the presence of risk factors like cancer.

Cardiovascular System

Age and aging have a significant impact on the cardiovascular system. Exercise capacity and cardiac functional reserves decline due to age-related physiologic changes and may be further compromised by the development of cardiovascular disease. Aging is associated with reduced elasticity and compliance of the aorta and great arteries. These changes result in a higher systolic arterial pressure, increased impedance to left ventricular ejection, and subsequent left ventricular hypertrophy and interstitial fibrosis [78]. Decreased cardiac output and altered myocardial perfusion present a substantially increased risk for clinical congestive heart failure and exacerbation of underlying cardiac disease [79]. Aging is also associated with a reduction in the intrinsic heart rate and decreased sinoatrial node conduction [80].

Chemotherapy administration represents an additional risk for the development of heart failure, dysrhythmias, changes in blood pressure, and acute coronary events [81, 82]. Advanced age and previous cardiovascular history are known risk factors for cardiac toxicity, but additional factors such as history of chest irradiation and metabolic abnormalities, together with drug-related factors such as cumulative dose, route of administration, schedule, and combination with other cardiotoxic agents, must be appreciated in elderly cancer patients. No definitive guidelines exist for monitoring cardiac toxicity from chemotherapeutic agents, but the most common noninvasive method is the assessment of ventricular function using either radionuclide ventriculography or echocardiography. These modalities, however, are not sensitive enough for the early detection of preclinical cardiac disease, so stress echocardiography should be considered in this setting [83]. Recent reports described a correlation between a high B-type natriuretic peptide level and left ventricular function impairment, although the use of this laboratory test to monitor the cardiac toxicity of chemotherapeutic agents has not been well studied [84, 85]. Anthracycline toxicity may be reduced by limiting the total dose of drug [86]—for example, by limiting the total doxorubicin dose to 400 mg/m^2—using liposomal formulations, using the cardioprotective agent dexrazoxane, and utilizing a continuous infusion over a bolus or more rapid rates of infusion. Reversible cardiotoxicity is usually observed with trastuzumab (herceptin), which has a different mechanism from that of anthracyline-induced cardiotoxicity [82]. Current evidence supports treatment of symptomatic heart failure with angiotensin-converting enzyme inhibitors and β-blockers, with a reported improvement in ventricular systolic function [87].

Pulmonary System

Age-related physiologic changes affect pulmonary reserve. Aging is associated with multiple changes in respiratory physiology, including structural changes in both the lungs and chest wall leading to an alteration in measurable mechanical properties of the respiratory system, a reduction in the arterial oxyhemoglobin saturation, and an impaired response to hypoxia [88]. Respiratory muscle strength consistently declines with age, increasing the work of breathing. While gas exchange may be well preserved at rest and during exertion, pulmonary reserve is diminished, and under conditions of positive fluid balance and increased metabolic demand, respiratory failure can occur. Increased sensitivity to respiratory depressants and muscle weakness pose additional risks for the development of respiratory complications in elderly patients. Chronic pulmonary conditions, smoking, and age-related lung function decline cause decreases in compliance, expiratory flow rate, vital capacity, mucociliary escalating function, and respiratory center sensitivity to hypercapnea and hypoxia [89]. A reduction in pulmonary reserve with reduced vital capacity presents significant limitations to the administration of certain chemotherapeutic agents such as bleomycin, with advanced age being one of the risk factors for developing pulmonary toxicity [90], performing curative surgical procedures, and/or delivering radiation. A blunted respiratory response to hypoxia and hypercapnea complicates the monitoring of pulmonary symptoms in elderly patients receiving chemotherapy [91]. It is recommended that practitioners pay close attention to indirect manifestations of respiratory compromise, such as decreased activity, loss of interest, somnolence, and confusion [89]. Pneumococcal and influenza vaccination and smoking cessation are important components of cancer management in elderly patients.

Musculoskeletal Systems

In the elderly, sarcopenia is a major contributing factor to falls, functional dependence, and frailty [92]. The prevalence of sarcopenia in community-dwelling older adults is estimated to be approximately 25% [93]. Age-related reductions in skeletal muscle mass are greater in men than in women, especially in the legs [94]. There is approximately a 5% loss of muscle mass per decade of life after the fourth decade, with more rapid loss after the age of 65 [95]. The progressive loss of skeletal muscle mass, or sarcopenia, is observed even in healthy, active patients at a rate of 1–2% per year after 50 years of age [96]. Etiologic factors include inflammation [97], nutritional deficiency [98], and neurological and hormonal [99] changes combined with a sedentary lifestyle, which can result in stiffer and smaller muscles [100] in addition to an increase in falls, fractures, and associated morbidity and a decrease in lean body mass. In older patients with sarcopenia, a lower lean muscle mass results in a net decrease in the volume of drug distribution, which can affect the metabolism of chemotherapeutic agents. On the other hand, an increase in the total fat composition of the aging body is manifested by a disproportionate increase in the amount of visceral and subcutaneous fat, which expands the volume of distribution primarily for lipid-soluble drugs while reducing it for hydrophilic or polar drugs [16]. In aging, the loss of muscle mass can lead to physical weakness and disability. There are significant age-related decreases in strength, with a loss of approximately 20–40% when comparisons are made between adults in their 20s compared to older adults in their 70s and 80s, and even greater losses over 50% reported when comparisons are made with older adults in their 90s [101, 102]. Several geriatric assessment studies have noted a high prevalence of physical performance abnormalities in older patients receiving chemotherapy, although it is unclear if the chemotherapy is a causal factor [10, 103]. Other cancer treatments, such as androgen deprivation therapy, are known to cause significant changes in body composition [104], resulting in an increase in fat mass and a decrease in lean body mass [105], which may be related to abnormal physical performance in older prostate cancer patients [106, 107]. Currently, little is known of the effects of chemotherapy on the development of sarcopenia, muscle weakness, and physical decline, and more research is necessary.

In addition to sarcopenia and muscle weakness, osteoporosis and fractures are much more prevalent in older populations than in their younger counterparts. Osteoporotic fractures are a significant health concern for the elderly; over 1.5 million fractures occur yearly in the United States. Fractures are associated with back pain, a decrease in functional capacity, an increased risk for further fractures, higher health-care costs, and a higher rate of institutionalization and hospitalization [108, 109]. In osteoporosis studies, fractures in men were associated with profound quality-of-life deficits, especially in physical functioning [110]. In addition, mortality within a year after osteoporotic fracture is markedly increased; in one study, these odds were 3.17 (2.90–3.44) for proximal femur, 2.38 (2.17–2.59) for vertebral, 2.22 (1.91–2.52) for other major, and 1.45 (1.25–1.65) for minor fractures [110]. The United States Preventive Services Task Force (USPSTF) recommends beginning to screen for osteoporosis starting at age ≥65 years for all women and at age 60 for women at increased osteoporosis risk [111]. Older men who are to receive chemotherapy and have other risk factors for osteoporosis should also be screened. Chemotherapy has been associated in multiple studies with an increased risk for osteoporosis [112–114]. Monitoring for bone loss and risk of fractures is imperative in the older population on chemotherapy. Glucocorticoid use with chemotherapy for the prevention of nausea can also increase the risk of osteoporosis. Patients should undergo complete physical examination and medical history in order to assess for other risk factors. Especially in older patients who are to receive chemotherapy in the adjuvant setting, a baseline bone mineral density assessment should be obtained with DEXA (dual-energy x-ray absorptiometry) scan or other effective screening tools. Follow-up tests should be performed depending on baseline assessment of BMD and risk factors for the development of osteoporosis and fractures, although there is controversy regarding how frequently these tests should be performed.

Gastrointestinal System

Aging affects all organs of the gastrointestinal system. Alterations in normal gastrointestinal physiological features include changes in neuromuscular function, changes in the structure of the gastrointestinal tract, and changes in the absorptive and secretory functions of the bowel. Neuromuscular changes primarily affect the upper gastrointestinal tract and can lead to symptoms consistent with numerous disease processes such as reflux and achalasia. Changes in function with aging of the oropharynx and esophagus are primarily related to neuromuscular degeneration and subsequent alterations in the ability to coordinate the complex reflexes that lead to successful swallowing and propulsion of food along the esophagus. Aberrant contractions can also be caused by weakness in the muscles. Weakening of the musculature of the oropharynx and upper esophagus can contribute to the formation of pharyngoesophageal diverticula and can cause functional problems. Similarly, although the gastric mucosa becomes atrophic with age, correlations between histologic change and disease processes, including atrophic gastritis, have been hard to establish [115]. The primary structures affected by age in the small bowel are intestinal villi. Starting around the age of 60 years, there is a progressive decrease in the height of the villi, with a concomitant decrease in the surface area available for absorption [116]. The colon is the most consistently affected portion of the gastrointestinal tract with regard to age-related structural alterations. Mucosal changes are noted but do not affect the absorptive capabilities of the colon. The primary process seen in the colon is a thickening of the muscular layers, which can contribute to hard stool, constipation, and fecal impaction. Diverticular disease, the most common age-related colonic disease, occurs as a result of concomitant weakening of the muscularis propria at locations where arteries and veins cross the bowel wall [117]. The absorption of drugs in older patients is altered by a delay in gastric and intestinal emptying [118], a decrease in gastric acid and digestive enzyme production, changed intestinal absorption with mucosal atrophy, and compromised gastric and intestinal blood circulation [15, 119]. Certain factors, such as the concomitant use of antacids, H2-blockers, and proton pump inhibitors, may unpredictably affect absorption.

Functional alterations in secretion and absorption are predominantly found in the oropharynx/stomach (secretion) and small bowel (absorption), although it is difficult to consistently link these age-related changes with pathological features. Age-associated xerostomia is a common complaint of many elderly, and an estimated 50–60% of patients over 65 present with symptoms of oral dryness [120]. Salivary gland secretion decreases and saliva composition changes with decreasing amylase and secretory leukocyte protease inhibitors that have antimicrobial activity [121]. These changes predispose elderly patients to the development of oral or esophageal mucositis [122], a dose-limiting complication that commonly interferes with nutrition, compromises treatment, causespain and life-threatening complications, and affects the quality of life [123].

Changes in the liver also occur with aging. The size of the liver decreases after the age of 50 years, declining from roughly 2.5% of total body mass to a nadir of just more than 1.5% [124, 125]. Alterations in blood flow parallel this decrease. Hepatic synthesis of several proteins, including clotting factors, can be reduced, although this reduction does not impair baseline function. However, perhaps because of the larger anabolic burden placed on fewer hepatocytes, the hepatic synthesis of these factors is unable to increase significantly beyond baseline when challenged [126]. Hepatic clearance may be affected by medicines that have inhibitory or inducing effects on liver microsomal enzymes, comorbid liver conditions, age-related decrease in total liver mass, and reduction of hepatocyte surface membrane permeability [127, 128].

Table 2 lists chemotherapy agents whose metabolism depends on hepatic function.

Renal System

Renal function decreases with age due to a decrease in renal mass, renal blood flow, the number of functional nephrons, and a fall in renal tubular secretion. Renal mass decreases at a constant rate after the age of 50 and is estimated to decrease by 25–30% from the age of 50 to 80 [129]. The loss of kidney volume is primarily due to cortical tissue loss from glomerulosclerosis (acellular obliteration of glomerular capillary architecture). Hypertension, diabetes

Table 2 Agents requiring dose adjustments based on hepatic function

Drugs	Level of hepatic extraction (clearance) (%)	Resulting oral bioavailability.
Capecitabine, cytarabine, docetaxel, doxorubicin, epirubicin, exemestane, fluorouracil, formestane, gemcitabine, idarubicin, medroxyprogesterone, mercaptopurine, mitoxantrone, vinblastine, vinorelbine	High (>60)	Oral bioavailability is less than 40% in the case of complete intestinal absorption (or accordingly lower, if intestinal absorption is not complete).
Bicalutamide, busulfan, cladribine, estramustine, gefitinib, irinotecan, melphalan, paclitaxel, topotecan	Intermediate (30–60)	Oral bioavailability is 40–70% in the case of complete intestinal absorption (or accordingly lower, if intestinal absorption is not complete).
Aminoglutethimide, anastrozole, bleomycin, carboplatin, chlorambucil, cisplatin, cyclophosphamide, cyproterone, dacarbazine, etoposide, fludarabine, fosfestrol, goserelin, hydroxycarbamide (hydroxyurea),	Low (<30)	Oral bioavailability is higher than 70% in the case of complete intestinal absorption (or accordingly lower, if intestinal absorption is not complete). In this category, protein binding may be relevant: for drugs with high binding to

Table 2 (continued)

Drugs	Level of hepatic extraction (clearance) (%)	Resulting oral bioavailability.
ifosfamide, imatinib, letrozole, leuprorelin, lomustine, methotrexate, temozolomide, thiotepa, toremifene, triptorelin, vincristine		albumin (>90%), hepatic clearance may increase.
Aldesleukin, alemtuzumab, amsacrine, buserelin, cetuximab, chlormethine (mechlorethamine), dactinomycin, daunorubicin, flutamide, megestrol, mitomycin, nimustine, oxaliplatin, raltitrexed, rituximab, tamoxifen, thioguanine, trastuzumab, tretinoin, vindesine	Unknown	Unknown.

Source: Adapted from Tchambaz et al. [146].

mellitus, and atherosclerosis accelerate the process of glomerulosclerosis. Glomerulosclerosis directly affects the glomerular filtration rate (GFR). After the age of 40 years, the GFR decreases by 0.75–1 ml/min/yr [130]. Because of the concomitant decrease in creatinine production in elderly persons, serum creatinine levels remain normal despite significantly reduced GFRs. The elderly patient has a low filtration reserve and is therefore more sensitive to any ischemic or nephrotoxic insult. In addition, the juxtaglomerular apparatus in elderly patients produces less renin than in young patients, blunting the response to aldosterone [131]. As a consequence, elderly patients are more susceptible to electrolyte and acid-base abnormalities, with hyponatremia most frequently reported [132]. Antidiuretic hormone (ADH) response is attenuated in elderly persons, making sodium and water conservation difficult [131, 133]. The urinary-concentrating ability in response to ADH is attenuated and, when coupled with a decrease in reserving sodium by kidneys, tends to induce hyponatremic dehydration when treated by water deprivation only. The administration of oral and intravenous sodium then results in an exaggeration of urinary sodium excretion and a failure of hyponatremia to be corrected [134]. Mineralocorticoid fludrocortisone acetate administration is suggested by some authors as an effective adjunct to the above measures [135].

Reduced renal reserve is seen in the disease-free elderly population. Glomerulosclerosis and senescence of tubules are the two main causes of decreased GFR with aging. Because of the diminished GFR of elderly persons, drugs that are cleared via the kidneys require dose modification based on creatinine clearance [3, 136]. To achieve required agent efficacy, adequate estimation of kidney function is important, as inappropriate dosing of renally excreted or nephrotoxic medicine may result in undertreating the cancer or increasing toxicity. Some studies, such as that by Esposito et al. exploring renal function in elderly individuals, concluded that the renal function of otherwise healthy patients is preserved, although there is a reduction of renal functional reserve [137]. Among methods developed for the evaluation of renal function, several are appropriate to use for older populations or patients with cancer. Careful comparisons of different formulas across different studies suggest that the Wright formula is the most precise and least-biased method for patients without underlying renal disease [138–141]. The MDRD (Modification of Diet in Renal Disease) equation can better account for variables such as age, ethnicity, serum albumin, and urea nitrogen levels in patients with chronic renal disease and is recommended for use in elderly patients [141, 142]. Most chemotherapeutic agents have a narrow therapeutic index, so presumably safe and effective doses may produce severe toxicity, particularly if the function of the eliminating organ is compromised. Renal function should be evaluated in all patients prior to chemotherapy, even in those with normal serum creatinine levels. Dose adjustments should be considered for nephrotoxic or renally excreted agents. There are no universal guidelines for such an adjustment; however, updates are published periodically with recommendations based on renal function. Table 3 summarizes the most commonly utilized renal calculations.

Chemotherapy may directly and indirectly affect renal function. Thus, common toxicities such as diarrhea and fever in neutropenic patients can result in hypoperfusion of the kidneys, affecting the elimination of chemotherapeutic agents and the accumulation of their metabolites, causing toxicity. Table 4 lists chemotherapeutic agents that are known to be nephrotoxic or depend on renal elimination. Agents such as carboplatin require dosing based on renal function [143, 144]. During treatment with a nephrotoxic agent, adequate hydration and renal function monitoring are mandatory if there is no alternative less nephrotoxic agent that may be used [145]. Prescription noncancer medicines with a known nephrotoxic effect such as NSAIDs and aminoglycoside antibiotics should be reviewed and replaced with less toxic equivalents or discontinued.

Table 3 Renal function calculations

Methodology	Formula/Calculation	Benefits (Pros)	Risks (Cons)
MDRD GFR (ml/min)	$170 \times [PCr]^{-0.999} \times [age]^{-0.176} \times$ [0.762 if patient is female] $\times$ [1.180 if patient is black] $\times$ $_{148-0.170} \times [Alb]^{+0.318}$	– Relatively simple, easy to report (anthropometric data such as weight are not required) – Low-cost, valid in renal transplant patients – More accurate than the Cockcroft-Gault formula in predicting GFR in patients with ESRD – More accurate at GFR > 120 ml/min	– It tends to underestimate GFR in patients with normal or mildly impaired renal function in comparison to one measured by a reference isotopic method (^{99m}Tc DTPA-GFR), – Limited value in variable settings such as extremes of age, body size, pregnancy, malnourishment, amputees, para-/ quadriplegics. – Calculation based on this formula may result in overdosing with renal-dosed drugs.
Cockcroft–Gault Creatinine clearance (ml/min)	(140 – age) × weight in kg/ plasma Cr (mg/dl) × 72 [× 0.85 if female]	– Simplicity of use, validated in number of earlier studies – Can be modified to BSA	– Provides higher estimates of creatinine clearance for younger ages, and lower

Table 3 (continued)

Methodology	Formula/Calculation	Benefits (Pros)	Risks (Cons)
[adjusted for for body surface area (BSA)]	$1.73 \times (140 - \text{age}) \times$ weight in kg/plasma Cr (mg/dl) $\times 72 \times$ BSA [x 0.85 if female]	– Accurate at a GFR of 60-120 ml/min	estimates at older ages (greater than 70 years). – Precision and accuracy in the elderly affected by reduced muscle mass and erroneous urine sampling. – In ESRD and in obese patients with normal renal function, overestimates creatinine clearance.
Wright GFR (ml/min)	GFR $= [6580–(38.8 \times \text{age})] \times$ BSA x $[1–(0.168 \times$ if female)]/ serum creatinine (µmol/l)	– More precise in GFR of 50-120 ml/min – Avoids the need for 24-hr urine collection – Was developed using data from patients with cancer	– Not validated prospectively. – Significantly overestimates GFR in older patients with poor renal function.

MDRD – Modification of Diet in Renal Disease formula; BUN – blood urea nitrogen; GFR – glomerular filtration rate; ^{99m}Tc DTPA-GFR - 99mTc-labeled diethylenetriaminopentacetic acid; ESRD – end-stage renal disease; Cr - creatinine; BSA – body surface area.

Source: From Lichtman et al. [129] and Launay-Vacher et al. [147].

Table 4 Dose adjustments based on renal function

	Creatinine clearance values		
	60	45	30
Bleomycin	0.70	0.60	No data
Carboplatin		Calvert formula	
Carmustine	0.80	0.75	No data
Cisplatin	0.75	0.50	No data
Cytarabine	0.60	0.50	No data
DTIC	0.80	0.75	0.70
Fludarabine	0.80	0.76	0.65
Hydroxyurea	0.85	0.80	0.75
Ifosfamide	0.80	0.75	0.70
Melphalan	0.65	0.50	No data
Methotrexate	0.85	0.75	0.70

*Source:*Adapted from Balducci and Extermann [149].

Clinical Pharmacology of Common Cancer Therapies in the Elderly

Anthracyclines

Anthracyclines are incorporated into many treatment protocols for cancers that are common in the elderly. These drugs as a group are associated with short- and long-term cardiotoxicity that is more pronounced in the elderly [150]. Age over 70 years is independently associated with an increasing incidence of congestive heart failure in patients receiving anthracyclines [151]. In practice, the greater risk of congestive heart failure with older age may lead a physician to treat an older person with less aggressive chemotherapy doses and regimens. The cumulative dose should be monitored and systolic function checked before and during therapy and at the onset of symptoms. Although monitoring may detect changes in left ventricular function, it may not decrease the incidence of cardiomyopathy. The use of dexrazoxane, a cardioprotective agent, should be considered in patients with a history of exposure to anthracyclines or at higher risk for cardiotoxicity. However, because of the possibility that it may impact antitumor activity, its use has been limited to higher-dose anthracyclines for selected malignancies. Idarubicin, epirubicin, and mitoxantrone may cause less cardiotoxicity than doxorubicin [152, 153].

Anthracyclines are 50–80% bound to proteins, and a dose reduction should be considered in settings of hypoalbuminemia [153]. The metabolism of anthracyclines occurs in the liver through aldo-keto reductases. The anthracylines are converted into alcohol metabolites. The primary metabolite of doxorubicin, daunorubicinol, is associated with a higher area under the curve (AUC) in the elderly because of slower metabolism of the drug in older persons. Anthracyclines enter the cells through passive diffusion across the cell membrane and concentrate in tissues 30- to 1000-fold over plasma concentrations [14]. Elimination of the parent compounds and metabolites occurs through the urine, bile, and feces. Since some of the metabolites have hepatic excretion, dosing may require adjustment with hyperbilirubinemia [154]. Idarubicin is primarily renally excreted and should be dose-reduced with abnormal renal function.

Pharmacokinetic analyses have demonstrated conflicting results about age-related differences in the clearance of doxorubicin. Dees et al. evaluated age-related differences in the pharmacokinetics and pharmacodynamics of 60 mg/m^2 of doxorubicin and 600 mg/m^{2}of cyclophosphamide in 44 women 35–79 years of age. Although there were no significant age-related differences in the clearance of the drugs, a significant age-related decrease in nadir absolute neutrophil count was noted in older patients [155]. In another study of 56 older patients who accrued to four studies, older patients experienced higher initial concentrations of doxorubicin [156]. The decrease in distribution clearance highly correlated with age. A significant association was also noted between age and the total body clearance of doxorubicin.

Pegylated liposomal doxorubicin may be a safer alternative for elderly patients with age- and disease-associated cardiac dysfunction. Liposomal anthracyclines are approved for Kaposi's sarcoma and have demonstrated activity in malignant lymphoma, ovarian cancer, and breast cancer [14]. Liposomal formulation changes the pharmacology and toxicity of the anthracycline agent. Cardiac toxicity, mucositis, and alopecia are much lower than with nonliposomal formulations [157]. Liposomal options should be considered for older patients with anthracyline-sensitive diseases.

Platinum Compounds

Cisplatin is utilized for a wide variety of malignancies, including bladder, lung, cervical, head and neck, and esophageal cancers. This drug has a complex clearance that depends on renal function. Cisplatin binds nonreversibly to plasma proteins, and only the unbound plasma cisplatin is active. There is a significant increase in the AUC of the free ultrafilterable platinum fraction and total plasma platinum with older age [158]. The concentration of ultrafilterable platinum fraction correlates with the toxicity [159].

Renal insufficiency is the major toxicity and the primary pharmacodynamic parameter for cisplatin [153]. Renal toxicity can be minimized by proper patient selection of those with good function up-front and intravenous hydration. In retrospective studies, aside from baseline kidney function differences, age alone does not seem to impact the incidence of nephrotoxicity [153]. Other toxicities include electrolyte abnormalities (including magnesium wasting), myelosuppression, nausea and vomiting, and peripheral neuropathy. Hearing loss is also a troubling toxicity for the elderly. Although cisplatin can be considered an appropriate therapy for selected patients, up-front dose reduction (e.g., 60 mg/m^2) and reduced infusion rates (e.g., over 24 hours) should be considered to help reduce toxicity and should be considered for all older patients [129].

Carboplatin is very similar to cisplatin in mechanism and elimination. Carboplatin also depends on renal elimination, and the remainder is inactivated after binding to tissue proteins. Due to significant interpatient variability with body surface area dosing, formulas were developed to take into account both body size and renal function [129, 159]. The Calvert and

Chatelut formulas are the most commonly used methods for dosing carboplatin to AUC target in the elderly and inpatients with compromised kidneys. The Calvert formula calculates carboplatin using the target AUC and GFR. Although the original formula utilized chromium-51 ethylene diamine tetracetic acid to measure the GFR, estimation of creatinine clearance is often performed with 24-hr creatinine clearance or formulas such as the Crockcroft-Gault formula (Table 1) [160]. The Chatelut formula uses age, sex, weight, and serum creatinine to calculate the dose. Because serum creatinine does not always reflect renal function in older patients, the Calvert formula is recommended for carboplatin dosing [153].

Oxaliplatin is a platinum agent utilized for both adjuvant therapy and treatment of metastatic colorectal cancer. This drug has a much lower incidence of nephrotoxicity and hematologic toxicity than cisplatin and carboplatin, respectively. Pharmacokinetic analyses comparing younger and older patients have not shown a significant association of unbound platinum clearance with increased toxicity [161]. Above a creatinine clearance of 20 ml/min, no dose reductions are required [162]. Hepatic dysfunction does not affect oxaliplatin clearance [163]. Oxaliplatin is associated with transient and reversible peripheral neurotoxicity that is dependent on cumulative dose, and parasthesias may be triggered by the cold. A retrospective analysis by Goldberg et al. [164] of 3,742 patients, including 614 patients aged 70 and over, receiving FOLFOX-4 revealed that older patients had higher incidences of myelosuppression, but overall the regimen was well tolerated. Trials of oxaliplatin in combination with capecitabine in patients aged 70 and over have also shown acceptable efficacy and tolerability [165, 166].

Topoisomerase Inhibitors

Topotecan, a topoisomerase-I inhibitor, is approved for the treatment of small cell lung cancer and refractory ovarian cancer, and it has some activity in myelodysplastic syndromes and acute granulocytic leukemia [153]. Approximately 30% of the clearance of topotecan is renal. Both age and serum creatinine level have been shown to affect clearance [167, 168]. The dose of topotecan should be adjusted for creatinine clearance <60 ml/min and for those who have undergone extensive prior therapy [169, 170]. In patients with moderate renal impairment who are not dose-reduced, severe myelosuppression may occur, which can be life-threatening. Myelosuppression may be reduced with weekly regimens [171].

Irinotecan, a topoisomerase-I inhibitor, is approved for the treatment of metastatic colon cancer as a single agent, in combination with 5-florouracil/leucovorin and cetuximab (an epidermal growth factor inhibitor) for refractory disease. It has activity against several other cancers, including glioblastoma multiforme, small cell lung cancer, esophageal and gastric cancers, and pancreatic cancer [172–174]. Delayed diarrhea and myelosuppression are the major toxicities of irinotecan [175]. SN-38, the primary metabolite of irinotecan, is much more potent than the parent compound, and delayed diarrhea may be due to the accumulation of SN-38 in the intestine [176]. Although delayed diarrhea is increased in older patients, the pharmacokinetic parameters of irinotecan and its metabolites were very similar in older patients as compared to their younger counterparts [177, 178]. Treatment with irinotecan every three weeks is associated with a lower incidence of diarrhea than weekly dosing regimens [179]. Older patients achieve similar response rates to younger patients with irinotecan [180, 181]. Although patients over the age of 70 with extensive prior therapy and/or poor performance status should receive lower doses, there are no specific dose reduction guidelines [153].

Etoposide, a topoisomerase-II inhibitor, is used for non-Hodgkin's lymphoma, germ cell tumors, and lung cancer. Although both intravenous and oral options are available, oral therapy can be complicated by difficulties with absorption and tolerance [182]. Drug interactions can also be a problem with oral etoposide. The absorption of etoposide is highly variable, ranging from 25-75% [182]. The clearance of etoposide is diminished in patients with reduced renal function. Age has no significant impact on etoposide metabolism when creatinine clearance is taken into account [183]. However, older age is associated with higher free plasma concentrations, which do correlate with increased myelosuppression [184, 185]. Dose reductions have been recommended for both renal and hepatic dysfunction, although specific guidelines are not available [185]. Poor performance status may place patients at a higher risk for toxicity. For example, Ando et al. described a subgroup of older lung cancer patients with lower performance status who were at higher risk for myelosuppression [186]. Etoposide is a useful drug, and although oral therapy may be more palatable to older patients, oral etoposide has more variability in pharmacokinetic profile than intravenous therapy and thus could be associated with decreased efficacy and increased toxicity [14]. Careful monitoring is imperative, especially for older patients undergoing oral therapy.

Antimetabolites

Antifolate

Methotrexate is the mainstay of treatment for many neoplastic disorders, usually in combination with other chemotherapeutic agents (e.g., CMF regimen for the adjuvant treatment of breast cancer). Its elimination is fully dependent on renal excretion, and patients with altered renal function are at significant risk for toxicity. Its excretion can be affected by nonsteroidals, cephalosporin antibiotics, and other drugs that are excreted by the kidneys. The half-life and clearance of methotrexate are prolonged in older patients, which can lead to increased toxicity [187]. The methotrexate dose should be adjusted in patients according to renal function [129]. Due to third-spacing into fluid-filled areas, which increases its half-life, methotrexate should be used with caution in patients with pleural effusion and ascites. Leucovorin rescue is commonly used to minimize toxicity [149].

Pemetrexed is active against non-small cell lung cancer that is refractory to the standard first-line therapy. Pemetrexed is primarily excreted in the urine and is contraindicated in those patients who have a creatinine clearance $<$40 mg/ml [129]. In a Phase I study of the drug in those with impaired renal function, doses of 600 mg/m^2 were tolerated with vitamin supplementation in those with good renal function, while 500 mg/m^{2}was tolerated in those with GFRs between 40–79 ml/min [188]. Elderly patients with adequate renal function achieve comparable efficacy and have similar toxicity profiles to their younger counterparts [148].

Cytidine Analogs

Gemcitabine is used in various carcinomas: non-small cell lung cancer, pancreatic cancer, bladder cancer, and breast cancer. It is also not as debilitating as other forms of chemotherapy. Although there may be small age-related and sex-related pharmacokinetic differences, the dosing is the same for all age groups. Dose reductions are recommended for patients with reduced renal and hepatic function, and dosing guidelines have been published [189]. Major side effects of gemcitabine are thrombocytopenia and neutropenia, which respond to dose modification [190], but with minimal toxicity observed in elderly, dose reduction is recommended only if myelosuppression has been an issue with previous doses. In general, if dosed taking into account a patient's hepatic function, gemcitabine has minimal toxicity in the elderly. In addition, caution should be used in patients with renal insufficiency.

Fludarabine, an agent commonly used for the treatment of chronic lymphocytic leukemia and other B-cell malignancies, is excreted renally, and dose reductions may be necessary in elderly patients with renal impairment. Dose reductions based on renal dysfunction resulted in similar clearance, exposure, and toxicity levels as full-dose therapy in the setting of no renal dysfunction [191, 192].

Cytarabine (Ara-C) is commonly used in the treatment of hematologic malignancies. Its metabolites are renally excreted, and the dose should be adjusted to renal function. Older patients with age-related alterations in renal function are at increased risk for toxicity with Ara-C. Elderly patients even with normal renal function are at higher risk of CNS toxicity and cholestasis with high-dose Ara-C. The risk for neurotoxicity is significantly increased in patients with creatinine $\geq$ 1.2 mg/dl, age $\geq$ 40, and/or alkaline phosphatase $\geq$ 3 times normal [193].

Fluoropyrimidines

The fluoropyrimidines are commonly utilized for the treatment of solid tumors. Although there can be significant variability in the pharmacokinetic profile and toxicity among individuals, no data suggest that dose reductions should occur based on age alone [153]. No significant impact of age was noted on the pharmacokinetics of 5-fluorouracil (5-FU) in a study of 380 patients aged 25–91 [194]. However, there was a lower clearance of 5-FU in women, which may be due to lower dihydropyrimidine dehydrogenase activity. 5-FU is metabolized by the liver, and renal insufficiency does not require dose adjustment.

Many studies have evaluated the risk of 5-FU toxicity in older patients. In a meta-analysis of six randomized trials of 1,219 patients with colorectal surgery, a higher incidence of diarrhea and mucositis was noted in the older patients and those with a poor performance status [195]. Older women were the most affected by nonhematologic toxicities. Bolus 5-FU was significantly associated with greater grade 3 or more hematologic toxicity than infusional 5-FU. An overview of clinical trials utilizing FOLFOX chemotherapy noted no increase in overall grade 3 or more toxicity with older age, although there was a higher incidence of grade 3 thrombocytopenia and neutropenia [164]. Randomized studies have not illustrated an association of age with worse outcome with 5-FU-based therapies [153]. Observational cohorts utilizing the Surveillance, Epidemiology, and End Results Medicare-linked database have been performed to evaluate outcomes for 5-FU adjuvant therapy. These analyses are thought to be more generally applicable to the general population, as they include all Medicare-insured patients chosen for 5-FU therapy, not just those who are selected for a clinical trial. Studies of adjuvant 5-FU for resected stage III colon cancer have demonstrated good tolerance and equivalent outcomes for older patients, even for very old patients without a major comorbidity [196–198]. However, the receipt of chemotherapy does decrease with older age and increasing comorbidity.

Capecitabine is an oral fluoropyrimidine that is easily absorbed from the gastrointestinal tract and enzymatically converted in the liver to 5-FU. The bioavailability depends on intestinal absorption, but its metabolic conversion may be unpredictable in patients with severely impaired hepatic function. No clear guidelines exist for dose adjustment in patients with compromised liver function. The metabolites of capecitabine are excreted in urine, and increased toxicity is observed in patients with impaired renal function. It is recommended to adjust the capecitabine dose in patients with creatinine clearance <50 ml/min and to avoid this drug in patients with a creatinine clearance <30 ml/min [199]. Although elderly patients tolerate capecitabine well, toxicity is markedly increased for those with renal dysfunction. There are published guidelines on dose reductions for those with renal impairment. The pharmacokinetics of capecitabine are similar in older patients with preserved renal function to their younger counterparts [200]. Capecitabine has the potential for multiple drug interactions. The coadministration of warfarin, for instance, may result in unpredictable anticoagulation levels; therefore, careful INR monitoring is important [201].

Capecitabine has demonstrated similar efficacy and tolerability at the dose of 1,250 mg/m^2 twice daily as 5-FU in older patients being treated for colorectal cancer and breast cancer with normal renal function [202–205]. Hand-foot syndrome was more common with capecitabine, although myelosuppression was less of a problem. The efficacy of 1,000 mg/m^2 twice daily has been shown to be similar to 1,250 mg/m^2 and should be considered as the starting dose for elderly patients with good renal function [206].

Taxanes

Paclitaxel is most commonly utilized for the treatment of breast cancer, ovarian cancer, and bladder cancer. Paclitaxel is primarily protein-bound and depends on hepatic metabolism via the cytochrome P450 systems 2C8 and 3A4 isoenzyme pathways. Altered liver function may increase toxicity; dose modification is recommended by some authors, but dose reduction is not necessary with preserved hepatic function even in the presence of liver metastases [207, 208]. Liver dysfunction and the coadministration of drugs affecting this pathway influence the metabolism of taxanes. Patients with decompensated liver disease should not be treated with paclitaxel, as clearance is decreased by $\sim$40% in transaminitis and hyperbilirubinemia [146]. Taxanes are only partially excreted by the kidneys; dose reductions are not needed for renal insufficiency. In a Cancer and Leukemia Group B study, the clearance of paclitaxel was decreased with older age, which was not associated with an increase in measured adverse effects such as fever, antibiotic use, or hospitalizations [209]. Several studies have demonstrated both the feasibility and efficacy of every third week dosing and weekly dosing of paclitaxel in elderly patients [210–212]. Weekly therapy may be associated with less myelosuppression [212]. Dose reductions for paclitaxel are not required based on age alone.

Docetaxel is a highly effective chemotherapeutic agent with demonstrated efficacy in many solid tumors. Currently, the drug is approved for the treatment of hormone-refractory prostate cancer, locally advanced or metastatic breast cancer, and non-small cell lung cancers. Docetaxel is also currently approved for the treatment of gastric and head and neck cancers. Phase II studies in elderly cancer patients have shown no age-related differences, or at most minimal changes, in docetaxel pharmacokinetics. A Phase II study by ten Tije and colleagues showed that docetaxel pharmacokinetics at the dose of 75 mg/m^2 every three weeks did not differ for older patients ($\geq$65) compared to younger patients; however, older patients had more grade 4 and febrile neutropenia [213]. Another study by Minami and colleagues showed no age-related differences in the pharmacokinetics of docetaxel or cisplatin in elderly patients ($\geq$75) with non-small cell lung cancer, compared to younger patients [214]. Phase II trials of weekly docetaxel (35–40 mg/m^2) in the elderly have also demonstrated no age-related pharmacokinetic differences with the weekly regimen [215, 216]. A population-based pharmacokinetic study of docetaxel by Bruno et al. showed only a modest decline of 7% in the mean clearance of docetaxel for a 71-year-old patient (at a dose of 75–100 mg/m^2) [217].

Only limited data are available on docetaxel pharmacokinetics in patients with renal or hepatic impairment, as these are generally exclusions in Phase II protocols. Since renal excretion is responsible for only 5% of the elimination of docetaxel, it is unlikely that drug clearance is significantly reduced in patients with renal impairment. Hepatic dysfunction, on the other hand, causes a 12–30% reduction in docetaxel clearance [218]. Phase I studies have reported significantly more toxicity, including toxic deaths, in patients with liver dysfunction as compared to those without liver dysfunction [218]. The manufacturer's recommendation is not to administer full doses of docetaxel to patients with liver dysfunction (bilirubin above the upper limit of normal or tranaminases more than 2.5 $\times$ upper limit of normal). It is also recommended that patients with mildly elevated transaminases undergo a 25% dose reduction [217]. Patients with liver metastases but with normal liver function tests do not need to undergo dose reduction.

Docetaxel has been found to be safe and effective in trials of elderly patients with solid-tumor malignancies [219]. In most cancer subtypes, weekly dosing is comparable in efficacy to every-third-week dosing schedules [220]. However, the toxicity profile and the incidence of myelosuppression, which is of particular concern in the elderly, are less with weekly dosing administration. Myelosuppression and fatigue are the most common side effects with docetaxel; other adverse events include alopecia, asthenia, dermatologic toxicity, hyperlacrimation, fluid retention, and hypersensitivity reactions. Most side effects are dose-related and are resolved through dose reductions or short delays in therapy.

Vinca Alkaloids

Vinorelbine is the most commonly utilized vinca alkaloid. This drug is indicated for non-small cell lung cancer, but it also has activity in other solid tumors such as breast and prostate cancer. Hepatic function affects the metabolism of vinca alkaloids, because they are excreted primarily through the biliary tract after being metabolized by the cytochrome P450 system. Dose adjustment of vinorelbine is recommended in severe liver impairment [3, 221, 222]. It is suggested to reduce doses by 50% if over 75% of the liver is replaced by tumor or if the serum bilirubin is over 34 mmol/l (1.9 mg/dl). A correlation was observed between the patient's age and the clearance of vinorelbine, with an estimated 30–40% decrease after the age of 70 [3, 223]. The higher AUC of vinorelbine correlated with greater myelosuppression. Another study, however, found no age-related pharmacokinetic changes or toxicity in a small sample of older patients [222]. Further studies are necessary to help clarify the impact of age on the pharmacology of vinorelbine [153].

Alkylating Agents

Alkylating agents were among the first chemotherapies and are used for a multitude of neoplastic conditions. These drugs are primarily metabolized in the liver. Age-related changes in cytochrome P450 systems can affect metabolism, efficacy, and toxicity. Myelosuppression is the dose-limiting toxicity.

Cyclophosphamide and melphalan are the most commonly utilized alkylating agents. Cyclophosphamide is incorporated into multidrug regimens for the treatment of breast cancer. It is metabolized in the liver to phosphoramide mustard and acrolein, which are renally excreted. Renal insufficiency may result in the accumulation of these toxic metabolites, and therefore dose reduction would be required [224, 225]. Age is not associated with pharmacokinetic differences for cyclophosphamide [24]. Reduced creatinine clearance, not older age itself, necessitated dose reductions of cyclophosphamide, methotrexate, and

5-fluorouracil (CMF) in women aged 70 or over receiving treatment for metastatic breast cancer [226]. Pharmacokinetic evaluation of cyclophosphamide in combination with doxorubicin also did not show age-related differences, although an age-related neutropenia was demonstrated [155]. Based on the available information, cyclophosphamide should not be dose-reduced based on age alone.

Melphalan is utilized for elderly patients with multiple myeloma. One third of the drug is excreted in the urine. Although a correlation exists between the AUC and renal insufficiency, interindividual variations in clearance have a larger impact than renal insufficiency [153, 227]. High-dose melphalan, used for the treatment of myeloma with autologous bone marrow transplant, is associated with higher toxicity levels in patients aged 70 and over and in those with decreased renal function [228, 229]. Although dose reduction is justified based on age alone, it is recommended primarily for those with reduced renal function.

Complications of Cancer Treatment and Approaches to Supportive Care in Older Persons

Age is a risk factor for several toxicities from chemotherapy. Myelosuppression, the major dose-limiting toxicity from chemotherapy, is increased in older patients with lymphoma [230, 231]. Myelosuppression in older patients is associated with higher rates of febrile neutropenia, days of hospitalization, and inpatient mortality. Age is also a risk factor for myelosuppression in older patients receiving chemotherapy for breast cancer [232, 233]. In addition to acute myelosuppressive toxicities, older persons receiving adjuvant chemotherapy are at greater risk of developing and dying from therapy-associated leukemia or myelodysplastic syndromes [234, 235]. Hematological growth factors can play an important role in diminishing hematological toxicity and allowing the administration of curative regimens. The RICOVER-60 trial investigated the use of standard and dose-dense regimens in elderly lymphoma patients and showed that a reduction in administered granulocyte colony-stimulating factors led to significant increases in neutropenia and infectious complications [236]. Another retrospective review of CALGB data revealed that women over 65 were 68% more likely to develop grade 4 leukopenia but derived the same clinical benefit when treated with newer adjuvant regimens as younger patients when treated with granulocyte colony-stimulating factor [234]. Granulocyte colony-stimulating factor support allowed for the maintenance of dose intensity and the prevention of hematologic toxicity. Because the risk of death is highest in the first cycles of chemotherapy, prophylaxis with colony-stimulating factor should be considered early in treatment for elderly patients [6, 37]. Granulocyte colony-stimulating factor, however, has been shown to increase the risk for the development of myelodysplastic syndrome or acute leukemia in observational studies, although other studies have not reported this association [237–239]. More data are necessary to clarify associations among age, chemotherapy, and the development of hematologic malignancies.

Erythropoiesis-stimulating agents, widely used to treat anemia in cancer patients, diminished anemia-related toxicity and improved quality of life [240]. However, a systematic review by Bennett et al. described a 1.57-fold increase in venous thromboembolism and a 1.10-fold increased mortality when erythropoietin-stimulating agents were administered to patients with anemia and cancer [241]. The risks and benefits of erythropoiesis-stimulating agents should be carefully considered prior to initiation.

Besides the prevention and support of hematologic toxicities, a number of nonhematologic toxicities can be mediated by supportive care agents. For example, oral mucositis is a frequent complication of chemotherapy and radiotherapy and can prevent adequate hydration and increase the risk of infectious complications. Mucositis, including stomatitis, diarrhea, and gastritis, is more common in older patients. Advanced age predicts more frequent and more severe diarrhea and stomatitis in patients who receive 5-fluorouracil-based regimens for colon cancer or breast cancer [6, 164, 242, 243]. Mucositis and diarrhea require prompt attention to prevent dehydration. Cryotherapy and attention to dental hygiene have been shown to be the most effective measures of mucositis prevention and treatment. Opioid and nonopioid analgesics can be used for pain control, and antibiotics are used for the treatment of secondary infections.

A number of protective agents are effective in agent-specific toxicities (Table 5). In elderly patients, anthracycline-induced cardiotoxicity, especially in those with risk factors, can be an issue. Although the risk of cardiotoxicity increases with age, its incidence is more dependent on the total anthracycline dose (e.g., risk significantly increases after a cumulative dose of 450 mg/m^2 of doxorubicin) [6]. Using alternative schedules or liposomal formulation in patients with previous cardiac histories, existing risk, or clinical signs of cardiac disease is recommended. Monitoring clinical symptoms and left ventricular ejection fraction while controlling preexisting hypertension can be helpful. In addition, pharmacotherapy with cardioprotective agents such as dexrazoxane is effective in the elderly population, although their routine use is not generally advised [6].

Table 5 Examples of treatments to decrease chemotherapy toxicity

Drug	Toxicity	Protector
Methotrexate	Myelosuppression, mucositis	Folinic acid
Doxorubicin	Cardiac	Dexrazoxane
Vinca alkaloids	Neuropathy	Glutamic acid
Cisplatin	Renal, neuropathy	Amifostine
5-FU	Diarrhea	Octreotide
Irinotecan	Diarrhea	Loperamide

In summary, careful attention to supportive care for older patients receiving chemotherapy is imperative. Since toxicity leads to dose reductions that could affect efficacy, aggressive management and prevention of toxicities would lead to better cancer-related and quality-of-life outcomes.

Conclusion

Aging is a highly individualized process, and common physiologic changes may increase the likelihood of toxicity with chemotherapy. Much remains to be learned regarding the impact of age on the pharmacokinetics of chemotherapy drugs. A few studies report age-related differences in pharmacokinetics, but most found no significant differences in pharmacokinetics with age. More importantly, however, even if there were no difference in pharmacokinetics, a difference in pharmacodynamics was commonly seen. Most often, older patients were at an increased risk of myelosuppression and other toxicities resulting from the age-related decline in organ function. The increased use of hematopoietic growth factors has led to a shift in the toxicity profile. The dose-limiting toxicity of many regimens has shifted to nonhematologic toxicity, particularly neuropathy and gastrointestinal toxicity, which remain significant problems for older patients.

Additional studies on the pharmacokinetics of cancer therapies in the older patient are needed. Factors other than pharmacokinetics and chronologic age likely will be significant predictors of the tolerance to chemotherapy. Future pharmacokinetic studies in older patients should include a thorough evaluation of physiologic factors such as baseline renal function, hepatic function, and hemoglobin and albumin levels. In addition, studies should include an assessment of factors apart from chronologic age that independently predict morbidity and mortality in the geriatric population, such as those captured in a geriatric assessment (functional status, cognitive state, number of comorbid illnesses, nutritional state, and psychological status). Studies that include these parameters might provide insight into the factors contributing to the tolerability of chemotherapy and lead to interventions to improve treatment tolerance in older patients.

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Radiation Therapy in Geriatric Oncology

Sarah E. Hoffe and Mark S. Russell

Personalizing a patient's course of cancer therapy is of utmost relevance to the geriatric population. Advances in diagnostic radiology and radiation technology have improved tolerability for this group and expanded treatment options. Better images to visualize the tumor with PET/CT or MRI can be registered to the CT data acquired with the patient in the treatment position so that a fused image of the tumor can be created. Radiation oncologists then contour the intended target and adjacent normal tissues on axial CT slices. By displaying these structures in three dimensions and even being able to see the effects of respiration (4D CT), a treatment plan can be generated that will optimize the balance between target versus normal tissue dose. Graphs called dose-volume histograms (DVHs) are formed to evaluate what dose a volume of a structure within the radiation field is receiving in the proposed treatment plan. This allows the physician to then decide which technique would be most feasible in that particular patient's case.

To the radiation oncologist, dose and volume effects are critical for enhancing the potential for a successful outcome. Each structure in the body is known to have a certain level of radiation exposure that it can tolerate without excessive risk of complications. Termed the "tolerance dose to produce a 5%

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risk of complications at 5 years" (TD 5/5), this parameter forms the foundation for treatment planning that strives to deliver the prescribed dose to the tumor while not exceeding the normal tissue tolerance. The current explosion in advancements in radiation oncology has resulted in a virtual alphabet soup spelling 3D-CRT (three-dimensional conformal radiation therapy), IMRT (intensity-modulated radiation therapy), IGRT (image-guided radiation therapy), SBRT (stereotactic body radiation therapy), SRS (stereotactic radiosurgery), and APBI (accelerated partial breast irradiation), to name just a few. This has catapulted a transcendence of conventional thinking to push the delivered doses to small volumes of tissue higher and higher. At no previous time have radiation oncologists been able to deliver such high doses so precisely to the tumor, dangling the carrot that "You can kill any tumor if you just can treat it to a high enough dose." How best to accomplish this safely, and with what technique, is being vigorously pursued by the global radiation oncology community. This chapter explores the new treatment techniques in greater detail by examining how they are being incorporated into the management of prostate, breast, lung, and GI malignancies.

Prostate

The evolution of modern prostate cancer radiotherapy over the past 30 years has translated to improved treatment options for the elderly patient. Traditionally, radiation oncologists designed external beam radiotherapy fields by using fluoroscopically generated images and estimating the position of the prostate, rectum, and bladder. Doses were prescribed to less than 70 Gy due to concern about injury to the adjacent normal tissue [1]. Patterns of care studies of patients treated in the 1970s were reported by Leibel and showed that local control was related to the dose received by the primary site, the periprostatic tissues, and the pelvic sidewall [2]. Complications in this study were noted to be correlated with the total dose and the treatment technique, with 9% of stage A patients experiencing major complications, 2% of stage B, and 6% of stage C patients. In the pre-PSA era, the patterns of care study noted an 85% three-year relapse-free survival (RFS) for stage A patients, a 77% RFS for stage B, and a 59% RFS for stage C. Analysis of patients treated on RTOG studies also revealed significant morbidity. Pilepich reported the experience of 526 patients treated from 1976–1980 and noted a 20–30% persistent proctitis rate beyond two years [3]. There were also reports of hematuria, symptoms secondary to urethral strictures, and genital as well as leg edema. These early studies demonstrated that with conventional techniques, doses were limited by the tolerance of the adjacent normal tissues.

This changed with the advent of CT scans and the development of treatment planning software that allowed the delivery of three-dimensional conformal radiation. For the first time, radiation oncologists were able to delineate the prostate and normal tissue volumetrically and create a multiple-beam plan that spared more normal tissue than was ever possible before. Investigators demonstrated that with this technique it was possible to safely deliver higher doses to the intended prostatic target. Dearnaley confirmed the importance of the treatment technique in a randomized trial [4]. His group showed that significantly fewer men developed radiation-induced proctitis and bleeding in the conformal group than the conventional group, with 37% vs. 56% $\geq$ RTOG grade 1 ($p = 0.004$) and 5% vs. 15% $\geq$ RTOG grade 2 ($p = 0.01$). With the conclusion of the NIH Consensus Development Panel that localized prostate cancer could be managed equally well with radical prostatectomy or radiotherapy, increasing attention was turned to strategies that capitalized on the improved planning techniques that would allow dose escalation and, it was hoped, improved chances for cure with nonoperative treatment [5].

In the 1990s, investigators from multiple institutions began to report improved results with modern external beam techniques and higher doses. Leibel reported the initial results of the Memorial-Sloan Kettering Cancer Center's Phase I dose escalation trial in 1994 [6]. The early findings from 123 patients treated with doses ranging from 64.8-75.6 Gy revealed that acute toxicity was decreased with conformal therapy and that the initial tumor response as assessed by PSA decline was encouraging. This initial experience was confirmed in a larger series of 743 patients where the dose was escalated from 64.8 Gy to a total dose of 81.0 Gy [7]. Zelefsky reported that for these patients, dose was a significant factor: 90% of those patients receiving 75.6 Gy or 81.0 Gy achieved a PSA nadir < 1.0 compared with 76% receiving 70.2 Gy and 56% receiving 64.8 Gy ($p < 0.001$). The five-year actuarial PSA relapse-free survival showed a worse outcome with higher-risk disease: with 85% for low-risk patients (stage T1-2, pretreatment PSA ≥ 10, Gleason score ≥ 6), 65% for intermediate-risk (one worse factor), and 35% for high-risk (two worse factors), $p < 0.001$. Those patients with intermediate- or high-risk disease who received doses of at least 75.6 Gy showed a significant improvement in PSA relapse-free survival compared with the lower-dose arms, $p < 0.05$. Investigators from MD Anderson Cancer Center also showed the clinical benefit of higher radiation doses after a trial of 301 patients at their institution that randomized patients to 70 Gy vs. 78 Gy. Kuban recently reported the long-term results of this trial with a median follow-up of 8.7 years [8]. Results have confirmed that the higher-dose arm is associated with superior rates of freedom from biochemical or clinical failure, 78% vs. 59%, $p = 0.004$. The higher dose in this trial was associated with an even greater benefit in the group of patients who had a PSA > 10: 78% vs. 39%, $p = 0.001$. Finally, there were also dose escalation reports from investigators treating patients with protons[1] who showed that there could be minimal treatment-related toxicity with this modality [9].

The data on improved outcomes with less morbidity for men with prostate cancer apply not only to external beam radiotherapy but also to internal radiation or brachytherapy.

[1] A specialized type of heavy particle external beam radiation characterized by rapid dose falloff beyond the effective delivery depth and the very high cost of equipment.

Treatment techniques have evolved dramatically since Paschkis and Tittinger first used a radium source inserted through a cystoscope [10]. Modern brachytherapy techniques take advantage of transrectal ultrasound delineation of the prostate to deliver dose via either low-dose-rate (LDR) permanent implants or by high-dose-rate (HDR) temporary techniques. Both techniques reflect the ability to deliver a conformal high dose to the prostate while minimizing the dose to the surrounding bladder and rectum. The Seattle group reported 10-year PSA relapse-free survival (RFS) rates for early-stage disease using permanent brachytherapy alone to be 87% [11] and found that a combined approach using a 45-Gy external beam with LDR results in 15-year biochemical RFS rates of 88% for low-risk disease, 80% for intermediate-risk, and 53% for high-risk [12]. Higher doses also confer improved brachytherapy outcomes. A multiinstitutional study of 11 centers and 2,693 patients reported by Zelefsky revealed that where the implant dose to 90% of the prostate was at least 130 Gy, the eight-year PSA RFS was 93% vs. 76% with lower levels, $p < 0.001$ [13]. Modern brachytherapy series report low rates of short- and long-term morbidity as well [14–15].

These improvements in technology have thus allowed better treatment outcomes with less morbidity for those patients who undergo both external as well as internal radiation for prostate cancer. The current challenge for investigators is to determine whether newer techniques will promote further gain. Three-dimensional conformal radiation therapy has now evolved into intensity-modulated radiation therapy (IMRT), which separates the radiation beam into individual beamlets that are then selectively weighted to sculpt the dose around the target dynamically during treatment. Considerable interest in studying how much the prostate moves has led to the development of techniques to implant radiopaque fiducial markers directly into the prostate gland itself and image such motion on a daily basis [16]. Such dedication to the study of organ motion and the concomitant daily differences in resulting position has spawned the era of image-guided radiation therapy (IGRT). Image-guided radiotherapy can be accomplished using a kilovoltage technique if the patient has radiopaque implanted internal markers or via a megavoltage technique by a machine-generated CT (MVCT). A modality that incorporates both helical IMRT and IGRT is also being pioneered for the treatment of men with prostate cancer [17]. With this technique, a radiation machine resembling a CT scanner is used for daily treatment (TomoTherapy®).[2] The machine is able to create a CT image that allows the radiation therapist to confirm the treatment position prior to each IMRT fraction. Given the potential for differences in prostate position based on the filling of the adjacent bladder and rectum, daily setup confirmation allows precision treatment. These continued advances have allowed further refinements in the delivery of the targeted treatment with smaller individualized margins that confer better protection of normal tissues.

One newer modality garnering increasing attention is also struggling to find its place in the prostate cancer armamentarium. Stereotactic body radiation therapy (SBRT) has evolved from the days of intracranial-only treatment to its current investigational pedestal of multiple body sites, with Phase I/II data accumulating in the arenas of lung, liver, spine, pancreas, kidney, and prostate malignancies [18]. With SBRT, higher than conventional doses can be delivered precisely to a target in one to five fractions of radiotherapy. Preliminary prostate cancer SBRT data are emerging and may hold promise with potentially less morbidity, higher radiobiologic dose delivery, and more convenient dosing. One recent study of 10 patients treated with just four fractions of definitive SBRT to a dose of 38 Gy appears to show advantages compared with prostate HDR brachytherapy [19].

Advanced technology has now given the geriatric patient with prostate cancer multiple nonoperative choices. Physicians can first tell the patient what risk strata he is in and what the probability is that the cancer will have clinically significant progression during his lifetime. If the cancer is low-risk and

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[2] TomoTherapy, Inc., 1240 Deming Way, Madison, WI 53717-1954.

the chance of lifetime clinical progression is low, the patient may opt for watchful waiting. On the other hand, if the cancer is clinically significant enough that the potential for progression is present, he has both external as well as internal radiotherapy options. Modern techniques allow the patient to anticipate a low risk of short- and long-term morbidity. Options range from a permanent or temporary prostate implant alone to a combination of five weeks of external beam radiation followed by an implant boost to a longer course of definitive external beam. The current options of 3D conformal RT, IMRT, and IGRT have all shifted the therapeutic ratio in favor of higher expectation of long-term PSA relapse-free survival while maintaining low toxicity rates. In the near future, as data accumulate, there may also be the possibility of definitive SBRT with treatment delivered noninvasively in a week or less. All of these advances have allowed older men with prostate cancer safe non-operative options.

Breast

Over the last 30 years, significant advances in breast cancer treatment have evolved that have important implications for the older woman. First, 25-year data from the randomized NSABP B-04 trial reported by Fisher showed no advantage from the Halsted radical mastectomy [20]. Second, 20-year data from the randomized NSABP B-06 trial showed no difference in disease-free survival, distant disease-free survival, or overall survival between mastectomy vs. lumpectomy with or without whole breast irradiation [21]. There was, however, a significant difference in the cumulative incidence of ipsilateral breast recurrence, 39.2% with lumpectomy alone vs. 14.3% in the lumpectomy/radiation arm, $p < 0.001$. Third, randomized data from the Danish 82c trial reported by Overgaard showed a survival benefit in addition to a locoregional control benefit in those high-risk (stage II or III) postmenopausal women who underwent postmastectomy locoregional irradiation and tamoxifen compared to tamoxifen alone [22]. At 10 years, this translated to an overall survival of 45% in the RT arm compared with 36% in the tamoxifen-only arm, $p = 0.03$.

Women with breast cancer can thus be offered irradiation postoperatively to prevent locoregional recurrence of their disease and, in the setting of high-risk disease postmastectomy, to also improve their chances of survival [23]. Left-sided breast cancer radiotherapy has been associated with controversy due to concerns of late cardiac morbidity. Recent data, has shown that such treatment is not associated with higher risks of cardiac death compared to right-sided treatment but may be associated with an increased risk of coronary artery disease and myocardial infarction [24].However, data from the Surveillance, Epidemiology, and End Results-Medicare review of approximately 8,000 women with left-sided as well as right-sided breast cancer followed for a median of 9.5 years noted no significant differences in cardiac morbidity [25]. Further, older age is not a contraindication to breast radiotherapy [26]. The older woman with left-sided breast cancer could thus be offered breast-conserving radiation and, if she had high-risk disease, following mastectomy. Data from a large cooperative group study of over 600 older women with stage I ER positive breast cancer treated with lumpectomy and hormonal therapy demonstrated that omission of radiation was associated with an increased risk of local recurrence but no difference in overall survival.

Recent technological advances are being incorporated into breast radiotherapy, particularly for left-sided lesions. Some centers are using IMRT to improve the treatment plans to allow for a more homogeneous dose distribution to lessen the risk of skin morbidity and to decrease the potential for cardiac morbidity. Pignol recently reported the results of a Canadian trial that randomized 358 patients to IMRT or to standard tangential treatment and found that breast IMRT was significantly associated with a decreased risk of moist desquamation ($p = 0.003$) [28]. The Memorial-Sloan Kettering Cancer Center group also reported the potential advantages with breast IMRT [29]. Hong reported their experience that IMRT significantly reduces the dose to coronary arteries, the ipsilateral lung, the contralateral breast, and the soft tissues. Other centers are pioneering techniques to control for breathing in order to reduce the dose delivered to the heart and underlying lung [30]. In this study reported by Korreman, a technique to have the patient voluntarily hold her breath at deep inspiration (DIBH) was shown to reduce cardiac and lung toxicity. Their data showed that the median heart volume receiving over 50% of the prescribed dose was decreased from 19.2% in the normal or free breathing state to 1.9% with the DIBH technique [31]. Moreover, the left anterior descending coronary artery volume decreased from 88.9% to 3.6%, while the median ipsilateral lung irradiated to >50% of the prescription dose decreased from 45.6% to 27.7% with the DIBH technique. Other investigators have evaluated the improved dosimetry that can be achieved by treating patients in the prone position; Stegman reported the Memorial Sloan-Kettering experience of similar long-term clinical outcomes of their early-stage breast cancer patients but with better dose homogeneity and less incidental cardiac and lung irradiation [32].

Most elderly women with breast cancer have early-stage disease and often complain to their oncologists about the inconvenience of a standard five- to six-week course of fractionated whole breast radiotherapy. Modern radiotherapy is offering these women more choices as well. A Canadian trial of accelerated hypofractionated whole breast irradiation following breast-conserving surgery in women with node-negative breast cancer randomized women to either 42 Gy to the whole breast in 16 fractions (262.5 cGy per fraction) or standard 50 Gy in 25 fractions (200 cGy per fraction) [33]. Long-term results have not shown any significant difference in disease-free or overall survival and no detrimental long-term toxicity [34].

Another option being explored in the breast conservation setting that is particularly appealing to older women is that of accelerated partial breast irradiation (APBI). Phase I/II trials evaluating the delivery of radiotherapy to the lumpectomy bed only and not the entire ispilateral breast have shown excellent local control and cosmesis [35]. A number of different approaches have evolved to deliver partial breast radiation, ranging from a single dose of radiation delivered intraoperatively (IORT) at the time of lumpectomy to a one-week program of twice-daily radiation delivered with external or internal radiation (brachytherapy) [36, 37].

Fifteen years ago, few centers were pioneering breast brachytherapy, predominantly because the techniques consisted of an invasive procedure with the temporary insertion of up to 20 catheters to encompass the lumpectomy site, a procedure termed interstitial brachytherapy. These catheters were loaded with radioactive sources and were not removed until the total dose had been delivered. The Oschner Clinic was one such center, and the results they reported in their early series showed promise, with equivalent local control and low morbidity [38]. Interest in brachytherapy increased, however, when the FDA approved a simpler method that consisted of a single balloon catheter (the MammoSite[3] device) inserted into the lumpectomy site (Fig. 1). The incorporation of this new intracavitary brachytherapy device allowed more practitioners and institutions to offer patients the option of partial breast radiotherapy, and the five-year results of the initial clinical trial have shown comparable local control compared to whole breast irradiation

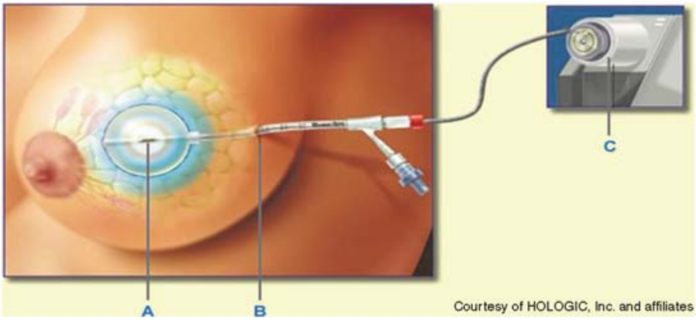

Fig. 1 A-Radioactive source positioned inside the balloon catheter B-Catheter inserted through the skin excision C-Radioactive loading device used to load source into treatment position for a specific amount of time and store source when not is use

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[3] Hologic, Inc., 250 Campus Drive, Marlborough, MA 01752 USA.

and to interstitial brachytherapy [39]. In addition to APBI brachytherapy options, there are now also multiple options to deliver radiation targeted to the lumpectomy site with external beam techniques. These options have been explored with patients in the supine as well as prone positions and have compared 3D conformal, IMRT, helical tomotherapy, and protons [40, 41]. Results have shown that there are multiple effective strategies to deliver radiation precisely to the lumpectomy cavity while minimizing the dose to the remainder of the healthy breast, the lung, and, in left-sided lesions, the heart. There is currently an ongoing Phase III NSABP B-39 study randomizing women with stage 0, I, or II breast cancer to receive either whole breast irradiation or accelerated partial breast irradiation delivered with interstitial, intracavitary, or 3D conformal external beam techniques. The modern older woman with breast cancer now has more choices than ever to discuss with her treatment team.

Lung

Multiple investigators have shown that the incorporation of PET/CT into radiation field design has significant potential to improve outcomes [42, 43]. Bradley reported that radiation targeting with fused FDG-PET and CT images resulted in alterations in radiotherapy planning in over 50% of non-small cell lung cancer patients [44]. For the elderly patient with lung cancer, the modern fusion of functional imaging with more conformal radiation treatment techniques has the potential to avoid geographic misses and reduce toxicity.

Historically, it was routine for radiation oncologists to irradiate elective nodal regions in the mediastinum, which increased normal tissue morbidity. Since local failure at the primary is such a profound entity in non-small cell lung cancer patients, modern investigators have sought to omit elective nodal areas. Rosenzweig reported the Memorial Sloan-Kettering experience of omission of elective nodal irradiation (ENI) and confirmed that this did not cause a significant amount of nodal failures [45]. The rate of elective nodal failure of 6% in his study evaluating 524 patients confirmed the value of involved field irradiation, with its attendant benefits of escalating the dose to the gross disease and minimizing the potential for lung, esophageal, and cardiac toxicity. Involved-field radiation has been studied specifically in the population of patients 70 years of age and has been confirmed to be well tolerated and associated with no significant increase in lymph node failures [46].

For those patients with medically inoperable early-stage disease, local failure at the primary site itself has thus been the significant clinical problem. Retrospective series such as that reported by Dosoretz have shown high rates of local failure and poor five-year overall and disease-free survival rate in this patient population with external beam radiation delivered over six to seven weeks [47]. This study did seem to show a reduced risk of local failure in those patients who received doses greater than 65 Gy, especially if they had T1 tumors. Additional retrospective series have shown that local failure is still an issue at 80.5 Gy [48]. The suggestion that there was a dose-response relationship in non-small cell lung cancers treated with radiotherapy was further explored by the RTOG in their Phase I/II dose escalation study [49]. By utilizing advanced treatment techniques to increase the dose safely and monitor for potential development of pulmonary toxicity, Bradley reported that the 93-11 trial was able to safely escalate dose to 77.4 and 83.8 Gy. Despite this, however, Werner-Wasik subsequently reported that increasing the radiation dose in this trial did not improve the median survival time (MST) or progression-free survival (PFS); on multivariate analysis, only a smaller gross target volume (GTV) was a significant prognostic factor [50]. Those patients with tumors less than 45 cm^3 achieved a longer MST and better PFS than did those patients with tumors larger than 45 cm^3: 29.7 vs. 13.3 months ($p < 0.0001$) and 15.8 vs. 8.3 months ($p < 0.0001$). Investigators are now looking beyond 3D conformal strategies to explore hypofractionated regimens with stereotactic techniques or protons so that high doses of radiation can be delivered in a shorter time to see if outcomes will improve.

Although Leskell developed a stereotactic halo for the delivery of precise intracranial radiation in the 1940s, it has only been within the last 15 years that a similar technology has been developed to treat extracranial tumor sites. The concept of radiosurgery evolved from the desire to deliver a high dose of radiation precisely to a relatively small target and to maximally spare the surrounding normal tissues. The traditional external beam doses of 180–200 cGy per fraction are transcended in stereotactic treatment to doses typically in the range of 1000–2000 Gy. The standard treatment delivered in six to seven weeks is shortened to a range typically delivered in one to two weeks. Blomgren described in 1995 the body frame used in Sweden to treat 31 patients with mostly solitary tumors of the liver, lung, and retroperitoneal region using one to four total fractions of radiation [51]. Results showed that 50% of the tumors were reduced in size or disappeared.

Since that time, Japanese and North American investigators have reported extensive promising data showing improved local control and efficacy with stereotactic body radiation therapy (SBRT) [52–53]. This treatment has taken advantage of the many advances incorporated into practice over the last 10 years. In the lung, radiopaque fiducial markers can be placed percutaneously or bronchoscopically. Once the markers are in place, the patient undergoes radiation treatment planning procedures that consist of several steps. First, the patient must be immobilized in a reliable way since the intent of stereotactic treatment is to precisely deliver high doses of radiation to a very small treatment area. This generally involves the patient being positioned in a custom-made cradle that supports the arms over the head. The patient then undergoes a 4D CT simulation such that the position of the tumor and the fiducial markers is known throughout the entirety of the patient's respiratory cycle. The individualization of the treatment planning is critical for each patient since there can be significant variations in tumor motion with breathing. To minimize the position of the tumor with respect to breathing motion, a variety of strategies are possible. Some institutions use abdominal compression whereby a plate on the abdomen decreases diaphragmatic motion. Other institutions use a form of respiratory gating whereby the linear accelerator only turns "on" during a specific phase of the respiratory cycle or whereby a breathing device fitted to the patient can be synchronized to the treatment planning unit such that the machine will only be turned "on" when the patient's breathing reaches a designated phase. Finally, other options include the ability to chase or track the tumor in real time to avoid excessively irradiating normal tissues. SBRT elegantly highlights the importance of incorporating image-guided radiation therapy (IGRT) since precision is of the utmost concern if the patient is only receiving a few fractions of definitive treatment.

Results from the SBRT literature for medically inoperable non-small cell lung carcinoma are indeed encouraging. Onishi reported the results of 257 stage I patients treated in a Japanese multiinstitutional trial [54]. The data showed that the five-year overall survival rate was 70.8% in those patients who received a biologically effective dose (BED) of 100 Gy or more vs. 30.2% if they received a BED < 100 Gy, $p < 0.05$. The local failure rate was only 8.4% if a BED of 100 Gy or more was delivered vs. 42.9% if the dose had a BED < 100 Gy, $p < 0.05$. Data from Timmerman's Phase I study of SBRT have also shown excellent local control [55]. In this study, the SBRT was delivered in three fractions, with the dose escalated up to 60 Gy in the T1 group. The T1 patients tolerated the treatment well, and there were only four local failures in the 19 patients. In the T2 group, there were six in 28 failures, and the maximally tolerated dose was 72 Gy if the tumor size was larger than 5 cm.

In addition to stereotactic treatment techniques, proton therapy techniques are also garnering clinical enthusiasm for improving local control. Investigators from MD Anderson Cancer Center have shown a significant reduction in doses to the lung, spinal cord, heart, and esophagus with protons compared with 3D conformal radiation and with IMRT [56]. Outcome data from Japan have shown proton delivery for non-small cell lung cancer to be safe and effective [57]. Shioyama has reported on 51 patients treated with protons and found a five-year overall survival of 70% and an infield local control of 89% in stage IA patients [58].

For the elderly patient with early-stage non-small cell lung cancer, the future appears brighter than ever. Improved metabolic targeting translates to improved accuracy in defining the gross tumor. Advanced CT simulation techniques allow the tumor's position to be accurately assessed, as it moves with the patient's breathing. Strategies to decrease the effect of respiratory motion so that the least amount of surrounding normal tissue is irradiated have been optimized. The delivery of ablative doses of radiation, which are not only more convenient to the patient, but also more effective clinically, holds significant promise. Future trials may evaluate the different hypofractionated regimens and compare these noninvasive alternatives to surgical resection.

Gastrointestinal

Advances in technology are also improving treatment options for elderly patients with gastrointestinal tumors (Fig. 2). Nowhere is this more apparent than in the setting of primary

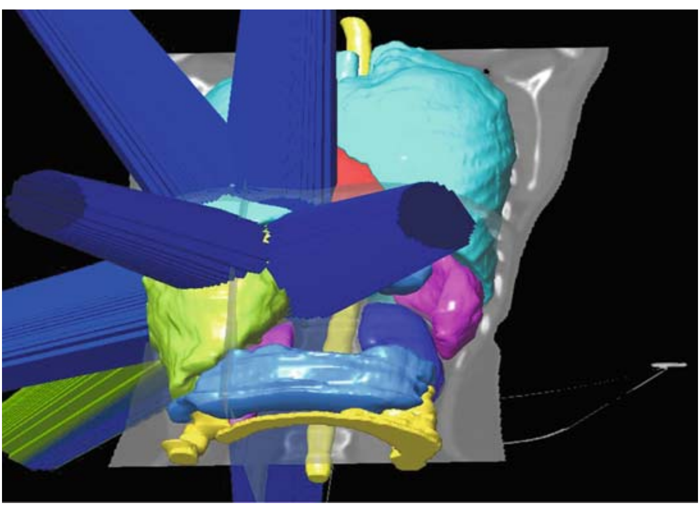

Fig. 2 Radiation beams focused on the tumor and sparing normal structures

and metastatic liver tumors. The gold standard for liver management has been surgical resection, with encouraging long-term outcome data. Fong reported a large-volume experience from Memorial Sloan Kettering Cancer Center (MSKCC) that showed a five-year survival rate for metastatic lesions of 37% and a 10-year survival rate of 22% [59]. Investigators from MD Anderson Cancer Center showed that survival following hepatic resection of a solitary metastasis from a colorectal primary can exceed 70% at five years [60]. However, many elderly patients with significant comorbid medical problems that are quantifiable using the weighted Charlson Comorbidity Index and the ASA classification may be estimated to have higher perioperative morbidity and mortality risk, making surgery less feasible [61]. In addition to medical comorbidities, a surgically inaccessible tumor location may be another rationale to consider other local modalities such as radiofrequency ablation (RFA). With the development of 4D CT techniques to study liver motion, safe noninvasive treatment of this moving target with external beam radiotherapy is now possible, providing even more treatment options.

Radiotherapy for liver tumors has been delivered since the 1990s at the University of Michigan. Investigators at Ann Arbor pioneered techniques to deliver high-dose partial liver radiation given the lower tolerance of the whole liver while minimizing the potential of radiation-induced liver disease (RILD) [62–63]. RILD is a potentially fatal clinical syndrome that can occur anywhere from two weeks to four months after radiation and is characterized by anicteric hepatomegaly, ascites, and elevated liver enzymes. Data at Michigan from the Phase I/II trial reported in 1995 found an objective response rate in 50% of patients.

The current state-of-the-art methodology in liver radiation oncology has been to pursue even higher radiobiologic dose delivery with stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT). Herfarth reported the results of a German Phase I/II trial of 60 liver tumors in 1997 with a local tumor control rate of 67% at 18 months [64]. Shefter reported the results of a Phase I study for — one to three liver metastases with doses of 20 Gy × 3 fractions [65]. The 18-month actuarial control estimate based on this work was 93%. Investigators at the University of Rochester reported on the treatment of 174 metastatic liver lesions with a median total dose of 48 Gy, with the dose per fraction ranging from 200–600 cGy [66]. The actuarial overall infield local control was 76% at 10 months and 57% at 20 months. The median overall survival time was 14.5 months, with no patient developing grade 3 or higher toxicity. Dawson reported on SBRT results for intrahepatic cholangiocarcinoma (IHC) and hepatocellular carcinoma (HCC) with six-fraction dosing individualized to the patient's risk of RILD, finding no severe sequelae in 41 patients, with a median survival for patients with HCC of 11.7 months and 15.0 months for IHC patients [67].

Stereotactic treatment of the liver takes into account organ motion strategies and can be delivered using a variety of equipment (Fig. 3). Some centers deliver liver SBRT by using 3D conformal or IMRT with image guidance on a conventional linear accelerator or with a helical-based unit. There is also the option of using CyberKnife®[4], a linear accelerator mounted on a robotic arm so that as the patient breathes, the position of the tumor can be tracked during the course of treatment. Some radiation delivery systems are equipped with a respiratory gating package so that the beam will turn on and off during specified times of the patient's breathing cycle. Image guidance is critical to ensure that the intended target receives the intended dose given respiration. Many institutions place fiducial markers percutaneously with CT guidance adjacent to the tumor to aid in treatment planning, target tracking, and verification of dose delivery. Stereotactic liver programs evolve with close cooperation among the radiologist, radiation oncologist, and medical physicist. Treating liver tumors noninvasively in one to two weeks significantly expands the applicability of this option to the elderly population.

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[4] Accuray, 1310 Chesapeake Terrace, Sunnyvale, CA 94089.

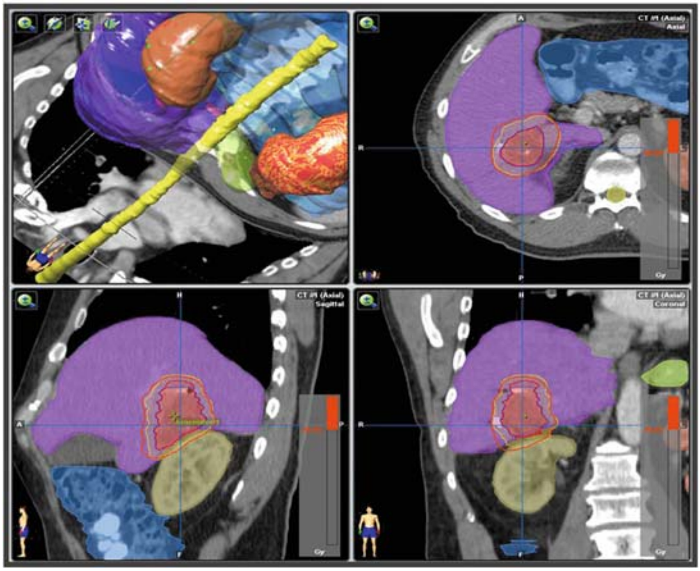

Fig. 3 Dose distribution surrounding gross tumor volume to deliver SBRT to a colorectal liver metastasis

If the patient has multiple liver tumors that are too diffuse to be treated with external beam irradiation, the strategy of selective internal radiation therapy (SIRT) with Yttrium-90 microspheres can be considered [68]. This technique involves using a transfemoral angiographic approach to inject microspheres directly into the hepatic arteries. By taking advantage of the liver's dual blood supply and the fact that the liver tumors are supplied by the hepatic arteries, the spheres can selectively deliver their radioactive dose to a smaller-volume target. Such treatment, while not considered curative, is nonetheless associated with improving quality of life, prolonging survival, and causing low rates of toxicity. The benefit is that the radiotherapy dose delivery is maximized in the liver tumors and minimized in the surrounding healthy parenchyma. For elderly patients who are not candidates for further chemotherapy, this is often a feasible option that will prolong survival and omit systemic side effects.

Such novel dose delivery strategies are also being offered to patients with unresectable locally advanced pancreatic cancer. Since the problem with this disease is the overwhelmingly high rate of distant disease progression, the benefit of radiation has seemed less certain, especially since upper abdominal radiation can be associated with short-term nausea, diarrhea, and attendant decreased oral intake. For the elderly patient with this disease, IMRT, tomotherapy, and stereotactic radiation are improving tolerability so that this potential option can be considered as well. Koong reported data from Stanford showing high rates of local control in this population with a single high-dose fraction of 25 Gy [69]. Such short-course treatment may be an especially good option for the elderly patient with significant local pain. Metabolic imaging has allowed more confident staging and selection of treatment options, especially when combined with a pancreatic protocol CT scan and with endoscopic ultrasound. Recent data exploring the efficacy of PET in pancreas cancer revealed that PET/CT in the initial management of patients with pancreatic neoplasms increased the sensitivity for detection of metastatic disease [70]. By more accurately determining which patients have metastatic disease at presentation, more appropriate regimens can be selected for the elderly patient.

In esophageal cancer, PET has been shown to confirm clinical staging and alter radiation tumor targeting [71]. Since preoperative combined modality therapy regimens may be offered to the fit elderly patient, it is more important than ever to minimize short- and long-term morbidity. Investigators from MD Anderson Cancer Center (MDACC) have shown that the amount of healthy lung exposed to radiation has a significant correlation with the potential for pulmonary perioperative complications [72]. To minimize these risks, radiation can be delivered with 3D-CRT or IMRT techniques to ensure that the total lung dose is kept as low as possible at doses of 5, 10, and 20 Gy. With distal esophageal lesions, tumor motion within the chest due to respiration can be significant. By incorporating a 4D CT scan into the treatment planning process, the patient's individual motion can be quantified and planned for accordingly. If significant motion exists and an IMRT plan is felt to be necessary to minimize the potential complications, the treatment can be delivered using compensators, which the radiation therapist places into the head of the machine on each field to shape the radiation dose distribution optimally. A compensator-based IMRT technique has been shown to improve efficacy with moving targets [73].

IMRT options have been explored in patients with anal cancer to minimize morbidity (Fig. 4). Standard techniques involve irradiating large volumes of normal tissue, especially the genitalia, to high doses, thereby increasing the potential of a treatment break. Recent data comparing conventional treatment for anal cancer to IMRT have shown a significant reduction in treatment duration. Bazan reported data on 29 patients who received definitive chemoradiotherapy, 16 with conventional RT and 13 with IMRT [74]. The mean treatment

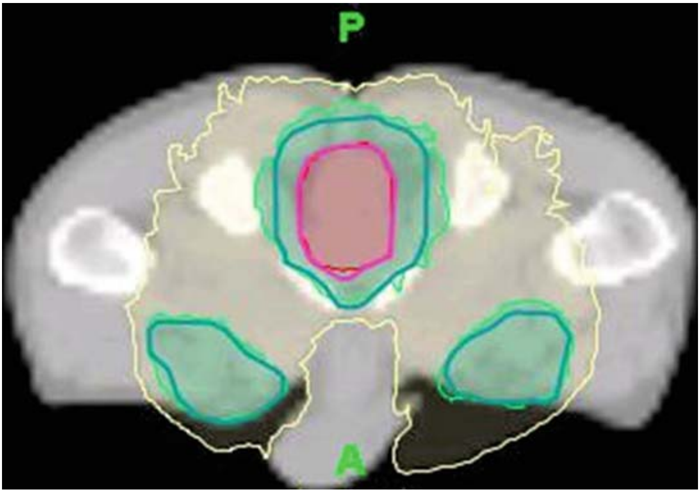

Fig. 4 Patient on a prone belly-board allowing dose sparing to genitals with an IMRT tomotherapy plan. The red area shows highest dose to the anal tumor with green showing elective nodal dose to the uninvolved groin nodes

duration was 59.1 days in the conventional RT group vs. 37.8 days in the IMRT group, $p < 0.0001$. Nine patients in the conventional group experienced grade >2 nonhematologic toxicity compared with only two patients in the IMRT group, $p = 0.02$. Salama reported a multicenter experience of 53 patients treated with IMRT, noting a complete response rate of over 92% [75]. Eighteen-month colostomy-free survival was 83.7%, with an overall survival of 93.4%. In a disease where local control is so critical to avoid a salvage APR, IMRT offers the advantage of sculpting the higher doses to the involved regions and minimizing the doses to the healthy tissues so that there is a significant chance for improving outcome. Studies with this technique are ongoing but provide a significant treatment advantage to the elderly patient with this disease.

In rectal cancer, the benefit of incorporating advanced technologies is less clear. Patients treated preoperatively with concurrent chemotherapy receive a standard dose of 45 Gy in 25 fractions followed by a three-fraction boost to 50.4 Gy. Techniques to displace mobile small bowel out of the irradiated field exist currently with prone positioning, belly-boards (devices with a cut-out in the center so that the patient's prone abdomen is displaced away from the treatment field), and full-bladder techniques. How much benefit IMRT or tomotherapy would offer in this setting is the subject of an ongoing international investigation [76, 77]. In the postoperative setting, however, the benefit may be greater. The German rectal cancer trial reported by Sauer in 2004 showed a significantly worse acute toxicity in the postoperative setting, with grade II/III toxicity of 27% in the preoperative setting vs. 40% in the postoperative setting, $p < 0.05$ [78]. Advanced technologies may have a role here to decrease morbidity.

Novel internal radiation therapy techniques are showing promise in patients with rectal cancer (Fig. 5). At McGill University, Vuong pioneered the modern incorporation of endorectal brachytherapy into preoperative treatment regimens [79]. By placing an applicator into the rectum and connecting it to a remote after-loader that houses a radioactive source that can travel into the patient, treatment can be delivered with

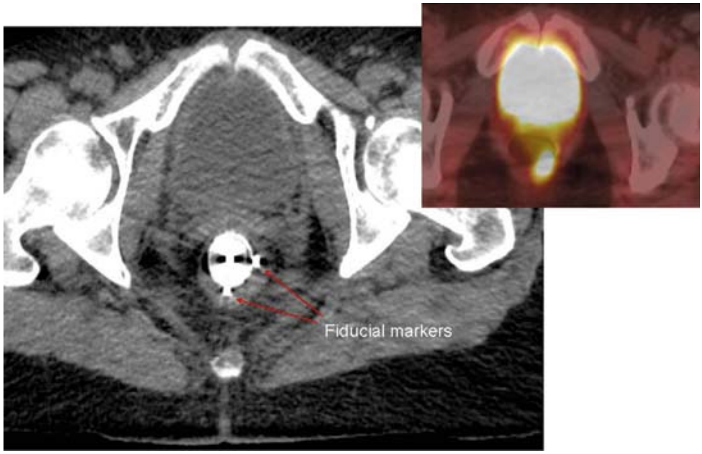

Fig. 5 Rectal applicator in place for administering brachytherapy radiation. Note fiducial markers are placed on either side of the tumor demonstrated with PET/CT imaging

high-dose-rate brachytherapy (HDRBT). After a dose of 26 Gy in four fractions of 650 cGy, operative findings showed a significant down-staging effect with a high rate of pathologic complete responders and near-complete responders. With a median follow-up time of 60 months, the five-year local recurrence rate for the largely T3 tumors treated was 5%, with a disease-free survival of 65% and an overall survival of 70%. HDRBT targets the endorectal tumor and mesorectum only, thus decreasing acute toxicity. For elderly patients, this strategy holds significant promise to decrease morbidity while potentially increasing efficacy and enhancing potential sphincter-preserving surgery.

Summary

In the last 20 years, radiation-computerized treatment planning and delivery systems have blossomed with new options for patients. Most recently, these advances have successfully shown that higher doses can be delivered more precisely. This has translated to decreasing short- and long-term morbidity such that elderly patients can now be offered a more potent treatment in less time.

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Palliative Care: Special Considerations for Older Adults with Cancer

Genevieve N. Thompson and Harvey M. Chochinov

A diagnosis of cancer can be devastating to an individual and his or her family. After the initial shock, the focus shifts to living with a chronic illness. However, the recurrence of disease, an initial diagnosis of advanced cancer, or metastasis often signals that a change in the course of care is required. Too often at this juncture, health-care providers tell their patients, "Nothing more can be done,"; a phrase that must be expelled from medical professionals' vocabulary, as there is always something that can be done, albeit with a different end goal. Palliative care is a philosophy of care that seeks to improve the quality of life along the cancer continuum. Though not all elderly individuals with cancer will require specialist palliative care services, all will benefit from the knowledge and implementation of its core tenets.

The elderly face unique challenges and have special needs that affect their cancer experience. The processes, events, and life transitions experienced by older adults can have profound effects on their physical, psychological, social, and existential well-being. For many older adults living with and dying from chronic illnesses such as cancer, the losses related to these life transitions are often difficult to deal with and may go unrecognized as important influences on their health, quality of life, and psychosocial well-

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being. Failing to attend to these factors may ultimately affect the dignity and quality of life and contribute to the suffering of older adults dying from cancer.

This chapter discusses the provision of palliative care to the older adult dying from cancer. Specifically, it describes the unique factors in the physical, psychological, social, existential, spiritual, and societal domains that affect the delivery of palliative care to the older adult. These factors are prefaced by a brief description of palliative care and its role in geriatric oncology.

Palliative Care—What Is It?

According to the World Health Organization, palliative care is an approach to care that

> improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain, and other physical, psychosocial and spiritual problems. [1]

The core components of any philosophy of palliative care can be identified to include (1) a patient and family focus, (2) active management of distressing symptoms, (3) total, individualized care of the patient, (4) an interdisciplinary team approach, (5) integration of the psychological and spiritual aspects of care, (6) support of the family throughout the patient's illness and in their own bereavement, and (7) offering support to the patient so he or she may live as actively as possible until death [2, 3]. Underpinning this philosophy of care is an open and positive attitude toward dying and death [4].

Forms of Palliative Care

In thinking about providing palliative care to older adults, it is important to consider different approaches to care based on the unique needs of the individual and where along the illness trajectory he or she may be. In this regard, it is important to distinguish among a palliative approach, specialized palliative care, and end-of-life or terminal care [5].

A Palliative Approach

The principles of a palliative care approach are integral and intrinsic to all good clinical care regardless of the nature or stage of the patient's illness [6]. In this manner, a patient still receiving active treatment for his or her disease may concurrently benefit from a palliative approach. However, the overall goal of a palliative approach is to improve the quality of life of the individual and reduce suffering, through improved comfort and level of function [4].

Specialist Palliative Care

When the patient's care needs extend beyond the practitioner's level of expertise or when the patient is experiencing multiple or complex care needs, patients benefit from a referral to a palliative care specialist or hospice services [6, 7]. This level of care augments the palliative care approach through targeted interventions delivered by multidisciplinary professionals with palliative care expertise. For example, the specialist palliative care team may provide an assessment and treatment of complex symptoms or offer information and advice regarding complex issues such as ethical dilemmas, family issues, or psychological or existential distress [4]. In this regard, the services provided by a specialist palliative care team serve as a resource to the primary care professionals [8].

End-of-Life or Terminal Care

As an individual approaches his or her last days or weeks of life, this approach to palliative care focuses on preventing suffering by attending to the physical, emotional, and spiritual comfort of the patient and family.

Role of Palliative Care in Geriatric Oncology

Older adults with cancer may suffer from a range of distressing symptoms related to their disease and its treatment. There is growing recognition of the importance of symptom control and attending to the psychosocial, spiritual, and existential needs of the patient from the time of diagnosis through the dying process. Patients should not have to choose between treatment with curative intent or comfort care; rather, there is a need for both in varying degrees throughout the course of cancer [9, 10]. The United Kingdom's Policy Framework for Commissioning Cancer Services recommends the formation of palliative care programs within cancer centers and stresses the importance of liaising with community palliative care services such as hospice programs. There is strong endorsement of a model in which

> Palliative care is required for many patients early in the course of their disease, sometimes from the time of diagnosis. It should not be associated only with terminal care. The palliative care team should integrate in a seamless way with all cancer treatment services to provide the best possible quality of life for the patient and their family. [11]

Palliative care is an integral part of geriatric oncology and strives to meet the unique needs of the older adult along his or her cancer trajectory.

Factors Unique to the Care of the Dying Elderly Cancer Patient

Approaching the care of an elderly individual with end-stage malignancy requires an understanding of not only the inherent physical changes that occurs as one ages, but also the impact aging has on other life domains. The role that aging plays on the end-of-life experience of the elderly cancer patient is complex. People grow old in a myriad of ways, influenced by social conditions, culture, and their own experiences and personality [12]. To understand the impact that dying from cancer has on an elderly individual, one must consider the prior life course of the individual, and the emotional, social, and spiritual context in which the person lives. Death and dying are experienced in relation to life as a whole; thus, knowledge of the experiences across a life span is essential. In this regard, older adults dying from cancer differ from younger cancer patients. By default, they have lived longer and are at a different developmental stage in life. Older adults have been noted to have a different outlook on life and death, display better mental well-being, and have adaptive strengths developed over a long life [13, 14]. Adults in later life have also often experienced multiple losses, such as the loss of a job, the loss of health, and the loss of friends and/or a spouse, all of which may have a profound impact on a person's identity, sense of self, and quality of life [15, 16]. Additionally, older adults have a higher prevalence of certain syndromes such as dementia, multiple comorbidities, and communication difficulties and may receive health and social care in a range of settings, including assisted-living facilities, nursing homes, hospitals, and at home. Assessing these changes and transitions for the impact they may have on the areas of life that give an elder meaning is a critical aspect in delivering quality care in the final stages of illness. The influence of these factors on an older person's sense of dignity and quality of life and achieving excellent care at the end of life are described here.

Physical Factors

The older adult with cancer typically experiences a different dying process than a younger adult in a similar position. Older people are more frequently affected by multiple medical problems of varying severity [17]. On average, adults over the age of 65 years report three or more comorbid conditions in addition to cancer [18, 19]. Thus, elderly cancer patients are not dying from cancer alone; rather, their cancer may be one of several existing conditions. Much has been written regarding the different dying trajectories: the short period of decline with advanced cancer patients; the long-term disability, exacerbations, and unpredictability of the time of death associated with many chronic diseases; and the slow and steady decline noted in conditions such as frailty [20, 21]. Having multiple comorbidities will alter the profile of dying from one in which there are few restrictions on physical abilities to a pattern of longer periods of functional decline and increasing dependence [22, 23]. Data suggest that the period before death among the elderly is often characterized by years of significant physical distress and that the cumulative effect of multiple comorbidities may be much greater than any individual disease [24, 25]. One study examining the end of life of elderly patients with advanced cancer reported a median number of 11 distressing symptoms (range: 1–27) and that more than 90% of patients with advanced cancer who are near death report more than three distressing symptoms [26]. Though not all specific to the elderly population, there is a plethora of research documenting the negative consequences of unrelieved symptoms on dignity, quality of life, and their contribution to suffering [27–32].

A key issue facing the older adult that influences his or her quality of life is the impact of the aging body on functional ability. Many older adults report limitations in their functional ability as they get older, restricting their ability not only to perform activities of daily living, but also to remain independent in other parts of their lives as well. This transition from independence to dependence has been noted to cause significant existential distress in the elderly and to impact on reported quality of life [33]. Living with functional impairment and transitioning from living an independent life to becoming dependent and needing assistance are significant challenges for older people. Our sense of self is often intimately tied to our functional abilities, and experiencing functional decline impacts our sense of control [34]. Indeed, for many elders, feelings of inferiority and loss of self-esteem can become major issues in late life as a result of physical decline and changes in mental capacities [35, 36]. Striving to achieve a balance between remaining independent and asking for help is a fine line many elderly adults tread in order to avoid the perceived sense of being a burden to others.

Feeling a burden to others is significantly related to notions of dignity [37, 38]. Wilson and colleagues have found that feeling a burden was more highly correlated with loss of dignity than to either physical symptoms or other social and psychological concerns [39]. Indeed, self-perceived burden has emerged as a significant predictor of loss of dignity, with individuals reporting a fractured sense of dignity having a greater sense of burden and a lower quality of life [40]. The finding that perceived burden is more highly correlated with psychological issues than physical problems has been noted by others [41, 42]. Though issues of dependency and the need for physical assistance are factors contributing to a sense of burden, psychological distress is a stronger predictor of perceived sense of burden than the actual degree of physical dependency [38, 39]. Feeling that one may become a burden often translates into requests for a hastened death, with physicians in one study reporting that 41–75% of requests for a hastened death are because the patients report feeling that they are a burden to others. Of patients who had previously made a request for a hastened death, family members report that 58–94% were distressed about being a burden to others [43, 44]. In Oregon, where physician-assisted suicide is legal, a strong sense of self-perceived burden was cited as a concern by 37% of patients who received a hastened death [45].

One area that receives little attention in the literature, yet affects many older adults, is sensory limitations, especially in terms of hearing and vision impairments. Hearing loss increases with age, becoming one of the most common chronic illnesses reported by older adults [46]. With limitations in hearing or vision, older adults may begin to withdraw from meaningful social networks, leading to a reduction in social activity, restricted independence, and ultimately more isolation [47–49].

Loneliness and social isolation are factors that have been reported to affect older adults disproportionately and are tied to feelings of worth, dignity, and quality of life [50]. Communication may become challenged as well due to sensory limitations, and at times it may appear that the older adult does not understand or may not be understood [51]. The inability to communicate impacts the ability of health-care providers to assess a person's comfort, establish goals of care, and provide emotional and spiritual support [52]. The provision of adaptive equipment is vital to ensure that the older adult is able to communicate effectively throughout the course of palliative care in order to reduce the chance of sensory isolation and unmet needs. The consequences of sensory limitations may thus have a significant impact on the quality of life of a person and the ability to appropriately plan for the end of life.

Psychological Factors

The psychological effects a diagnosis of cancer has on the older adult have been fairly well documented in the literature. Though there is literature discussing psychological distress during the terminal or palliative phase of illness, few studies have examined these issues specifically within the older adult cancer population. Too often, researchers report findings for a range of ages and fail to conduct analyses that examine psychological issues in persons over 65 years of age. Despite these limitations, what can be gleaned from this body of work is that individuals dying of cancer are at risk of experiencing mental health problems, which are too frequently unrecognized and underdiagnosed [53–55]. Despite research indicating they cope with cancer better and have less diagnosed anxiety and depression than younger patients [56], older cancer patients may be at higher risk of psychological distress due to other life-cycle events and losses, such as retirement, widowhood, presence of comorbidities, and alterations to their physical abilities [57]. Studies have noted that psychological distress stems from unmet physical, psychological, spiritual, and existential needs, resulting in undue suffering for many [58–62]. Often times when such distress reaches a critical level, many patients feel they can no longer go on living. Chochinov and colleagues noted that 75% of patients who had a significant desire for hastening their death had moderate to severe pain compared to 46% of patients with mild to no pain [27]. Similarly, Coyle and Sculco identified uncontrolled pain as one of several antecedents preceding the expression of desire for a hastened death in patients with advanced cancer [63].

In the older cancer patient, depression, anxiety, delirium, and dementia are prevalent psychological factors that have the potential to cause significant distress during the terminal phase of illness. Each of these factors will be explored for their effect on an elder's quality of life, dignity, and potential to cause suffering.

Depression

Depressed mood and sadness are normal and appropriate responses for individuals living with a life-limiting illness [64]. However, depression is not a normal part of aging or a common occurrence at the end of life [53]. Depression has been identified in 7–20% of elderly individuals treated in the primary care setting, of which 30% have been diagnosed with major depression [65–67]. Major depression is more common in elderly persons with medical comorbidities and severe or chronic diseases including cancer. Between 10-25% of adult terminally ill cancer patients meet the criteria for major depression [68, 69]. More frequently occurring in the elderly, however, is minor depression, which requires fewer symptoms than major depression to meet the criteria for diagnosis [64]. Diagnosing depression may be complicated by the fact that there are significant commonalities between the somatic symptoms of depression and the manifestations of cancer [70]. Additionally, it is well documented that elderly persons often do not voluntarily discuss their loneliness or depression as frequently as younger patients [71, 72], with approximately 25% of older patients not reporting their psychiatric symptoms [57]. A thorough discussion of the assessment and treatment of depression in the older cancer patient is beyond the scope of this chapter; however, several sources are available for consultation [73–75]. Regardless of the clinical diagnosis, depressive symptoms in later life and in the palliative or terminal phase of cancer often go undiagnosed, resulting in their undertreatment and increasing the risk for suffering and distress [76, 77].

Studies have noted that depression in the elderly is a risk factor for morbidity, cognitive impairment, poor quality of life, and diminished sense of purpose and meaning [66, 78, 79]. In their literature review, Chochinov and Wilson report that clinical depression, poor pain control, and lack of social support are significantly related to desires for hastened death and that the degree of distress in these individuals is very high [27]. In a more recent study examining depression and anxiety disorders in palliative care, Wilson and colleagues identified that those who met the criteria for an anxiety or depressive disorder were significantly more likely to express a desire for death, report they were suffering, and feel a loss of dignity [68]. For many who experience depression, a profound sense of hopelessness exists [80–82]. The desire for a hastened death was noted by Breitbart and colleagues to be significantly related with clinical depression and hopelessness [80]. This finding was noted by Chochinov et al., whereby hopelessness was highly correlated with suicidal ideation [83]. A sense of hopelessness has been reported throughout the literature as a main reason many terminally ill patients would request a hastened death [68, 84, 85].

Anxiety

Epidemiological studies examining the prevalence of anxiety disorders in the older adult population report a range of findings. In community-dwelling older adults, rates of anxiety disorders are reported to be 7–18% or as low as 2% of older patients seen in primary care [86–88]. Donnelly and Walsh reported that 23% of advanced cancer patients who received a palliative care consultation had anxiety [26]. This finding is similar to that reported by

Massie and Holland [89] and Wilson and colleagues [68]. There is speculation, however, by several authors that these reports may actually underestimate the prevalence of anxiety in older adults because the instruments developed to assess anxiety were developed with younger individuals and are weighted heavily on the presentation of somatic symptoms [90–92]. Some argue that these instruments fail to capture the unique experiences and concerns of older persons, such as being a burden to other or worries about health [91].

Anxiety in terminally ill elderly patients most often is a manifestation of depression, delirium, dementia, or the result of medical complications [93]. For example, in the palliative care setting, a common cause of anxiety is uncontrolled pain. In the dying person, anxiety can often signal impending cardiac or respiratory arrest, pulmonary embolism, electrolyte imbalance, or dehydration [94]. Though anxiety may result from these factors, psychological and existential issues frequently are contributors to the terminally ill person's anxiety. Grappling with fears of isolation, dependency, disability, and death may increase anxiety [64]. Death anxiety, or the fear of death, is a phenomenon associated with being human [93, 95]. The fears and anxieties associated with death vary across the life span, with some reports indicating that death anxiety decreases with age [96]. Others, however, report that though older adults are more accepting of the finiteness of life and are able to put death into the context of the life lived, the fear of dying increases as humans age [13, 97]. Discussions aimed at demystifying the experience of death and presenting information about the dying process has been found helpful in alleviating anxiety and psychological distress in the terminal phase of illness [93].

Delirium and Dementia

Delirium is a disorder characterized by impairments in attention, concentration, and cognition often resulting from medical illness and medications [98]. Among elderly cancer patients, delirium has been found to be the second most common mental disorder, and approximately 80% of persons in the last weeks of life may experience delirium [99, 100]. The risk of developing delirium increases with age and approaching death [98]. The most common precipitants of delirium in palliative care are medications, infection, metabolic disorders, and end-stage organ disease. The hallmark of delirium is an acute change in consciousness and cognition that is not explained by an existing or emerging dementia [64]. It may be difficult to distinguish between delirium and dementia; however, delirium is often reversible, is more acute in onset, fluctuates in presentation, and the sleep-wake cycle is more impaired [94]. Studies indicate that 30-60% of delirium episodes are reversible [101]. More prominent in dementia are short- and long-term memory difficulties, impaired judgment, and abstract thinking, aphasia, and apraxia [94]. The presence of dementia may even increase the likelihood of delirium [102].

Delirium is a common cause of suffering and distress for family members and patients. In their study, Breitbart et al. found that the delusions during the delirious event were the strongest predictor of patient distress, whereas the severity of illness, delirium severity, and perceptual disturbance were the strongest predictors of caregiver and nursing staff distress, respectively [103]. Most delirious patients struggle to focus and sustain their attention and may have disorganized thinking and incoherent speech [98]. Two subtypes of delirium, defined by the arousal and psychomotor changes experienced by the patient, exist: hypoactive (lethargic or hypoalert) and hyperactive (agitated or hyperalert), or a mixed presentation. Among elderly individuals, hypoactive delirium is often mistaken for depression or is often not diagnosed [79]. Hyperactive delirium, on the other hand, is often very distressing, as it is characterized by restlessness, wandering, irritability or agitation, and perceptual disturbances. Studies of older adults in different settings found that approximately one quarter experience hyperactive delirium, one quarter have hypoactive delirium, and about half have a mixed presentation. Irrespective of the diagnoses, delirium can negatively impact the quality of life of the patient and his or her family. Unmanaged cognitive disorders rob the patient the opportunity to strengthen relationships with loved ones, to maintain a sense of control over the future, and to resolve past issues and contribute to others [101, 104]. Maintaining mental alertness and the sense of one's self are components terminally ill patients have identified as important to maintaining dignity and achieving a good death [105, 106].

Social Factors

Human beings are social by nature, and our sense of self and dignity is derived through our interactions with others [107, 108]. The presence of social support and social networks has been shown to have a positive influence on physical and mental health outcomes [109, 110]. Social support can provide an older adult with practical help, but also with emotional connectedness and acceptance, both of which contribute to feelings of enhanced self-efficacy [111]. In later life, support needs may become more complex, and more medical in nature, as is the case with a cancer diagnosis. As one ages, however, several factors conspire against the availability of social support. In general, the family network, often the key provider of social support to older adults, is aging itself; thus, it may become smaller, frailer, and less able to provide the needed support to the dying adult [111]. These issues add to the complexity of family/caregiver needs for information, support, and assistance, as changes in the patient's condition can tax scarce family resources needed to meet patient-care demands [112].

There is a general thinning of one's social network in later life, through the deaths of friends, family and/or a spouse, the need for relocation to a nursing home or assisted living facility, retirement, or worsening health. The combination of these losses may create a sense of isolation, loneliness, and potential suffering in the older cancer patient. Social isolation caused by restricted mobility or deteriorating health can negatively impact a chronically ill individual and his or her caregiver(s) [113]. Several authors have noted the important link between social support, especially in terms of close relationships with family and friends, and the feeling that life has purpose and meaning [114, 115]. Studies exploring the experience of older adults living with a chronic illness have noted that individuals longed to have social spontaneity [116], that often they suffered from loneliness because of their inability to participate in social activities, and as such, that they felt life lacked meaningful content [117]. Having the support of close friends and family contributes to one's sense of identity and self-esteem [117]; when these are lacking, a loss of dignity and suffering may ensue. This was prominent in a study of elderly nursing home patients who described that daily life contained much loneliness and that family and supportive attitudes from staff helped bolster the elderly individual's sense of self, meaning, and dignity [118].

Due to the nature of advanced terminal illness, older adults may face a change in the nature of their role within the family. With the progression and worsening of their condition, older adults may experience role reversal whereby they become the recipient of care from their children. However, caregiver issues are a significant concern in that there is often a lack of informal caregivers available to older adults. Teunissen et al. noted that those over 70 years of age had a greater shortage of informal caregivers than younger adults [119]. Alterations in societal structures and demographics mean that families may be dispersed over wide geographic areas [120], thereby reducing the potential number of available caregivers. The lack of available caregivers is a risk factor for nursing home placement [121].

Existential/Spiritual Factors

Spirituality is a difficult concept to define and assess. Some equate spirituality with religiosity, whereas for others, religion is a small part of a much broader concept capturing the essence of what it means to be human [122–124]. Recognizing that all humans have a spiritual dimension, spirituality is related to maintaining hope in hospice patients [125], enables one to cope more effectively with terminal illness [71], and is imperative to quality of life [126]. Gerontological theorists suggest that the key developmental tasks in older age are to find purpose and meaning in life, two core aspects of spirituality [127]. Indeed, spiritual development increases in importance as one ages [128]. Other spiritual tasks of aging include transcending loss, finding new intimacy with God and/or others, and finding hope, sometimes in the face of despair [126]. Many of these tasks correspond to the spiritual needs reported by Moadel and colleagues in their study of ethnically diverse, urban cancer outpatients [129]. Patients reported wanting help to overcome their fears, finding hope and meaning in life, finding spiritual resources, and having someone to talk with about the meaning of life and death as their most prevalent needs. However, patients reported 25–51% of their spiritual needs were not being met. Similarly, Greisinger and colleagues reported that terminally ill cancer patients rated existential concerns highest, and yet their spiritual, existential, and emotional concerns were rarely addressed by clinicians [130].

Failing to adequately address these needs can contribute greatly to the suffering experienced by many older adults, often resulting in spiritual and existential distress. Researchers have found that spiritual well-being is negatively correlated with loneliness, depression, and anxiety [131–133]. Indeed, spiritual despair or pain may manifest in different dimensions: physically, psychologically, religiously, or socially [134]. This despair may translate into feelings of hopelessness and demoralization, both of which can contribute to feeling a loss of will to live and a desire for a hastened death [80, 135]. The ability to find and sustain meaning in life during terminal illness is a strong deterrent to despair at the end of life [135]. The intimate connection between spirituality and a sense of purpose or meaning is especially important in light of research highlighting the importance of these dimensions in defining older adults' sense of dignity. Older adults report that serving a purpose, feeling important, feeling involved, and belonging are essential to their notions of dignity and, thus, spiritual well-being, yet report difficulty in meeting these needs [136, 137].

Living with meaning and having hope are important aspects for older adults living with and dying from advanced cancer. Lin and Bauer-Wu's review of the literature identified that psychospiritual well-being is largely predicated on the ability to find meaning and maintain hope [138]. Traditionally, within oncology, hope has focused solely on hoping for a cure or remission of disease [139, 140]. The challenge faced by elderly patients with advanced cancer is to find hope in the face of advancing disease; thus, the source of hope must be transformed in the face of life-threatening illness. Palliative care patients have identified several areas that provide them with hope, including hope for relief of pain [81], a peaceful death [130], being well cared for and supported [139], the well-being of their family [141], life after death [125], and living day by day [142]. As hope is central to life and an essential dimension for successfully dealing with critical illness, encouraging elderly patients to explore hope-fostering strategies is imperative [143]. Several studies have identified hope-fostering strategies used by palliative care cancer patients, including setting short-term goals, drawing on their faith, leaving a legacy, finding meaning and purpose, and conducting a life review [115, 144–147].

Societal Factors

Despite many advances in eradicating discrimination based on gender and cultural affiliation, ageism remains prevalent in Western cultures. Discrimination may take the shape of disrespect, to assumptions of frailty, disability, and cognitive impairment, to restricted access to medical interventions and social activities [148, 149]. To age is often seen in a negative light or as having entered an inferior state of being [149]. The dying elder may also experience what one author terms "triple jeopardy"; dying older adults represent two stigmatized fears in society: the fear of aging and the fear of death [150]. Negative attitudes toward aging and dying have potentially harmful consequences for the older adult. Family members as well as health-care professionals may share the notion that because a person is of advanced age, he or she has lived his or her life and therefore should be ready to die. Both family members and physicians have been found to underestimate older patients' desires for life-prolonging care [151]. By assuming the older adult is accepting of death negates the opportunity for open, honest discussions concerning his or her fears and concerns regarding dying. Some suggest that these negative attitudes may make it easier for society to restrict resource allocation for this population [152]. Research findings illustrate that not only are older adults less likely to have their pain managed adequately [153, 154], but they are also less likely to be referred to or use specialist palliative care services [155–157]. The SUPPORT study eloquently documented that older age was associated with lower resource intensity and less aggressive treatment and with more decisions to withhold life-sustaining treatments for older patients [151]. These findings concur with others [158, 159]. Ageist attitudes may also limit communication between an older adult and clinician if there is the perception that one's life is not valued. In short, ageist attitudes may impede care provided to older adults and have a significant impact on a person's self-esteem and dignity.

Strategies

This chapter has highlighted key factors that oncologists working with older adults dying from cancer should be attuned to in order to redress and prevent undue suffering in this population. Physical, psychological, social, spiritual, and societal factors play a significant role in shaping the dying experience of the older adult. Attending to concerns in these areas is of paramount importance to ensure that the dignity of the older cancer patient is bolstered and that a good death is achieved. Guidance in resolving conflicts in these areas is informed by the work of Chochinov and colleagues, who have systematically explored the concept of dignity in the terminally ill. Their early research work sought to uncover the meaning of dignity and the factors that relate to this issue. Based on their qualitative study of 50 palliative cancer patients, an empirically derived model of dignity in the terminally ill was developed [115, 160]. This model provides an understanding of the experiences that shape one's sense of dignity in light of a life-limiting illness and the ways in which dignity-conserving care may be applied.

The Dignity Model suggests that an individual's perception of dignity is related to and influenced by three major areas: (1) illness-related concerns; (2) dignity-conserving repertoire; and (3) social dignity inventory (see Table 1). These categories capture the broad experiences and events that determine how individuals experience a sense of dignity at the end of life. Each category contains several themes and subthemes, which further inform our understanding of dignity and the potential for therapeutic intervention.

Table 1 The dignity model (previously published: Chochinov et al. Dignity in the terminally ill: An empirical model. Soc Sci Med 2002;54:433–43.)

MAJOR DIGNITY CATEGORIES, THEMES AND SUB THEMES		
Illness-Related Concerns	**Dignity-Conserving Repertoire**	**Social Dignity Inventory**
Level of Independence – **Cognitive Acuity** – **Functional Capacity**	**Dignity-Conserving Perspectives** • continuity of self • role preservation • generativity/legacy • maintenance of pride • hopefulness • autonomy / control • acceptance • resilience / fighting spirit	**Privacy Boundaries** **Social Support** **Care Tenor** **Burden to others** **Aftermath Concerns**
Symptom Distress – **Physical Distress** – **Psychological Distress** • medical uncertainly • death anxiety	**Dignity Conserving Practices** • living "in the moment" • maintaining normalcy • seeking spiritual comfort	

Illness-related concerns are issues that derive from or are related to the illness itself, which threaten to or actually do hamper a patient's sense of dignity. As these concerns are mediated by the illness, they are very specific to the individual's experience of his or her life-limiting illness. The two themes subsumed in this category include the "level of independence," which is determined by the ability to maintain one's cognitive and functional capacities. The second theme, "symptom distress," captures both the physical and psychological distress an individual may experience as a result of his or her illness. For many, the intensity of physical symptoms may affect their sense of dignity, whereas psychological distress captures the mental anguish brought about by not knowing or being unaware of aspects of the illness (medical uncertainty) and the worry or fear associated with one's impending death (death anxiety).

The social dignity inventory refers to those environmental factors external to the patient that may strengthen or undermine the quality of interactions with others and, thus, their sense of dignity. Five externally mediated factors are included in this category. The first, privacy boundaries, explains how dignity can be affected by encroachments on one's personal environment when receiving care or support. Social support, the second subtheme, refers to the availability or presence of friends, family, or health-care providers who are perceived as helpful. Third, care tenor, is the attitude others demonstrate when providing care or interacting with the patient. The fourth subtheme, burden to others, explores the distress patients experience when they either feel they are or fear they will become a burden to others as their personal care or management becomes more difficult for them to manage alone. Finally, aftermath concerns are those anticipated fears or worries of the impact their death will have on their loved ones.

Mediating these two categories, the patient's dignity-conserving repertoire consists of those internally held and socially mediated approaches the individual uses to maintain his or her sense of dignity. Consisting of two major themes, dignity-conserving perspectives and dignity-conserving practices, these areas incorporate aspects of a patient's psychological and spiritual views that may influence his or her sense of dignity. Dignity-conserving perspectives are the ways a patient perceives or copes with the current situation and includes eight subthemes. Continuity of self is the sense that the core essence or identity of who one is remains intact despite progressing illness. Role preservation is the manner in which patients strive to maintain a sense of congruence with prior views of the self through one's ability to continue to function in usual roles. Generativity/legacy describes the comfort patients feel in knowing that their accomplishments, contributions, and connections to life (e.g., children) will live on and be a testament of their life. The maintenance of pride speaks to the ability of patients facing death to maintain a personal sense of positive self-regard or self-respect. Seeing that life not only was enduring but had meaning and purpose allowed patients to maintain a sense of hopefulness, and thus retain their dignity. Maintaining a sense of control or influence over life circumstances impacts a patient's sense of dignity, and in this regard the degree of autonomy a patient subjectively feels is of utmost importance. Acceptance is the ability to integrate and accommodate to life's changing circumstances. Finally, resilience/fighting spirit is a mental strategy some patients use to overcome their illness or to optimize their quality of life.

Dignity-conserving practices are the personal approaches or strategies that individuals use to improve or maintain their sense of dignity. These can include "living in the moment," whereby one focuses on immediate issues; "maintaining normalcy" involves continuing with usual routines and schedules; and "seeking spiritual comfort" draws on previously held religious or spiritual beliefs in an attempt to find comfort.

The research literature to date and the model of dignity developed by Chochinov and colleagues help to illuminate the key factors, issues, and experiences that both bolster and hamper a dying patient's sense of dignity. From this knowledge, interventions aimed at restoring and improving dignity in the dying can be developed. One such intervention is Dignity Therapy, a brief psychotherapeutic intervention whose focus is to provide the patient the opportunity to engage in a discussion regarding aspects of life he or she wants remembered or the opportunity to share wisdom and instructions for his or her soon-to-be-bereft loved ones. These sessions are tape-recorded, transcribed, edited, and returned to the patient, thereby creating a tangible document that acknowledges the importance of generativity and legacy. Reminiscence and life review activities are normal and important aspects of successful aging, emerging from the desire to grow, enjoy, change, or cope [161, 162]. Several authors have noted that elderly patients in palliative care desire the opportunity to conduct such a life review [137, 144, 161], and evidence suggests that patients who participate in the dignity intervention report a heightened sense of dignity, an increased sense of purpose, a heightened sense of meaning, and an increased will to live [163, 164]. A recent meta-analysis indicated that structured life review interventions have a significant effect on the psychological well-being of older adults [165]. These findings also resonate with the model developed by Coyle, which describes the hard work cancer patients undertake when living in the face of death [166]. The struggle to find meaning and create a legacy was of utmost importance to participants. Indeed, creating a legacy was a means to provide evidence of their value, significance, and at times a justification for how they lived, all factors that resonate with a person's sense of dignity.

The unique aspect of the Dignity Model is that it provides the clinician with guidance and direction on how he or she may approach dignity concerns, even through less structured approaches than interventions such as dignity therapy [147]. In this manner, the clinician can use the themes and subthemes of the Dignity Model as a jumping-off point to initiate conversations and address issues with patients that are of importance to them.

Summary

Caring for older adults dying from advanced cancer presents unique opportunities and challenges for oncologists and other health-care providers. Providing excellent care to the older adult with life-limiting illness requires the clinician to move beyond solely examining physical distress to addressing the psychological, spiritual, social, and societal dimensions that may influence the dying experience. By attending to concerns in these areas, undue suffering and distress may be prevented, thereby augmenting dignity, maximizing quality of life, and ensuring a good death is achieved for the older individual with advanced cancer.

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