National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Senior Adult Oncology

V.1.2010

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NCCN Guidelines Panel Disclosures

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§ Radiation/Radiation Oncology
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This section is being updated to correspond with the newly updated algorithm.

Clinical Trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus

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Summary of changes in the 1.2010 version of the Senior Adult Oncology Guidelines from the 1.2009 version include:

SAO-1

- Added recommendation for screening polypharmacy: "Update list of current medications (including nonprescription medications and supplements) and doses at each visit."

SAO-2

- Mucositis removed:
  - "Consider capecitabine instead of 5-FU, using caution in capecitabine dosing pending publication of additional data."
  - "Consider amifostine with head and neck RT."
  - "Nutrition if RT induced mucositis."

SAO-3

- Footnote "f" is new to the page: "Evaluate functional dependency prior to the diagnosis of malignancy."

SAO-B

- Added the following bullets to Specific Issues Related To The Management Of Cancer In Older Patients:
  - Impact of cancer therapies on bone health
  - Adherence to oral treatment recommendations for maintaining bone health.
  - Management of patients unfit for standard treatment
  - Targeted Therapy
    - Bevacizumab - Increases side effects in patients over 70 without increase in survival
    - Erlotinib - No evidence of increase efficacy, increased toxicity
    - Trastuzumab - should be used with caution in patients with prior cardiac history.
- Maintenance of independence after surgical therapy: Consider physical therapy or occupational therapy as clinically indicated
- Delirium and Dementia - See NCCN Distress Management Guidelines

SAO-C

- Colorectal, unresolved issues added:
  - Adjuvant chemotherapy is more effective but also more toxic.

SAO-D

- Added Screening Tools for Common Geriatric Syndromes
  - Dementia - Mini Mental State Examination (MMSE)
  - Depression - Geriatric Depression Scale (GDS)
  - Delirium - NCCN Distress Management Guidelines
  - Osteoporosis - DEXA Scan, See NCCN Bone Health Task Force
  - Fatigue - See NCCN Fatigue Guidelines
  - Nutrition deficiency- Mini-Nutritional Assessment (MNA)

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SCREENING

- Estimate life expectancy based on function and comorbidity[a]
- Estimate risk of morbidity from cancer:
  - Stage at diagnosis
  - Risk of recurrence and progression
  - Aggressiveness of disease
- Assessment of comorbid conditions (including geriatric syndromes) that would interfere with cancer treatment and tolerability:[b,c]
  - Malnutrition
  - Sensory deficits
  - Polypharmacy
    - Update list of current medications (including nonprescription medications and supplements) and doses at each visit
  - Lack of social support
  - Depression
  - Dementia
  - Fall risk

Social work consultation

- Assess patient goals of treatment and values

FINDINGS

Moderate or high risk of dying or suffering from cancer or experiencing complications within lifetime →

COMPREHENSIVE GERIATRIC ASSESSMENT[d]

- Evaluate functional dependency and comorbidity[e]
- Re-evaluate/discuss patient's lifetime goals

→ See Findings for Baseline Status (SAO-2)

Low risk of dying or suffering from cancer or limited life expectancy makes likelihood of developing morbidity from cancer low →

Symptom management
Supportive care
See NCCN Supportive Care Guidelines

[a] See Histograms for age-specific future life expectancy (SAO-A).
[b] See Specific Issues Related to the Management of Cancer in Older Patients (SAO-B) and Disease Specific Issues Related to Age (SAO-C).
[c] Patients with complex biomedical, functional, and psychosocial needs may benefit from a comprehensive geriatric assessment.
[d] See Comprehensive Geriatric Assessment (SAO-D) and Research Criteria Used to Define Frailty (SAO-E).
[e] See Procedure for Functional Assessment Screening in Elderly Persons (SAO-F) and Vulnerable Elders Survey (VES-13) (SAO-G).

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FINDINGS FOR BASELINE STATUS[f]

Functionally independent (ADL and IADL independent)

- Contraindication to treatment or declines therapy → **Symptom management, Supportive care** — See NCCN Supportive Care Guidelines
- No contraindication to treatment → See Special Considerations for Treatment (SAO-3)

Intermediate functional impairment → **Specialized precautions, individualized treatment according to patient preferences and caregiver availability**

- Contraindication to treatment or declines therapy → **Symptom management, Supportive care** — See NCCN Supportive Care Guidelines
- No contraindication to treatment → See Special Considerations for Treatment (SAO-3)

Major functional impairment and/or complex comorbidity[g] → **Symptom management, Supportive care** — See NCCN Supportive Care Guidelines

[f]Evaluate functional dependency prior to the diagnosis of malignancy.
[g]It is expected that this will comprise 5-10% of patients.

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SPECIAL CONSIDERATIONS FOR TREATMENT[h]

Surgical
- In general, age is not a primary consideration for surgical risk
- Assess physiologic status (Using standard surgical evaluation tools)

Radiation
- Use caution with concurrent RT/Chemotherapy, dose modification of chemotherapy may be necessary
- Consider amifostine for head and neck cancer
- Nutrition and pain control if RT induced mucositis
- Hearing evaluation if ear in RT fields

Able to tolerate treatment

Chemotherapy

Neurotoxicity
- Consider alternative regimens with non-neurotoxic drugs
- Monitor hearing loss and avoid neurotoxic agents if significant hearing loss present
- Monitor cerebellar function if high dose cytarabine

Cardiac toxicity
- Assessment of ventricular function
- Symptomatic or asymptomatic with ejection fraction of < 45%
  - ▸ No use of anthracyclines; may consider liposomal doxorubicin; consider dexrazoxane or alternative treatment

Bone marrow suppression
- Prophylactic colony stimulating factors when dose intensity required for response or cure (eg, Use of growth factors for all patients age ≥ 65 y treated with CHOP or CHOP-like chemotherapy) (See NCCN Myeloid Growth Factor Guidelines)
- Decreased dose of chemotherapy if palliation is the goal
- See NCCN Cancer and Treatment Related Anemia Guidelines

Diarrhea
- Consider early aggressive rehydration
- Management with octreotide if oral preparations are ineffective

Renal toxicity
- Adjust dose for glomerular filtration rate (GFR) to reduce systemic toxicity

Mucositis
- Drug holiday if prolonged infusion
- Early hospitalization in patients who develop dysphagia/diarrhea
- Nutritional support
- Oral prophylaxis
- See NCCN Task Force: Prevention and Management of Mucositis in Cancer Care

Nausea/vomiting
- See NCCN Antiemesis Guidelines

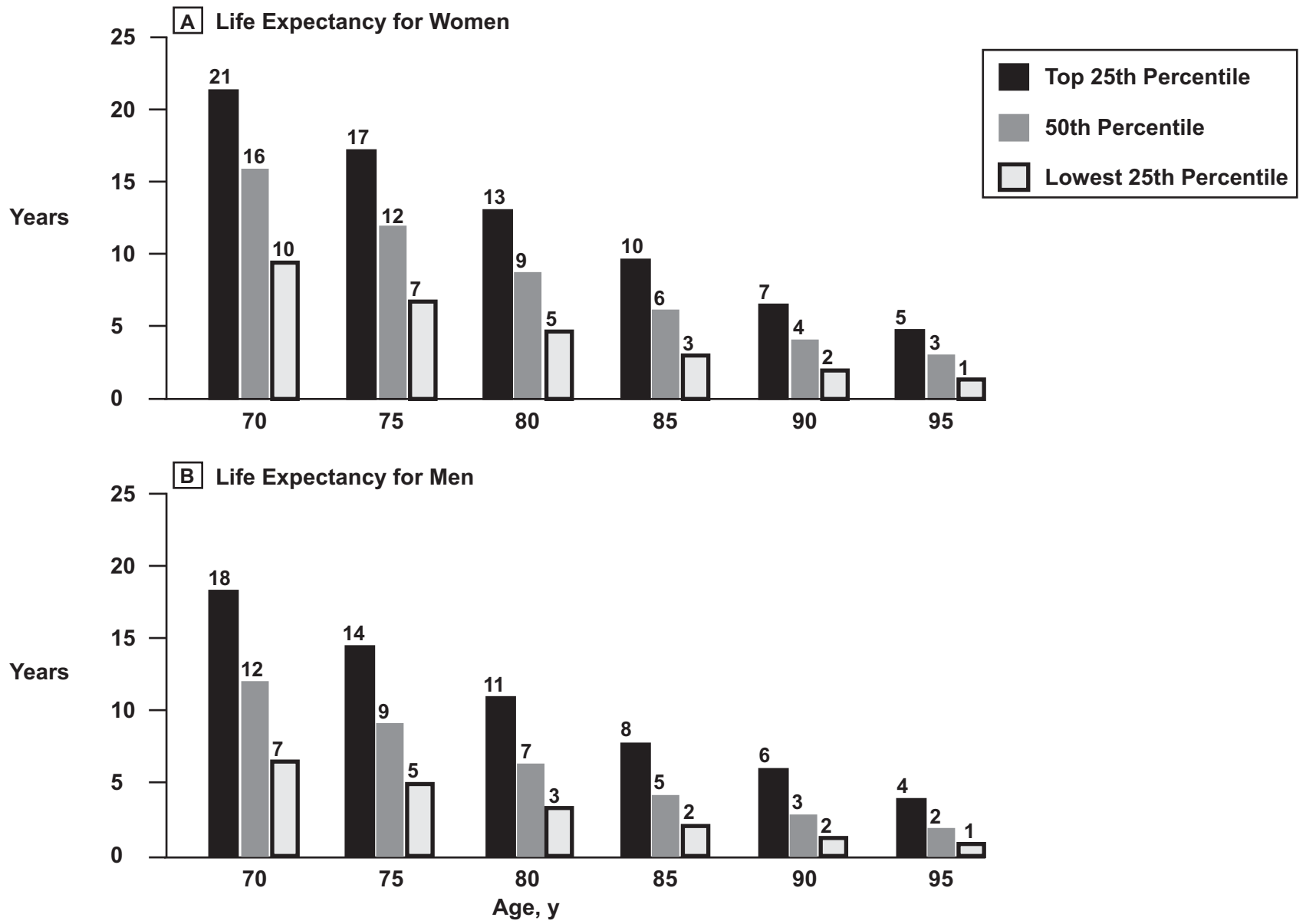
[h]Monitor function, comorbidities, social circumstances, pain, nutrition and distress for all therapies.

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UPPER, MIDDLE, AND LOWER PERCENTILES LIFE EXPECTANCY FOR WOMEN AND MEN AT SELECTED AGES



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SPECIFIC ISSUES RELATED TO THE MANAGEMENT OF CANCER IN OLDER PATIENTS

- **Geriatric assessment of the older individual (See SAO-D)**
  - Life expectancy
  - Tolerance for treatment
    - Detect and correct reversible conditions that may interfere with treatment
  - Ability of patient to make decisions
- **Prevention/Amelioration of treatment complications**
  - Use of hematopoietic growth factors
  - Control of anemia
  - Dose adjustment of chemotherapy agents
- **Disease-specific issues (See SAO-C)**
  - Acute myelogenous leukemia
  - Non-Hodgkin's lymphoma
  - Breast cancer
  - Colorectal cancer
  - Lung cancer
  - Impact of cancer therapies on bone health See NCCN Task Force Report - Bone Health in Cancer Care
  - Adherence to oral treatment recommendations for maintaining bone health
- **Management of patients unfit for standard treatment**
  - Targeted Therapy[1]
    - Bevacizumab - Increases side effects in patients over 70 without increase in survival
    - Erlotinib - No evidence of increased efficacy, increased toxicity
    - Trastuzumab - should be used with caution in patients with prior cardiac history.
- **Maintenance of independence after surgical therapy: Consider physical therapy or occupational therapy as clinically indicated**
- **Delirium and Dementia - See NCCN Distress Management Guidelines**

[1] There is some evidence indicating increased toxicities associated with targeted terapies in elderly patients compared to younger patients. See Discussion section for details.

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DISEASE-SPECIFIC ISSUES RELATED TO AGE

Disease	Age-Related Changes	Unresolved Issues
AML	• Decreased sensitivity to chemotherapy secondary to increased prevalence of MDR1 • Unfavorable cytogenetic profiles	• Reversal of MDR1 • Role of low-dose cytarabine • Supportive care
Non-Hodgkin's Lymphoma, large cell	• Decreased duration of complete response, possibly secondary to increased circulating levels of interleukin-6	• Use of chemotherapy in higher doses • Biological treatment • Alternative regimens
Breast cancer	• More indolent course, secondary to higher prevalence of a well-differentiated hormone-receptor rich, slowly proliferating tumor(s) and to a hormonal and immunologic milieu that is unfavorable to the tumor(s)	• Value of radiotherapy after lumpectomy (See NCCN Task Force Report: Breast Cancer in Older Women) • Primary hormonal treatment • Value of adjuvant chemotherapy
Colorectal cancer	• Decreased tolerance of fluorinated pyrimidines	• Alternative forms of adjuvant therapy • Adjuvant chemotherapy is more effective but also more toxic
Lung cancer (non-small cell)	• Reduced tolerance of combined-modality treatment in stage III	• Alternative approaches
Ovarian cancer	• Decreased response rate to cytotoxic chemotherapy	• Alternative forms of treatment

AML, acute myelogenous leukemia; MDR1, multiple drug resistance gene

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COMPREHENSIVE GERIATRIC ASSESSMENT (1 of 2)

Comorbidity

- May affect treatment decisions in 4 ways:
  - Cancer treatment may interact with comorbidity to impact functional status or worsen the comorbidity (i.e renal insufficiency). This includes any drug-drug interactions.
  - Cancer treatment may be too risky because of the type and severity of comorbidity (i.e. cardiomyopathy). These may include cardiovascular problems, congestive heart failure, mild dementia, depressions, anemia, and osteoporosis.
  - Cancer treatment may not impact future life expectancy due to risk of morbidity[1] associated with comorbid condition. The effect of comorbidity on life expectancy should be evaluated before patient receives treatment. Renal insufficiency, diabetes, lung disease, tobacco use and heart failure all decrease life expectancy.
  - Comorbidity may affect treatment outcome
- Seriousness of comorbid conditions (comorbidity index)
- The following should be used as a guide to evaluate comorbidity:
  - GI problems
  - Renal Insufficiency
  - Cardiomyopathy (cardiovascular problems)
  - Diabetes
  - Anemia
  - Dementia
  - Depression
  - Osteoporosis
  - Lung Disease
  - Tobacco or Alcohol Use

Function

- Activities of daily living (ADL) - Eating, dressing, continence, grooming, transferring, using the bathroom
- Instrumental activities of daily living (IADL) - Using transportation, managing money, taking medications, shopping, preparing meals, doing laundry, doing housework, using telephone
- Performance status

Socioeconomic issues

- Living conditions
- Presence and adequacy of care giver
- Income
- Access to transportation
- Financial counsel to discuss cost, coverage options etc.

Common geriatric syndromes

- Dementia
- Depression
- Delirium
- Falls
- Osteoporosis (spontaneous fractures)
- Neglect and abuse
- Failure to thrive
- Persistent dizziness
- Nutritional deficiency

[1]Mortality can be predicted using weight, body mass index, nutrition, fatigue and existing medical conditions.

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COMPREHENSIVE GERIATRIC ASSESSMENT (2 of 2)

Polypharmacy

- **Drug-drug interactions**[2]
- **Number of medications**
- **Avoid inappropriate drugs**
  - **Medication Appropriateness Index**[3]
  - **Beers Criteria**[4]
- **Use caution when using medications that can contribute to delirium**[5,6]
  - **Benzodiazepines**
  - **Anticholinergics**
  - **Antipsychotics**
  - **Opioids**

Screening Tools for Common Geriatric Syndromes

- **Dementia - Mini Mental State Examination (MMSE)**[7,8]
- **Depression - Geriatric Depression Scale (GDS)**[9,10]
- **Delirium - NCCN Distress Management Guidelines**
- **Osteoporosis - DEXA scan, NCCN Bone Health Task Force**
- **Fatigue - NCCN Fatigue Guidelines**
- **Nutrition deficiency- Mini-Nutritional Assessment (MNA)**[11,12]

[2] Riechelmann RP, Saad ED. A systemic review on drug interactions in oncology. Cancer Investigation. 2006; 24: 704-712.

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[9] Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res. 1982;17(1):37-49).

[10] D'Ath P, Katona P, Mullan E, Evans S, Katona C. Screening, Detection and Management of Depression in Elderly Primary Care Attenders: The Acceptability and Performance of the 15 Item Geriatric Depression Scale (GDS15) and the Development of Short Versions. Fam. Pract. 1994;11(3):260-266.

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[12] Rubenstein LZ, Harker JO, Salva A, Guigoz Y, Vellas B. Screening for Undernutrition in Geriatric Practice: Developing the Short-Form Mini-Nutritional Assessment (MNA-SF). J Gerontol A Biol Sci Med Sci. 2001;56(6):M366-372.

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RESEARCH CRITERIA USED TO DEFINE FRAILTY

Variable	Question	Criteria
Weight loss	"In the past year, have you lost more than 10 lb unintentionally (ie, 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 Kcals/wk are frail.‡ **Women:** Those with physical activity < 270 Kcals/wk are frail.‡
Walk time (cutoff times are gender and height specific)	**Men:¶** Height ≤ 173 cm Height > 173 cm **Women:¶** Height ≤ 159 cm Height > 159 cm	Cutoff for time to walk 15 ft criterion for frailty: **Men:** ≥ 7 seconds ≥ 6 seconds **Women:** ≥ 7 seconds ≥ 6 seconds
Grip strength (cutoffs are gender and BMI specific)	**Men:** BMI ≤ 24 BMI = 24.1 – 26 BMI = 26.1 – 28 BMI > 28 **Women:** BMI ≤ 23 BMI = 23.1---26 BMI = 26.1---29 BMI > 29	Cutoff for grip strength (Kg) criterion for frailty: **Men:** ≤ 29 ≤ 30 ≤ 30 ≤ 32 **Women:** ≤ 17 ≤ 17.3 ≤ 18 ≤ 21

BMI, body mass index; CES, Center for Epidemiological Studies.

Adapted with permission from Fried L, Tangen C, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol Med Sci 2001;56A:M146-M156.

*At follow-up, weight loss is calculated as: (weight in previous year minus current measured weight)/(weight in previous year) = K. If K ≥ 0.05 and the subject does not report that he/she was trying to lose weight (ie, unintentional weight loss of at least 5% of previous year's body weight), then subject is considered frail for weight loss.

†0 = rarely or none of the time (< 1 day); 1 = some or a little of the time (1-2 days); 2 = a moderate amount of the time (3-4 days); or 3 = most of the time.

‡Kcals/wk expended are calculated using a standardized algorithm.

¶A medium height is used.

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PROCEDURE FOR FUNCTIONAL ASSESSMENT SCREENING IN ELDERLY PERSONS

Target Area	Assessment Procedure	Abnormal Result	Suggested Intervention
Vision	Test each eye with Jaeger card while patient wears corrective lenses (if applicable)	Inability to read > 20/40	Refer to ophthalmologist
Hearing	Whisper a short, easily answered question, such as “What is your name?” in each ear while the examiner's face is out of direct view.	Inability to answer question	Examine auditory canals for cerumen and clean if necessary. Repeat test; if still abnormal in either ear, refer for audiometry and possible prosthesis.
Arm	Proximal: “Touch the back of your head with both hands.” Distal: “Pick up the spoon.”	Inability to do task	Examine the arm fully (muscle, joint, and nerve) paying attention to pain, weakness, limited range of motion. Consider referral for physical therapy and occupational therapy.
Leg	Observe the patient after asking “Rise from your chair, walk 10 ft, return, and sit down.”*	Inability to walk or transfer out of chair	Do full neurologic and musculoskeletal evaluation, paying attention to strength, pain, range of motion, balance, and traditional assessment of gait. Consider referral for physical therapy and occupational therapy.
Urinary incontinence	Ask patient: “Do you ever lose your urine and get wet?”	Yes	Ascertain frequency and amount. Search for remediable causes including local irritations, polyuric states, and medications. Consider urologic referral.
Nutrition	Weigh the patient. Measure height.	Weight is below acceptable range for height	Do appropriate medical evaluation Consider dietician referral.
Mental status	Tell the patient: “I am going to name three objects (pencil, truck, book). I will ask you to repeat their names now and then again a few minutes from now.”†	Inability to recall all 3 objects after 1 min	Administer Folstein mini-mental status examination. If score is < 24, search for causes of cognitive impairment. Ascertain onset, duration, and fluctuation of overt symptoms. Review medications. Assess consciousness and affect. Do appropriate laboratory tests.
Depression	Ask patient: “Do you often feel sad or depressed?”	Yes	Administer Geriatric Depression Scale. If positive (normal score, 0 to 10), check for antihypertensive, psychotropic, or other pertinent medications. Consider appropriate pharmaceutical or psychiatric treatment.
ADL-IADL	Ask patient: “Can you get out of bed yourself?”; “Can you dress yourself?”; “Can you make your own meals?”; “Can you do your own shopping?”	No to any question	Corroborate responses with patient's appearance; question family members if accuracy is uncertain. Determine reasons for the inability (motivation compared with physical limitation). Institute appropriate medical, social, or environmental interventions.
Home environment	Ask patient: “Do you have trouble with stairs inside or outside of your home?”; ask about potential hazards inside the home with bathtubs, rugs, or lighting.	Yes	Evaluate home safety and institute appropriate countermeasures.
Social support	Ask patient: “Who would be able to help you in case of illness or emergency?”	…	List identified persons in the medical record. Become familiar with available resources for the elderly in the community. Consider social worker referral.

ADL, activities of daily living; IADL, instrumental activities of daily living.
Adapted with permission from Lachs MS, Feinstein AR, Cooney LM Jr, et al. A simple procedure for general screening for functional disability in elderly patients. Ann Intern Med 1990;112:699-706.
*This test is similar to the “timed up and go” (TUG) test, except that for the TUG test patients are also asked to walk 20 ft briskly. For the TUG test, a score of “one” is assigned for each of these findings: (1) use of the arms to get up, (2) uncertain steps, and/or (3) more than 10 seconds to complete the activity. The higher the total score, the higher the risk of functional dependence and death.
†This test is also referred to as the “three-item recall.” It can be supplemented by the clock drawing test to assist in assessment for dementia.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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VULNERABLE ELDERS SURVEY (VES-13)

A total score of ≥ 3 indicates that patients are vulnerable.

1. Age_____

Score: 1 point for age 75---84 years; 3 points for age ≥ 85 years

2. In general, compared to other people your age, would you say your health is:

- ❑ Poor* (1 point)
- ❑ Fair* (1 point)
- ❑ Good
- ❑ Very good
- ❑ Excellent

Score: 1 point for fair or poor

3. How much difficulty, on average, do you have with the following physical activities:

	None	A Little	Some	A Lot*	Unable to Do*
a. Stooping, crouching, or kneeling?	❑	❑	❑	❑	❑
b. Lifting or carrying objects as heavy as 10 pounds?	❑	❑	❑	❑	❑
c. Reaching or extending arms above shoulder level?	❑	❑	❑	❑	❑
d. Writing or handling and grasping small objects?	❑	❑	❑	❑	❑
e. Walking a quarter of a mile?	❑	❑	❑	❑	❑
f. Heavy housework, such as scrubbing floors or washing windows?	❑	❑	❑	❑	❑

Score: 1 point for each * response in questions 3a-f. Maximum of 2 points.

4. Because of your health or a physical condition, do you have any difficulty:

a. shopping for personal items (like toilet items or medicines)?

- ❑ YES ? Do you get help with shopping?..... ❑ YES* ❑ NO
- ❑ NO
- ❑ DON'T DO ? Is that because of your health?..... ❑ YES* ❑ NO

b. managing money (like keeping track of expenses or paying bills)?

- ❑ YES ? Do you get help with managing money?..... ❑ YES* ❑ NO
- ❑ NO
- ❑ DON'T DO ? Is that because of your health?..... ❑ YES* ❑ NO

c. walking across the room?
USE OF A CANE OR WALKER IS OKAY.

- ❑ YES ? Do you get help with walking? ..... ❑ YES* ❑ NO
- ❑ NO
- ❑ DON'T DO ? Is that because of your health?..... ❑ YES* ❑ NO

d. doing light housework (like washing dishes, straightening up, or light cleaning)?

- ❑ YES ? Do you get help with light housework? ..... ❑ YES* ❑ NO
- ❑ NO
- ❑ DON'T DO ? Is that because of your health?..... ❑ YES* ❑ NO

e. bathing or showering?

- ❑ YES ? Do you get help with bathing or showering? ❑ YES* ❑ NO
- ❑ NO
- ❑ DON'T DO ? Is that because of your health?..... ❑ YES* ❑ NO

Score: 4 points for one or more * responses in questions 4a-e.

Adapted with permission from Saliba D, Elliott M, Rubenstein LZ, et al. The Vulnerable Elders Survey: a tool for identifying vulnerable older people in the community. J Am Geriatr Soc 2001;49(12):1691-1699.

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Manuscript

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

Cancer is the leading cause of death in women and men aged 60 to 79 years.[1] More than 60% of all cancers and 80% of cancer-related deaths in the United States occur in patients who are 65 years or older. It is estimated that 20% of the U.S. population will be 65 years or older by 2030 and 70% of cancers and 85% of all cancer-related deaths will occur in this older population. Older individuals are more prone to develop cancer than younger individuals as a result of physiological changes associated with ageing, which in turn favor the development and growth of cancer. In addition, behavior of certain neoplasms changes with patient's age. Acute myelogenous leukemia, non-Hodgkin's lymphoma (large cell and follicular lymphoma) and ovarian cancer are associated with poor prognosis in patients 60 years and older, whereas breast cancer and lung cancer are more indolent in the elderly.[2] Increased incidence and prevalence of cancer in elderly people and increased life-expectancy of the elderly mean that cancer in older individuals is becoming an increasingly common problem.

Unfortunately, elderly cancer patients are under-represented in clinical trials for new cancer therapies.[3] Advanced age alone should not preclude the use of effective cancer treatment that could improve quality of life or extend meaningful survival.[4] Proper surgery and adjuvant treatment can decrease relapse and improve survival in some women with breast cancer who are older than 80 years.[5] However, treatment that diminishes quality of life with no significant survival benefit should be avoided. Older patients in good performance status are able to tolerate commonly used chemotherapy regimens as well as younger patients, when adequate supportive care is provided.[6-8]

The NCCN Senior Adult Oncology guidelines address specific issues related to the management of cancer in older individuals including geriatric screening and assessment, preventing or decreasing complications from therapy, accounting for disease-specific issues, and management of patients unfit for standard treatment, as well as for assessing the risks and benefits of treatment in the older patient with cancer.

Comprehensive Geriatric Assessment

Older patients can be classified into three categories: (i) young old patients are 65-75 years of age; (ii) old patients are 76-85 years of age; and (iii) oldest old patients are more than 85 years of age.[9] Proper selection of patients is the key to administering effective and safe cancer treatment. The challenge of managing the older cancer patient is to assess whether the expected benefits of treatment are superior to the risk in a population with decreased life expectancy and decreased tolerance to stress.

However, chronological age by itself is not reliable in estimating life expectancy, functional reserve, or the risk of treatment complications.[10] This information is best provided by a comprehensive geriatric assessment (CGA), which is a multidisciplinary in-depth evaluation of

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elderly cancer patients which help physicians develop a coordinated plan for cancer treatment as well as appropriate interventions to the patient's problems.[11]

CGA can assess life expectancy based on functional status and comorbid conditions (including geriatric syndromes), risk of morbidity from cancer; it can identify reversible problems that may interfere with cancer treatment, such as malnutrition, sensory deficits, polypharmacy, insufficient social support, depression and dementia (SAO-D).[11-14] Hurria and colleagues have developed a brief but comprehensive, geriatric assessment of older patients with cancer.[15-16] A multicenter study involving 500 older patients (median age: 73) with cancer demonstrated that this brief geriatric assessment is largely self-administered and can be completed by the majority of older patients without assistance.[15] The geriatric assessment also identified deficits and problems that may impact morbidity and mortality.[16] Prospective data are being collected to identify the factors in the geriatric assessment that can predict toxicity of chemotherapy in elderly cancer patients.

Life expectancy is better predicted by health status than age alone; therefore, function and comorbidity should be taken into account. While it is not possible for a physician to predict the exact life expectancy of an individual patient, it is possible to provide an estimate of whether a patient is likely to live longer or shorter than an average person of similar age. Life expectancy at a given age can be estimated using life table data as suggested by Walter and Covinsky (SAO-A).[17] For example, about 25% of the healthiest 75-year-old women will live more than 17 years, 50% will live at least 12 years, and 25% will live less than 7 years. Lee and colleagues developed and validated a potentially useful tool for clinicians to estimate the 4-year mortality risk.[18] Patients can be stratified into three groups of varying risk of mortality (high, intermediate or low) based on the prognostic index which incorporates demographic variables (age and sex), self-reported comorbid conditions and functional measures.[18] Carey and colleagues also developed a similar functional morbidity index based on self-reported functional status, age and gender to stratify elders into varying risk groups for 2-year mortality.[19]

Elderly cancer patients aged 70 years or more have an increased prevalence of comorbidities which can exert a significant effect on the behavior of cancer.[20] Cardiovascular problems, congestive heart failure (CHF), renal insufficiency, dementia, depression, anemia and osteoporosis are some of frequently encountered comorbid conditions in elderly cancer patients. Comorbidity may affect the outcome of cancer treatment in three ways: cancer treatment may be too risk due to severity of comorbidity, interaction of comorbidity with cancer treatment impacting functional status and finally cancer treatment may not have any impact on life expectancy due to the risk of morbidity associated with comorbid condition. The effect of comorbidity on life expectancy should be evaluated prior to initiation of treatment (SAO-D).

Increased comorbid conditions are also associated with polypharmacy, which in turn increases the risk for adverse drug reactions, drug-drug interactions, and non-adherence in elderly cancer patients.[21,22-23] Inappropriate medication prescription is an important problem in the elderly cancer patients. Drug-drug and disease-drug interactions are significant clinical issues in the elderly. Popa et al assessed the impact of polymedication on toxicity from chemotherapy in elderly patients.[24] Their findings suggest that drug distribution factors play important roles in chemotherapy toxicity in elders. The role of protein binding in the pharmacokinetics/dynamics of chemotherapy drugs should be further explored.

The Beers' Criteria identifies medications that have potential risks that outweigh potential benefits in elderly cancer patients.[25-26] The criteria are appropriate for persons older than 65 years of age and provide a

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rating of severity for adverse outcomes as well as a descriptive summary of the prescribing information associated with the medication. Samsa and colleagues developed the Medication Appropriateness Index (MAI) to measure the appropriate prescribing.[27] MAI appears to be a valid and relatively reliable measure for prescribing appropriateness. Drug-related adverse events can be minimized by the application of Beers criteria and MAI.

The risk of morbidity from cancer is generally established by the stage at diagnosis, the aggressiveness of the tumor and risk of recurrence and progression. It is also essential to determine the patient's overall goals, including whether proposed treatment is desired. Consultation with a social worker should be encouraged to allow patients to verbalize their ultimate treatment goals.

Following initial screening and CGA, the guidelines stratify patients into two groups: patients with moderate or high risk of dying or suffering from cancer or experiencing complications within their lifetime and those who are at a low risk of dying or suffering from cancer (SAO-1).

Patients in the moderate or high risk group can then be further assessed to estimate their fitness or desire for treatment, because some of these patients will not tolerate therapy or will decline therapy. In addition, several provisions are available to decrease the risk of treatment complications and to preserve the function of older individuals receiving chemotherapy. Patients in the low risk group have limited life expectancy and they have a very low likelihood of developing morbidity from cancer. These patients can receive symptom management and supportive care as detailed in the appropriate NCCN Guidelines for Supportive Care.

Irrespective of age, a person who is functionally independent and without serious comorbidity should be a good candidate for most forms of cancer treatment, if there are no contraindications (SAO-2).

However, the patient, with or without severe comorbidity, who is dependent on some instrumental activities of daily living (IADL) is at increased risk of treatment complications. For these patients with intermediate functional impairment who have milder problems (such as dependence in one or more IADL, milder comorbidity, depression, minor memory disorder, mild dementia, inadequate caregiver), treatment may still be administered with special individualized precautions, including attempts to reverse the problem and cautious dosing of treatment (SAO-2).[28-29] Functionally independent patients with contraindications to treatment and patients with major functional impairment with or without complex comorbidity should be managed according to the appropriate NCCN Guidelines for Supportive Care.

Screening Tests for Geriatric Syndromes

CGA is time-consuming and may not be practical or necessary for all patients. Several screening tests may be used as an alternative to CGA to decide which patients need either a full assessment or a more thorough assessment for a specific problem.[12,30-34] These screening tests can be used to determine which patients may benefit from a CGA.

Frailty is a biologic syndrome of decreased reserve and resistance to stressors, causing vulnerability to adverse outcomes.[35] Frail patients may be at increased risk of therapeutic complications from cancer treatment; thus, it is useful to assess whether cancer patients are frail. The cardiovascular health study (CHS) has developed a screening tool to identify frail patients on the basis of five simple tests (SAO-E).[34] Frail patients have three or more of the following criteria: unintentional weight loss (10 pounds or more in past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and/or low physical activity.[34] Fit, frail, and prefrail patients had different 5-year mortality rates and different risks of developing functional dependence at 3 and 7 years. Frail and prefrail patients are at risk for falling, disability, hospitalization, and death. The CHS instrument has been tested in

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5317 men and women who were 65 years and older. This form of assessment is now commonly used and may be helpful to screen whether elderly cancer patients require a CGA. However, determining if someone is frail is more difficult in cancer patients, because cancer confounds the problem.

Cancer-related fatigue is a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning. In advanced cancer, the prevalence of fatigue is greater than 50-70%.[36] Patients perceive fatigue to be one of the most distressing symptoms associated with cancer and its treatment; fatigue is more distressing even than pain or nausea and vomiting, which can generally be managed by medication in most patients.[37-38] In contrast to normal fatigue, cancer-related fatigue is refractory to sleep and rest, perhaps because cancer patients have aberrant sleep patterns. It is reasonable to expect that fatigue may precipitate functional dependence, especially in patients who are already dependent in IADL.[39-41]

Multiple factors can contribute to fatigue, including pain, emotional distress, anemia, comorbidities, and/or sleep disturbance; many of them are treatable. Certainly, the best strategy is avoidance of any fatigue that may precipitate functional dependence in older individuals. Energy conservation, exercise programs, stress management, sleep therapy, and psychostimulants are some of the interventions that have proved valuable. Screening for fatigue can be done using a brief screening questionnaire: “Since your last visit, how would you rate your worst fatigue on a scale of 0 to 10 (0 = no fatigue and 10 = worst fatigue)?” See the NCCN Cancer-Related Fatigue Guideline.

Cancer-related fatigue and depression frequently occur together; therefore, patients reporting fatigue should probably be assessed for depression.[42-44] Geriatric depression scale (GDS) is a reliable and valid tool for screening depression in older patients with no cognitive impairment and in patients with mild to moderate cognitive impairment. GDS was originally developed by Yesavage and colleagues as 30-item scale.[45] Recently, shortened versions of GDS have been found be equally accurate and less time-consuming in screening for depression in older adults.[46-47]

Falls are one of most common geriatric syndromes. In the United States, 30-40% of adults older than 65 years fall each year. Risk factors include older age, muscle weakness and impairments in gait, balance, vision, cognition and activities of daily living.[48] Evidence from a meta-analysis of randomized trials and a systematic review found that interventions are very effective preventing falls in older adults and they also reduce both the risk and rate of falling.[49] CGA of elderly cancer patients should include assessment of all falls.

Osteoporosis and its associated increase in fracture is a major risk factor in cancer patients especially in women receiving chemotherapy or hormonal therapy for breast cancer and in men receiving hormonal therapy for prostate cancer. Osteoporosis can be prevented with appropriate screening, lifestyle interventions and therapy. Management of bone health has become an integral part of comprehensive cancer care. Elderly patients should be made aware of the impact of cancer therapies on bone health and should adhere to oral treatment recommendations for maintaining bone health. The NCCN Task force report on Bone Health in Cancer Care discusses effective screening and therapeutic options for the management of treatment-related bone loss. See the NCCN Task Force Report: Bone Health in Cancer Care.

Nutritional deficiency or malnutrition is a common and serious condition in older patients. While some of the malnutrition is attributed to the underlying illness, in most of the patients it is due to inadequate intake of calories. Mini-Nutritional Assessment (MNA) has been designed and validated to provide a single, rapid assessment of nutritional status in elderly patients in the outpatient settings.[50-51] MNA is composed of

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simple measurements and brief questions that help to identify people at risk for malnutrition before severe changes in weight or albumin levels occur. Rubenstein et al have developed a shortened version of MNA which also has good diagnostic accuracy.[52] Early detection is important to provide proper nutritional intervention and MNA should be an integral part of CGA. Special attention should also be devoted to the deficiency of Vitamin D since that may be related to osteoporosis and fractures.[53]

Geriatric patients with cancer who are cognitively impaired have poor performance status, higher incidence of depression, and are at greater risk for death. In addition, some cognitively impaired patients are unable to make decisions related to their treatment. Therefore it is important to assess whether patients are cognitively impaired. Dementia and delirium are two of the most common causes for cognitive impairment. Screening for dementia can done using a brief screening test called the mini-mental state examination (MMSE), which quantitatively assesses the severity of cognitive impairment and documents cognitive changes occurring over a period of time.[54-55]

Cognitively impaired patients should be cared for by an experienced multidisciplinary geriatric oncology team along with good supportive care throughout the treatment.[56] Medications with anticholinergic properties and other psychotropic medications that are widely used in older adults lead to cognitive impairment.[57] Hilmer and colleagues have developed a drug burden index which is a useful evidence-based tool for assessing the effect of medications on the physical and cognitive performance in elderly people.[58] Medications that can contribute to delirium should be used with caution in elderly cancer patients (SAO-D). See the NCCN Distress Management Guideline for the management of dementia and delirium.

The Distress Thermometer (DT) and the accompanying 36-item problem list is a well-known screening tool, specifically developed for cancer patients by the NCCN Distress Management Panel (See the NCCN Distress Management Guideline).[59-60] Patients can quickly fill out this distress assessment tool in the waiting room and the tool can alert the physician to potential problems. This tool identifies whether cancer patients have problems in five different categories: practical, family, emotional, spiritual/religious and physical. The NCCN Distress Thermometer has been validated by several studies in patients with different types of cancer and has revealed good correlation with the more comprehensive Hospital Anxiety and Depression Scale (HADS).[61]

A quick screening test to assess mobility is the “timed up and go” (TUG) test. Older individuals are asked to get up from an armchair without using their arms, walk 20 feet forward briskly, turn around, walk back to the chair, and then sit down again. A score of “one” is assigned for each of these findings: (1) use of the arms to get up, (2) uncertain steps, and/or (3) more than 10 seconds to complete the activity. The higher the total score, the higher the risk of functional dependence and death. Lachs and colleagues developed a screening assessment for elderly patients (SAO-F).[30] This screening test quickly assesses many areas including vision, hearing, arm/leg mobility, urinary incontinence, nutrition, mental status, depression, ADL-IADL, home environment, and social support. Lachs’ screening test is done by a physician (or office staff); it may be very useful to assess if a CGA is necessary.

Saliba and colleagues have developed a useful questionnaire called the Vulnerable Elders Survey (VES-13) that patients can quickly fill out at home or in the office (SAO-G).[33] A score of 3 or more on the VES-13 indicates that patients are vulnerable. They tested the questionnaire in 6205 Medicare beneficiaries aged 65 years and older. The VES-13 assesses whether elderly patients are at risk for functional decline or death. The advantage of this questionnaire is that it minimizes the amount of time required to examine patients in the office; this survey assesses age, self-rated health, limitation in physical function, and functional disabilities. The VES-13 is the official screening test for older

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individuals in the EORTC (European Organization for Research and Treatment of Cancer).

In the future, laboratory tests may be used to assess whether elderly patients are at risk for development of functional decline or mortality. Cohen and colleagues have demonstrated that high levels interleukin-6 and D-dimer were associated with mortality and functional dependence in home dwelling individuals aged 71 years and older.[62] In addition, cognitive decline has been found to be associated with elevated levels of D-dimer.[63] Thus, assessment of inflammation markers (interleukin-6 and D-dimer) may be used to predict physiologic age in elderly patients.

Management of Cancer in Older Patients

The benefits of cancer treatment include prolonged survival, maintenance and improvement of quality of life and function, as well as palliation of symptoms. For patients who are able to tolerate curative treatment, options include surgery, radiation therapy and chemotherapy (SAO-3).

Surgery

The Surgical Task Force report from SIOG (International Society for Geriatric Oncology) reported that in many neoplasms (breast, gastric and liver) the surgical outcomes in the elderly cancer patients were not significantly different from their younger counterparts.[64] Preoperative Assessment of Cancer in Elderly (PACE) was developed to determine the suitability of elderly patients for surgical intervention.[65] PACE incorporates CGA, brief fatigue inventory (BFI), performance status (PS) and American Society Anesthesiologists (ASA) grade. In an international prospective study 460 consecutive elderly patients received PACE prior to surgery.[66-67] In a multivariate analysis, moderate to severe fatigue, a dependent IADL and an abnormal PS were identified as the most important independent predictors of post-surgical complications. Disability assessed by ADL, IADL and PS were associated with an extended hospital stay. This study demonstrated that PACE is a useful tool which will enable the physicians in evaluating the fitness of elderly patients for surgery. The reliability of this tool has to be confirmed in large prospective trials as applied to specific cancer types in elderly patients.

In general, age is not a primary consideration for surgical risk, although the physiologic status of the patient needs to be assessed. Performance status and comorbidities of the patient are more important factors than the age when considering surgical treatment options for elderly patients.[68] Following surgery, physical and/or occupational therapy should be considered (SAO-B).

Radiation Therapy

Radiation therapy (RT) is beneficial to elderly cancer patients especially when surgery and chemotherapy are contraindicated. RT can be offered either in the curative or in the palliative setting.[69] External beam radiation therapy or brachytherapy are two possible modalities. Long courses of external beam RT are used for local tumor control, whereas hypofractionated regimens are used for palliation and symptom control. Hypofractionated RT may be an alternative treatment option in patients who are unable to tolerate conventional dose RT.[70] Available data from the literature indicate that radiation therapy is highly effective, well tolerated and age is not a limiting factor in elderly cancer patients.[71-73]

CGA should be performed before radiation therapy to establish baseline functional status. Concurrent chemoradiation should be used with extreme caution; dose modification of chemotherapy may be necessary to reduce toxic side effects. Amifostine can be considered for patients receiving RT for head and neck cancer (SAO-3).

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Chemotherapy

Several retrospective studies have reported that the toxicity of chemotherapy is not more severe or prolonged in persons older than 70 years.[74-78] These studies are important, because they demonstrate that age, by itself, is not a contraindication to cancer chemotherapy. However, the results of these studies cannot be generalized for the following reasons:

- Only a few patients were 80 years or older; therefore, minimal information is available on the oldest patients.
- The older patients involved in these studies were highly selected by the eligibility criteria of the cooperative group protocols and were not representative of the general older population, because they were probably healthier than most older patients.
- Many of the treatment regimens used in these trials had lower dose intensity than those in current use.

In elderly patients chemotherapy should be individualized based the nature of the disease and the performance status of the patient. CGA may be useful in the proper selection of patients when chemotherapy is considered as a treatment option. Chemotherapy is generally contraindicated at full dose for patients with severe problems such as dependence on one or more activities of daily living (ADL) except for incontinence, presence of geriatric syndromes (such as severe dementia, depression, delirium, neglect and abuse, failure to thrive, multiple falls, spontaneous bone fractures, continuous dizziness), and/or presence of severe comorbidity. However, chemotherapy may still be used in these patients for symptom management at low doses.

Adjuvant chemotherapy has improved survival in patients with breast, non-small cell lung and colon cancers. However, since older patients have been excluded or underrepresented in these trials, it is not possible to extrapolate the benefits of adjuvant chemotherapy to older cancer patients. Limited data in this group of patients suggest that those who have life expectancies exceeding 5 years may benefit from adjuvant therapy.[79,80] Therefore, patient selection is extremely important to maximize the benefits of adjuvant chemotherapy in older patients with breast and colon cancer.

Side Effects of Chemotherapy

In older patients undergoing chemotherapy, the most common complications include myelosuppression resulting in neutropenia, anemia or thrombocytopenia, mucositis, renal toxicity, cardiac toxicity and neurotoxicity. Older patients appear to be at special risk for severe and prolonged myelosuppression and mucositis, increased risk of cardiomyopathy, as well as increased risk of central and peripheral neuropathy. In addition, they are also at risk for infection (with or without neutropenia), dehydration, electrolyte disorders, and malnutrition either as a side effect of the chemotherapy or directly from the tumor. Chemotherapy can also affect cognition, function, balance, vision, hearing, continence, and mood.[32] The combination of these complications enhances the risk of delirium and functional dependence. It is essential to detect and correct these complications (that may interfere with treatment) in order to achieve maximum benefit from chemotherapy. Prevention and/or amelioration of some of the common chemotherapy-related complications are discussed below.

Myelosuppression

Available data from various studies has shown that the risk of myelosuppression increases substantially by age 65 years.[81-84] In persons 70 years or older, the incidence of neutropenic infection-related mortality varies between 5% and 30%. Rocha Lima and colleagues found that elderly patients with lung cancer had more leukocyte toxicity after treatment.[85] Neubauer and colleagues also found that elderly patients receiving weekly paclitaxel plus carboplatin for small cell lung cancer had neutropenia.[86] The risk of

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myelosuppression is decreased by 50% when using growth factors.[87-89] Dose reductions of chemotherapeutic agents may compromise the effectiveness of treatment. The use of growth factors in these circumstances does not appear to be associated with increased cost and may even be cost saving if it prevents lengthy hospitalizations for neutropenic infections in older persons.

Neutropenia

Neutropenia is the major dose-limiting toxicity associated with chemotherapy, especially in older patients. Several prospective studies of older patients with large cell lymphoma have shown that the incidence of neutropenic infections may be as high as 50% in individuals aged 65 years and older treated with regimens like CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone).[89-95] In persons age 60 years or older receiving induction or consolidation chemotherapy for acute myeloid leukemia (AML), the prophylactic use of hematopoietic growth factors is recommended on the basis of studies showing that growth factors may increase therapeutic response and improve survival. Moreover, growth factors have consistently decreased the duration of hospitalization and, thus, may be cost saving (GELOAM study).[96-100]

Meta-analysis of controlled clinical trials on the use of prophylactic recombinant colony-stimulating factors has confirmed their effectiveness in reducing the risk of febrile neutropenia.[101] Some concerns have been expressed that the combination of growth factors and topoisomerase II inhibitors may be associated with increased risk of acute leukemia.[102] Despite these caveats, the use of growth factors appears to be the best-established strategy to improve treatment in this group of patients.[103] The EORTC has issued similar recommendations for the prophylactic use of granulocyte colony stimulating factors (G-CSF) in older patients with cancer.[104]

NCCN guidelines recommend prophylactic use of hematopoietic growth factors along with CHOP or CHOP-like chemotherapy regimens in the treatment of lymphoma in patients who are 65 years or older. See the NCCN Myeloid Growth Factor Guidelines.

Anemia

Anemia has been shown to be a risk factor for chemotherapy related toxicity and it is one of the factors responsible for reduction in volume of distribution, which may result in increased peak concentration and in increased toxicity of drugs. Evidence from at least three studies suggests that anemia is associated with enhanced myelodepression and can result in decreased distribution of water-soluble drugs.[105] Anemia is also associated with cardiovascular disease, congestive heart failure, coronary death, and dementia.[106-109] In patients with severe anemia, blood transfusions are necessary to prevent serious clinical consequences.

Since the relationship between volume of distribution and red blood cells has been confirmed in a number of studies, anemia can be prevented with the use of erythropoietic stimulating agents (ESAs). ESA therapy has been demonstrated to decrease the need for transfusion in cancer patients receiving chemotherapy.[110] It also appears beneficial to complement the administration of erythropoietin with oral or parenteral iron although this is not specific for elderly patients.

However, recent randomized studies have reported decreased survival and poorer tumor control among cancer patients receiving erythropoietic drugs for correction of anemia and target hemoglobin levels greater than 12 g/dL.[111] The use of ESAs in patients with cancer is also associated with increased risks of venous thromboembolism (VTE) and mortality.[112] The risks of shortened survival and the disease progression have not been excluded when ESAs are dosed to a target of hemoglobin levels of less than 12 g/dL.

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In July 2008 based on the results of these trials, Food and Drug Administration (FDA) strengthened its warnings to alert the physicians of increased risk of tumor progression and shortened survival in patients with advanced breast, cervical, head and neck, lymphoid and non-small cell lung cancers. Physicians were advised to use the lowest dose necessary to avoid transfusion. In addition, use of ESAs is restricted to the treatment of anemia specifically related to myelosuppressive chemotherapy without curative intent. ESAs should be discontinued once the course of chemotherapy has been completed, and the anemia has resolved. The panel recommends that anemia in elderly cancer patients should be managed as described in the NCCN Cancer and Treatment-Related Anemia Guideline.

Thrombocytopenia

Chemotherapy-induced thrombocytopenia is a common hematologic toxicity associated with cytotoxic and myeloablative chemotherapy. Dose reductions and/or interruptions of chemotherapy regimens are necessary in patients with severe thrombocytopenia. While chemotherapy-induced anemia and neutropenia can be managed with hematopoietic growth factors, safe and effective treatment of CIT is still a significant problem. Recombinant interleukin-11 (IL-11) is the only currently approved for the treatment of CIT in patients with nonmyeloid malignancies.[113] However, it is toxic and of minimal clinical benefit. Ongoing clinical trials are also evaluating the efficacy of thrombopoietin-like agents such as romiplostim and eltrombopag for the treatment of CIT.[114]

Diarrhea

Diarrhea is a well-recognized side effect associated with a number of chemotherapeutic agents, particularly greater for regimens containing 5-fluorouracil and irinotecan. Chemotherapy-induced diarrhea (CID) can lead to discontinuation of chemotherapy and poorer clinical outcomes. Loss of fluid associated with persistent and severe diarrhea can lead to dehydration, renal insufficiency and electrolyte imbalance. There is no evidence based treatment approach for CID. Recently, ASCO published guidelines for the treatment of CID.[115] These guidelines recommend comprehensive evaluation at the onset of diarrhea to determine the severity. Based on the results from various clinical trials, ASCO guidelines recommend loperamide therapy for mild to moderate diarrhea; octreotide (subcutaneous or intravenous if the patient is severely dehydrated) treatment for severe diarrhea or for treatment of CID that is refractory to loperamide therapy.

Patients with chemotherapy-induced diarrhea should be treated with aggressive rehydration. Pharmacological management with octreotide is recommended if oral preparations are ineffective. There is no effective pharmacological intervention for diarrhea induced by radiation therapy.

Mucositis

Oral and gastrointestinal mucositis are significant complications of radiotherapy and chemotherapy, especially following treatment with fluoropyrimidine. Risk of mucositis increases with age, thereby increasing morbidity and mortality associated with cancer therapy. Guidelines for preventing, evaluating, and treating oral as well as gastrointestinal mucositis have been developed by the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology.[116]The NCCN Task force has also published a comprehensive approach to the management of mucositis in patients with cancer. See the NCCN Task Force Report: Prevention and Management of Mucositis in Cancer Care. Once mucositis has occurred, patients should be kept well hydrated with intravenous fluids and hospitalization if necessary.

Until recently, no pharmacological agents have been shown to effectively treat mucositis. In 2004, FDA approved palifermin (Kepivance™), human keratinocyte growth factor (KGF) for the

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treatment of oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support.[117] Rosen et al have recently reported that palifermin was well tolerated and resulted in significant reduction of oral mucositis in patients with metastatic colorectal caner treated with fluorouracil-based chemotherapy.[118] However, the safety and efficacy of palifermin is yet to be firmly established in non-hematologic malignancies. Recently, Saforis, a new time-released preparation of glutamine appears promising in the management of oral mucositis in breast cancer patients receiving anthracycline-based chemotherapy.[119]

Cardiac Toxicity

Anthracyclines are associated with increased cardiac toxicity resulting in congestive heart failure (CHF). Other antineoplastic drugs may have additional effect on anthracycline-induced cardiac toxicity.[120] Doxorubicin is the most commonly used drug belonging to this class. Risk factors of doxorubicin-induced CHF include cumulative doses especially greater than 550 mg/m^2, hypertension, pre-existing cardiac disease and advanced age.[121] Dexrazoxane, an iron chelator has been shown to reduce doxorubicin-induced cardiac toxicity in randomized clinical trials.[122-123] Pegylated liposomal doxorubicin is associated with less cardiac toxicity and may be a useful alternative to doxorubicin for patients 70 years or older when its efficacy is comparable to doxorubicin especially in metastatic breast cancer. [124-126] In addition, several agents including weekly taxanes, vinorelbine, gemcitabine, and capecitabine have a more favorable toxicity profile and may be used safely in older individuals.Capecitabine at reduced doses is particularly convenient, because the oral formulation allows home treatment.[127-128] Furthermore, since capecitabine, prodrug of 5-fluorouracil is activated in the tumor, the normal tissues are largely spared.

The NCCN guidelines recommend that any patient symptomatic for CHF, irrespective of ejection fraction and asymptomatic patients with an ejection fraction less than 45% should not receive anthracyclines. Liposomal doxorubicin, dexrazoxane or alternative treatment options should be considered for this class of patients (SAO-3).

Renal Toxicity

The glomerular filtration rate (GFR) decreases with age, which in turn delays elimination of many drugs. Delayed renal excretion may enhance the toxicity of drugs whose parent compounds are excreted by the kidneys (carboplatin, oxaliplatin, methotrexate, bleomycin) and drugs that are converted to active (idarubicin, daunorubicin) or toxic metabolites (high-dose cytarabine).[9] Dose adjustment to the measured GFR should be considered for these drugs as well as for drugs whose parent compounds are excreted through the biliary tract, to decrease systemic toxicity (SAO-3).

Renal insufficiency is common in elderly cancer patients, particularly in patients receiving nephrotoxic drugs, patients with genitourinary cancers or multiple myeloma. Dose adjustments and regular renal monitoring is essential. In patients with preexisting renal problems who are at a greater risk of renal impairment, the use of nephrotoxic drugs should be limited or avoided. The International Association of Geriatric Oncology (SIOG) Task Force provides number of recommendations for the clinical management of renal insufficiency.[129]

Neurotoxicity

Neurotoxicity is also a dose-limiting toxicity associated with chemotherapy.[130] Vinca alkaloids, cisplatin and taxanes indue peripheral neurotoxicity. Methotrexate, cytarabine and ifosfamide are associated with central neurotoxic side effect. Purine analogs (eg. fludarabine, cladribine and pentostatin) are associated with life-threatening neurotoxicity at significantly higher doses than the recommended clinical dose.[131] High dose cytarabine can cause an acute cerebellar syndrome. Patient's age (greater than 60 years), drug dose and schedule, renal and hepatic dysfunction are the most

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important risk factors for cytarabine-induced cerebellar toxicity.[132] Management of neurotoxicity mainly consists of dose reductions or lower dose intensities. Older patients are particularly susceptible to the toxicity of cytarabine-based regimens due to decreased renal excretion of the toxic metabolite ara-uridine, and increased vulnerability of the cerebellum.

Particular attention should be paid to the use of cytarabine in high doses especially in patients with renal insufficiency. Dose reductions are necessary in patients with reduced GFR. The guidelines recommend alternative therapy with non-neurotoxic drugs particularly in patients with significant hearing loss and monitoring for cerebellum function (SAO-3).

Dose Reduction and Substitution

Age has been associated with pharmacokinetic and pharmacodynamic changes and with increased susceptibility of normal tissues to toxic complications. In general, all of these changes increase the risks of chemotherapy. [133-134] Pharmacodynamic changes of interest include reduced repair of DNA damage and increased risk of toxicity. Pharmacokinetic changes of major concern include decrease in GFR and volume of distribution of hydrosoluble drugs. Although the hepatic uptake of drugs and the activity of cytochrome P450 enzymes also decrease with age, the influence of these changes on cancer chemotherapy is not clear. Intestinal absorption may decrease with age, but it does not appear to affect the bioavailability of anticancer agents. The pharmacokinetics of antineoplastic drugs is unpredictable to some extent; thus, drug doses should be adjusted according to the degree of toxicity that develops. However, adequate dosing is necessary to ensure the effectiveness of therapy. Extermann and colleagues have devised a convenient index (MAX2) for estimating the average per patient risk for toxicity from chemotherapy.[135]

Targeted Therapies

In recent years the emergence of targeted therapies such as monoclonal antibodies (MABs) and tyrosine kinase inhibitors (TKIs) have revolutionized the treatment and improved outcomes in a variety of malignancies. There is limited data available on the toxicity of these targeted therapies in elderly cancer patients.[136]

Bevacizumab has been associated with age-related toxicities in clinical trials. In a subset analysis of phase III study (ECOG 4599), elderly patients with NSCLC who were randomized to paclitaxel and carboplatin with bevacizumab experienced a higher degree of toxicity with no improvement in overall survival compared to those who received paclitaxel and carboplatin.[137] A recent pooled analysis of randomized trials of bevacizumab and chemotherapy also confirmed that the addition of bevacizumab to chemotherapy was associated with an increased risk of arterial thromboembolism (ATE) compared to chemotherapy alone.[138] Investigators of the BRiTE study also reported a higher rate of ATEs in older patients with metastatic colorectal cancer although the safety and efficacy of bevacizumab-based therapy in elderly patients (65 years or older) were comparable to that of younger patients.[139]

In a phase II trial of erlotinib as first-line therapy in chemotherapy naïve patients 70 or older with advanced NSCLC, 12% of patients required toxicity-related discontinuation compared to only 5% of patients in the erlotinib arm of previous trial (BR.21) where the median age was only 62 years.[140]A recent retrospective analysis of BR.21 trials also confirmed that elderly patients experienced greater toxicity compared to younger patients, even though both groups has similar survival and QOL benefits.[141]

Older age (50 years or more) and a lower left ventricular ejection fraction were identified as risk factors for CHF associated with

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trastuzumab as demonstrated by the NSABP-31 study which compared doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in HER-2-positive patients with breast cancer.[142] However, the investigators of the HERA trial concluded that limited data available from their trial does not provide grounds for withholding trastuzumab in women older than 60 years.[143] Trastuzumab should be used with caution in patients with prior cardiac history.

Rituximab has been effective in the treatment of elderly patients with diffuse large B-cell lymphomas with no apparent toxic effects.[144] Limited data available on cetuximab and sorafenib have shown that their efficacy in fit elderly patients is same as that observed in younger patients with tolerable toxicity profile.[145,146]

Thus, the use of targeted therapies in elderly cancer patients should be individualized. In patients who are not able to tolerate cytotoxic chemotherapy, risk-benefit ratio should be considered prior to initiation of targeted therapy. Prospective clinical trials which include sufficiently large number of older patients are needed to accurately determine the efficacy and tolerability of targeted therapies in this cohort of patients.

Disease-Specific Issues

Several disease-specific issues related to age have been identified in patients with certain types of cancers (SAO-C). These issues occur partly because of the different behavior of certain cancers in older versus younger patients and partly because of the decreased tolerance of treatment by older patients.

Older patients with AML may have decreased sensitivity to chemotherapy due to increased prevalence of multi-drug resistance and unfavorable cytogenetic profiles. In view of the seriousness of the complications of AML treatment, the panel recommends that older patients with AML should be treated according to the NCCN Acute Myeloid Leukemia Guideline in centers skilled in the management and supportive care of AML.

Elderly patients with colorectal cancer, advanced stage non-small cell lung cancer (NSCLC) may have decreased tolerance to fluoropyrimidine-based regimens and combined modality treatment respectively. The panel recommends that these issues in elderly cancer patients should be managed according to the disease specific NCCN Guidelines for Treatment of Cancer by Site (www.nccn.org).

Summary

Because aging is highly individualized, the best guide as to whether cancer treatment is appropriate may be provided by careful assessment of the older patient. Screening can be used to identify patients who can benefit from a CGA. Chronological age is not reliable in estimating life expectancy, functional reserve, or the risk of treatment complications. Careful assessment, using the criteria described in this NCCN Senior Adult Oncology Guideline, allows oncologists to divide older patients into three groups as follows:

- patients who are functionally independent (ADL and IADL independent) and without comorbidity and, thus, are candidates for most forms of standard cancer treatment;
- patients with major functional impairment and/or complex comorbidity (dependent in one or more ADL with severe comorbidity or advanced geriatric syndromes, who are candidates only for palliative treatment;
- patients with intermediate functional impairment who cannot tolerate life-prolonging curative therapy but who may benefit from some special pharmacological approach (such as reduction in the initial dose of chemotherapy with subsequent dose escalation as tolerated);

All three groups of patients are expected to die of cancer or experience complications within their lifetimes. A fourth group of patients includes those whose life expectancy is so short that they are unlikely to develop

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morbidity from cancer; these patients can receive symptom management and supportive care.

Elderly patients who are able to tolerate curative treatment have special needs. In general, age is not a primary consideration for surgical risk. However, concurrent radiation therapy/chemotherapy should be used cautiously; dose modification of chemotherapy may be necessary. Chemotherapy can lead to problems such as neurotoxicity, cardiac toxicity, mucositis, that can be decreased or prevented by using specific recommendations from the NCCN Senior Adult Oncology Guidelines (SAO-3). While targeted therapies have been shown to be effective in elderly cancer patients, some of these therapies are associated with age-related toxic side effects. Therefore, the use of targeted therapies in elderly cancer patients should be individualized and risk-benefit ratio should be considered prior to initiation of targeted therapy.

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