Cancer is the leading cause of death in women and men aged 60 to 79 years.1 More than 50% of all cancers and more than 70% of cancer-related deaths in the United States occur in patients who are 65 years or older.2 Experts estimate that by 2030 approximately 70% of all cancers will be diagnosed in adults aged 65 years or older.3 Older adults are more prone to develop cancer than younger adults. Furthermore,
aging in the US population and increased life expectancy mean that cancer in older adults is becoming an increasingly common problem.

Caring for an older adult with cancer involves unique issues. The biology of certain neoplasms and responsiveness to therapy changes with the patient's age. Furthermore, the patient's physiologic status, comorbidities, and preferences may influence the selection and tolerance to certain therapies. Together, these age-related issues form the basis for the development of guidelines that address special considerations in older patients with cancer.

Older patients with cancer are underrepresented in clinical trials for new cancer therapies. Therefore, fewer evidence-based data are available to guide the treatment of these patients. However, advanced age alone should not preclude the use of effective cancer treatment that could improve quality of life or extend meaningful survival. Treatment that diminishes quality of life with no significant survival benefit should be avoided. The available data suggest that older patients with good performance status are able to tolerate commonly used chemotherapy regimens as well as younger patients, particularly when adequate supportive care is provided. However, few studies have addressed patients at the extremes of age or those with poor performance status. The physiologic changes associated with aging may impact an older adult's ability to tolerate cancer therapy and should be considered in the treatment decision-making process.

Proper selection of patients is the key to administering effective and safe cancer treatment. The
Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.
Does the patient have risk factors for adverse outcomes from cancer treatment?

- Comorbidities
  - cardiovascular disease
  - renal insufficiency
  - neuropathy
  - anemia
  - osteoporosis
  - See NCCN Bone Health Task Force (available at JCCN.org)
- GI problems
- diabetes
- lung disease
- hearing or vision loss
- prior cancer diagnosis and treatment
- chronic infections
- decubitus or pressure ulcers

- Geriatric syndromes
  - functional dependency (ADL, IADL)
  - mobility problems
  - falls
  - dementia
  - delirium
  - depression
  - nutritional deficiency
  - polypharmacy
- Socioeconomic issues
  - poor living conditions
  - no caregiver or limited social support
  - low income
  - transportation barriers/access problems
  - under-insurance and/or high out-of-pocket costs for medications

**ASSESSMENT OF RISK FACTORS**

Does the patient have decision-making capacity?

Patients must have the ability to:
- Understand the relevant information about proposed diagnostic tests or treatments
- Appreciate their situation (including their underlying values and current medical situation)
- Use reason to make a decision
- Communicate their choice

If the patient has decision-making capacity:

1. Obtain information from:
   - Patient’s proxy
   - Advance directive
   - Living will
   - Health care power of attorney

2. Consider consult from ethics committee or social worker or consider Palliative Care (See NCCN Guidelines for Palliative Care)*

3. Assess the patient’s goals and values regarding management of the cancer

4. Are the patient’s goals and values consistent with wanting anticancer therapy?

If the patient is not at moderate or high risk of dying or suffering from cancer considering their overall life expectancy:

- Symptom management/supportive care (See NCCN Guidelines for Palliative Care*)

5. Consider alternate treatment options to reduce toxicity

6. Treat risk factors

7. See special considerations for patients able to tolerate treatment (SAO-3 and SAO-B)

8. See NCCN Guidelines for Supportive Care, available at NCCN.org

9. Symptom management/supportive care

10. Treat as recommended in disease-specific treatment guidelines

See Disease-Specific Issues Related to Age (SAO-B, SAO-3), and NCCN Guidelines for Treatment of Cancer by Site, available at NCCN.org

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[SAO-2]

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*SSee Comprehensive Geriatric Assessment (SAO-C).
†Older age has been associated with increased risk for congestive heart failure (CHF) in patients receiving cytotoxic and targeted therapies.
‡The panel recommends calculation of creatinine clearance to assess renal function for all patients.
**SPECIAL CONSIDERATIONS FOR PATIENTS ABLE TO TOLERATE TREATMENT**

- In general, age is not the primary consideration for surgical risk.
- Emergency surgery carries increased risk of complications.
- Assess physiologic status.
- American Geriatrics Society (AGS) Task Force and American College of Surgeons provided general guidelines for older adults undergoing surgery. These guidelines can be applied to older patients with cancer undergoing surgery.
- Data suggest that an increased need for functional assistance presurgery (measured by ADL, IADL, and PS) predicts postoperative complications, extended hospital stay, and 6-month mortality in older patients undergoing cancer surgery.
- Impaired cognitive status is a risk factor for postoperative complications, prolonged length of stay, and 6-month overall mortality postoperatively.
- In patients undergoing general surgery:
  - Older age is a risk factor for postoperative delirium.
  - Delirium is a risk factor for functional decline. See Assessment of Cognition (SAO-E).
- Preventive measures exist for delirium.
  - Yale Delirium Prevention Trial and Hospitalized Elder Life Program (HELP): http://info.med.yale.edu/intmed/elp/print_version/background_print.htm

**Systemic Therapy**

- Use caution with concurrent chemoradiation therapy; dose modification of chemotherapy may be necessary.
- Nutritional support and pain control are needed if radiation therapy-induced mucositis is present.
- Chemotherapy toxicity risk can be predicted by parameters that are typically included in a Comprehensive Geriatric Assessment (CGA). These tools are awaiting additional validation.
  - Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score (http://eforms.moffitt.org/crashScore.aspx)
  - Cancer and Aging Research Group (CARG) Chemo Toxicity Calculator (http://www.mycarg.org)

**Systemic Therapy Continued on SAO-4**

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Monitor the patient’s functional status, comorbidities, social circumstances, pain, nutritional status, and distress.

See Disease-specific issues related to age (SAO-B).


Monitor the patient’s functional status, comorbidities, social circumstances, pain, nutritional status, and distress.


Preventive measures exist for delirium postoperatively.

Impaired cognitive status is a risk factor for postoperative complications, prolonged length of stay, and 6-month overall mortality in the elderly.

Data suggest that an increased need for functional assistance pre-surgery (measured by ADL, IADL, and PS) predicts an increased risk of postoperative delirium.

Systemic Therapy

Diarrhea
- Consider early aggressive rehydration
- Manage with octreotide if oral preparations are ineffective (see NCCN Guidelines for Palliative Care*)

Constipation
- See NCCN Guidelines for Palliative Care*

Nausea/vomiting
- See NCCN Guidelines for Antiemesis* and NCCN Guidelines for Palliative Care*

Mucositis
- Early hospitalization is needed for patients who develop dysphagia/diarrhea
- Provide nutritional support
- See NCCN Task Force: Prevention and Management of Mucositis in Cancer Care, available at jnccn.org

Bone marrow suppression
- Prophylactic colony-stimulating factors are needed when dose intensity is required for response or cure (See NCCN Guidelines for Myeloid Growth Factors*)

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

Falls
- Assessment of history of falls, balance, and gait difficulties is recommended for all patients.®,®

Cardiac toxicity
- Monitor for symptomatic or asymptomatic congestive heart failure (CHF)
  - Caution with use of anthracyclines; consider alternative treatment
  - Caution with use of trastuzumab® (among patients with a normal ejection fraction, risk factors for CHF include receipt of an anthracycline-based regimen, baseline LVEF of 50%-54%, and hypertensive medicines)

Renal toxicity
- Calculate creatinine clearance to assess renal function
- Adjust dose for glomerular filtration rate to reduce systemic toxicity

Insomnia®
- Benzodiazepines or other sedative-hypnotics should not be used as first-line treatment for insomnia in older adults.®
- Nonpharmacologic methods, such as cognitive behavioral therapy and lifestyle modifications, are preferred.

*To view the most recent version of these guidelines, visit NCCN.org.

®See Comprehensive Geriatric Assessment (SAO-C).
®Monitor the patient’s functional status, comorbidities, social circumstances, pain, nutritional status, and distress.
®See Disease-specific issues related to age (SAO-B).
®See Insomnia (SAO-G).
## DISEASE-SPECIFIC ISSUES RELATED TO AGE

### Acute Lymphoblastic Leukemia†

See NCCN Guidelines for Acute Lymphoblastic Leukemia*

It is strongly recommended that older adults with acute lymphoblastic leukemia (ALL) be treated in a specialized center.

**Philadelphia Chromosome-Positive ALL**

- A randomized study of patients older than 55 years with Philadelphia chromosome-positive ALL (Ph+ALL) compared imatinib with chemotherapy as front-line treatment. The study demonstrated that imatinib is well tolerated with a higher remission rate and comparable overall survival (OS) in comparison to chemotherapy alone. ¹
- Phase II studies of adults with Ph+ALL treated with a tyrosine kinase inhibitor (imatinib or dasatinib) with steroids and intrathecal chemotherapy demonstrated a high response rate (100% with complete hematologic remission) and no early deaths. ²,³
- A phase II study of patients aged 55 years and older with Ph+ALL of induction chemotherapy followed by imatinib with steroids demonstrated higher complete response (CR) rate and survival than historical studies of chemotherapy alone. ⁴

**Other ALL Studies**

- Hyper CVAD in older patients with ALL results in higher CR rates and OS (compared with historical regimens); however, there is a higher risk of myelosuppression-related deaths. Of note, the dose of Ara-C was reduced to 1 g/m² in patients older than 60 years. ⁵
- A randomized phase II study of pegylated liposomal doxorubicin versus continuous-infusion doxorubicin in patients older than 55 years with ALL demonstrated no benefit to pegylated liposomal doxorubicin versus continuous-infusion doxorubicin. ⁶
- The benefit of adding rituximab to chemotherapy in older adults with Ph(−) CD20+ ALL has not been demonstrated. ⁷

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**Other ALL Studies**

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  - Hyper CVAD in older patients with ALL results in higher CR rates and OS (compared with historical regimens); however, there is a higher risk of myelosuppression-related deaths. Of note, the dose of Ara-C was reduced to 1 g/m² in patients older than 60 years.

- **A phase II study of patients aged 55 years and older with Ph+ALL of induction chemotherapy followed by imatinib with steroids**
  - The benefit of adding rituximab to chemotherapy in older adults with Ph(-) CD20+ ALL has not been demonstrated.
  - A randomized phase III trial of patients older than 60 years with ALL demonstrated no difference in CR rate between AD (Ara-C, 200 mg/m²/d IV continuous infusion on days 1-7 and daunorubicin, 45 mg/m²/d on days 1-3) and ME (mitoxantrone, 10 mg/m²/d IV on days 1-5 and etoposide, 100 mg/m²/d IV on days 1-5); however, poorer OS at 2 years was seen in the ME arm.
  - Therefore, if standard induction chemotherapy (off protocol) is given, an Ara-C-containing regimen should be used.

- **A randomized phase II trial of patients older than 60 years with Ara-C (100 mg/m²/d IV for 7 days) demonstrated that higher doses of daunorubicin (90 vs 45 mg/m² given IV over 3 h days 1-3) was associated with a superior CR rate but no difference in OS; however, a post hoc analysis showed a potential benefit to the higher dose of daunorubicin in patients older than 65 years, especially in those with CBF-AML.**

- **Standard-induction chemotherapy is associated with a 10% to 20% risk of death in patients older than 56 years. The risk of obtaining a CR and the risk of treatment-related mortality (taking age into account) can be calculated using a Web-based tool (http://www.aml-score.org/).**

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**DISEASE-SPECIFIC ISSUES RELATED TO AGE**

**Acute Myeloid Leukemia**

- Increasing age is a poor prognostic indicator in older adults with acute myeloid leukemia (AML). Other poor prognostic indicators are: FLT3 internal tandem duplications, unfavorable cytogenetics, increasing white blood cell count, poorer PS, and presence of secondary AML. Prediction tools are available to assist in counseling older adults regarding the safety and efficacy of standard induction chemotherapy.⁴

- A randomized phase II trial of patients older than 55 years receiving induction chemotherapy for AML with Ara-C (100 mg/m²/d IV for 7 days) demonstrated no difference in efficacy with the addition of the following anthracycline-containing regimens: daunorubicin, 45 mg/m²/d IV on days 1-3; mitoxantrone, 12 mg/m²/d on days 1-3; and idarubicin, 12 mg/m²/d on days 1-3.⁵

- A randomized phase III trial of patients older than 56 years with previously untreated AML demonstrated no difference in CR rate between AD (Ara-C, 200 mg/m²/d IV continuous infusion on days 1-7 and daunorubicin, 45 mg/m²/d on days 1-3) and ME (mitoxantrone, 10 mg/m²/d IV on days 1-5 and etoposide, 100 mg/m²/d IV on days 1-5); however, poorer OS at 2 years was seen in the ME arm.

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*To view the most recent version of these guidelines, visit NCCN.org.

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Multiple Myeloma

**Initial Therapy:**
- **Choice of treatment** depends on the side effect profile but also the ability to travel for IV therapy. Initial evaluation should determine whether the patient is transplant-eligible before exposure to alkylating agents. For more information regarding transplant eligibility, go to http://www.cms.gov/.

**Immunomodulator-Based Initial Therapy:**
- **Older adults with multiple myeloma receiving MPT (melphalan, prednisone, and thalidomide) in comparison to MP (melphalan and prednisone) had a higher** response rate at the cost of increased toxicity (constipation, fatigue, increased venous thromboembolism [VTE], neuropathy, cytopenias, and infection).1-9
- **A survival benefit has been seen with MPT compared with MP, although studies are conflicting and varying doses of thalidomide have been used.10**
- **MPT is associated with higher response rate and OS than transplant with intermediate-dose melphalan (MEL 100).5**
- **Melphalan, prednisone, and lenalidomide followed by lenalidomide maintenance (MPR-R) significantly prolonged PFS in patients 65 years or older with newly diagnosed multiple myeloma who were ineligible for transplantation. The greatest PFS benefit was observed in patients 65 to 75 years of age.10**

**VTE Prophylaxis:**
- In elderly patients receiving immunomodulator-based regimen, VTE prophylaxis is recommended.11

**Bortezomib-Based Initial Therapy:**
- **VMP (bortezomib, melphalan, and prednisone) in comparison to MP is associated with an increased response rate and OS at the cost of increased toxicity (eg, peripheral neuropathy, cytopenias, fatigue). The survival benefit is maintained across age groups.12,13**
- **VMP versus VTP (bortezomib, thalidomide, and prednisone) have similar response rates and OS but differing side effect profiles (VMP [ie, hematologic toxicity, infections, and VTE [cardiac complications]]) Rates of neuropathy were similar in both groups.14**
- **VMP (bortezomib, melphalan, prednisone, and thalidomide) followed by maintenance VT (bortezomib and thalidomide) versus VMP is associated with a higher response rate but does not improve OS. Weekly bortezomib is associated with a decreased rate of peripheral neuropathy without a decrement in response.15** An updated analysis (with a median follow-up of 47.2 months) showed that VMP-VT regimen significantly prolonged OS compared with VMP, especially in patients younger than 75 years.16

**High-Dose Dexamethasone Is Excessively Toxic in Older Adults:**
- **High-dose dexamethasone is associated with an increased risk of mortality and severe hematologic toxicities compared with MP.17**
- **Lenalidomide plus low-dose dexamethasone (in comparison to lenalidomide plus high-dose dexamethasone) is associated with an improvement in OS and lower toxicity (less DVT and fatigue and fewer infections).18**

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Senior Adult Oncology, Version 2.2014

DISEASE-SPECIFIC ISSUES RELATED TO AGE

Myelodysplastic Syndromes

- Azacitidine is the standard of care in patients with higher-risk MDS with improvement in OS, time to AML transformation, and quality of life, as well as decreased transfusion dependence. Subgroup analysis demonstrated similar benefits, with no increased risk of toxicity in patients 65 years of age and older and those 75 years of age and older. Predictors of a better response include a bone marrow blast count less than 15%, a normal karyotype, and no previous treatment with low-dose cytosine arabinoside.1-3

- The standard of care for patients with higher-risk MDS is azacitidine given 7 days in a row; however, this may be challenging due to logistic or transportation problems. A phase II study evaluating patients 65 years of age and older showed that the 5+2+2 (5 days on, 2 days off, 2 days on) schedule did not seem to negatively impact the response rate or duration of response. A 5-day schedule is not recommended for these patients.1,4

- Two large studies have evaluated the 5-day decitabine regimen for treatment of lower- and higher-risk MDS patients, in a predominantly elderly patient population.5,6 Substantial responses and hematologic improvements were demonstrated, with median survivals of 20 months in both studies. These results are comparable to those reported with azacitidine.

- Among patients with higher-risk MDS, decitabine delivered on an inpatient schedule over 3 days is not associated with a survival advantage in comparison to best supportive care.7

- Lenalidomide can reduce red blood cell (RBC) transfusion requirements in patients with lower-risk MDS with the 5q31 deletion.8 It can also reverse cytologic and cytogenetic abnormalities in these patients. The drug may reduce RBC transfusion requirements in a subset of other lower-risk MDS patients.9 Although the median age of patients included in these studies is early 70s, few data are available regarding the risks and benefits at the extremes of age.8,9

- Older age is associated with a lower chance of response to immunosuppression strategies (cyclosporine or antithymocyte globulin [ATG] +/- cyclosporine) in patients with low-risk MDS.10

*To view the most recent version of these guidelines, visit NCCN.org.


SAO-B
4 of 4
COMPREHENSIVE GERIATRIC ASSESSMENT

Functional status
- 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 the telephone
- Performance status
- Falls
  - In patients who have experienced a fall in the last 6 months or if the patient is “afraid of falling,” consider the following evaluations:
    - Assessment of gait using Timed Up and Go (TUG) test: See SAO-D
    - PT or OT evaluation
    - Checking and replacing vitamin D levels
    - Referral to geriatrics or primary care physician
- Gait speed

Socioeconomic issues: See SAO-2

Psychosocial distress: See NCCN Guidelines for Distress Management*

Comorbidities
- May affect treatment decisions in 5 ways:
  - Comorbidity may modify cancer behavior.
  - Cancer treatment may interact with comorbidity to impact functional status or worsen comorbidity. This includes any drug-drug interactions.
  - Cancer treatment may be too risky because of the type and severity of comorbidity.
  - Comorbidity may influence life expectancy (independent of the cancer).
  - Comorbidity may affect treatment outcome.

Cognitive function (See Assessment of Cognitive Function, SAO-E)
- Dementia
  - Mini-Mental State Examination (MMSE)2,3
  - Montreal Cognitive Assessment (MoCA)4 (http://www.mocatest.org/)
- Depression
  - Geriatric Depression Scale (GDS)5,6
  - See NCCN Guidelines for Distress Management*
- Delirium
  - Confusion Assessment Method and/or Memorial Delirium Assessment Scale7,8
  - See NCCN Guidelines for Palliative Care* and NCCN Guidelines for Distress Management*

*To view the most recent version of these guidelines, visit NCCN.org.

1See Procedure for Functional Assessment Screening in Elderly Persons (SAO-H).

SAO-C (1 of 2)
COMPREHENSIVE GERIATRIC ASSESSMENT

Polypharmacy
- Medication review (prescription and over-the-counter medications, vitamins, and supplements) for duplication and appropriate use should be performed at every visit and evaluated for potentially inappropriate medication use.
  - Medication Appropriateness Index
  - Beers Criteria
  - STOPP/START Criteria
- Review drug interactions and drug-supplement interactions
  - http://medicine.iupui.edu/clinpharm/ddis/
- Carefully review indications, duration of therapy, and dosage when using these medications or classes of medications

- Benzodiazepines
- Anticholinergics
- Antipsychotics
- Opioids
- Corticosteroids
- Antihistamines
- Oxybutynin
- Sleep medications
- Neuroleptics
- Antidepressants
- Anticonvulsants
- Class 1A antiarrhythmics

*Evaluate adherence to therapy (See Assessment of Adherence, SAO-F)

Nutritional status
- Body mass index
- Weight loss
- Nutritional deficiency - Mini Nutritional Assessment (MNA)

REFERENCES


SAO-C (2 of 2)
Gait should be assessed using the Timed Up and Go (TUG) test.\(^1\)
- The TUG test is calculated as the time in seconds it takes a patient to stand up from a chair (without using his or her arms), walk 10 feet straight ahead, turn back, and return to the chair and sit down. The patient may use an assistive device, such as a cane or walker, but may not have assistance from another person.
- A normal TUG test score is less than 13 seconds. For patients with above-normal TUG test scores, consider comprehensive evaluation as indicated below.

### ASSESSMENT OF GAIT AND TREATMENT RECOMMENDATIONS

<table>
<thead>
<tr>
<th>ASSESSMENT</th>
<th>TREATMENT RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assess proximal muscle strength</td>
<td>• Diagnose and treat underlying causes</td>
</tr>
<tr>
<td></td>
<td>• Consider physical therapy evaluation</td>
</tr>
<tr>
<td>Check orthostatic blood pressure</td>
<td>• Diagnose and treat underlying causes</td>
</tr>
<tr>
<td></td>
<td>• Review medications</td>
</tr>
<tr>
<td></td>
<td>• Address salt intake, adequate hydration, and compensatory strategies</td>
</tr>
<tr>
<td></td>
<td>(eg, elevating head of bed, rising slowly, using pressure stockings)</td>
</tr>
<tr>
<td>Ask about changes in vision</td>
<td>• Diagnose and treat underlying cause of vision changes</td>
</tr>
<tr>
<td></td>
<td>• Consider referral to ophthalmologist</td>
</tr>
<tr>
<td></td>
<td>• Consider neurologic evaluation</td>
</tr>
<tr>
<td>Assess for neurologic changes</td>
<td>• Evaluate if cancer or cancer treatment-related and modify treatment if possible</td>
</tr>
<tr>
<td></td>
<td>• Consider neurologic evaluation</td>
</tr>
<tr>
<td>Review medications</td>
<td>• See “Polypharmacy” (SAO-C, 2 of 2)</td>
</tr>
<tr>
<td></td>
<td>• Minimize the use of high-risk medications such as: benzodiazepines, sleeping medications, neuroleptics, antidepressants, anticonvulsants, or class 1A antiarrhythmics</td>
</tr>
<tr>
<td>Environmental hazards</td>
<td>• Consider home safety evaluation</td>
</tr>
<tr>
<td></td>
<td>• Educate patients to reduce risk</td>
</tr>
<tr>
<td></td>
<td>(<a href="http://www.cdc.gov/HomeandRecreationalSafety/Falls/CheckListForSafety.html">http://www.cdc.gov/HomeandRecreationalSafety/Falls/CheckListForSafety.html</a>)</td>
</tr>
<tr>
<td>Footwear assessment</td>
<td>• Assess type, condition, and fit of shoes</td>
</tr>
<tr>
<td></td>
<td>• Perform foot exam</td>
</tr>
</tbody>
</table>

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\(^1\)Pondal M, del Ser T. Normative data and determinants for the timed "up and go" test in a population-based sample of elderly individuals without gait disturbances. [Research Support, Non-U.S.-Gov’t]. J Geriatr Phys Ther 2008;31(2):57-63.

SAO-D
ASSESSMENT OF COGNITIVE FUNCTION

<table>
<thead>
<tr>
<th>WHEN TO ASSESS FOR COGNITIVE FUNCTION</th>
<th>RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Would impaired cognitive function affect the planning or delivery of care? (e.g., impact life expectancy or risk/benefit, impact adherence to treatment plan)</td>
<td>No (to all) Reassess periodically or when considering treatment plan changes</td>
</tr>
<tr>
<td>Is the medical team concerned about decision-making capacity? See SAO-1</td>
<td>Yes (to any) Consult with a clinician experienced in cognitive evaluation (i.e., geriatrician, neurologist, geriatric psychiatrist, neuropsychologist) OR Initiate the evaluation yourself</td>
</tr>
<tr>
<td>Does the medical team suspect impaired cognitive function?</td>
<td></td>
</tr>
<tr>
<td>Has the patient or patient’s family suggested that the patient has impaired cognitive function?</td>
<td></td>
</tr>
</tbody>
</table>

See SAO-E (2 of 2)

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### ASSESSMENT OF COGNITIVE FUNCTION

<table>
<thead>
<tr>
<th>Definition</th>
<th>Mild Cognitive Impairment</th>
<th>Dementia</th>
<th>Delirium</th>
</tr>
</thead>
</table>
| **Definition** | An intermediate state between normal cognition and dementia characterized by:  
- Subjective memory impairment  
- Preserved general cognitive function  
- Intact ability to perform daily functions | A progressive condition characterized by:  
- Impairment of memory and at least one other cognitive domain (aphasia, apraxia, agnosia, executive function)  
- Interference with ability to perform daily functions | Disturbance of consciousness with:  
- Reduced ability to focus, sustain, or shift attention  
- Onset over a short period of time (usually hours to days)  
- Fluctuation during the course of the day |
| **Distinguishing features** |  
- Subjective memory complaints and awareness of memory changes  
- Preserved function |  
- Progressive (not sudden) loss of multiple cognitive abilities  
- Affects the ability to function independently |  
- Acute onset  
- Waxing and waning attention  
- Associated with physiologic disturbances |
| **Differential Diagnosis** | CNS metastases  
Psychiatric disease (depression, anxiety, apathy)  
Endocrine dysfunction (thyroid)  
Metabolic causes (B12 deficiency)  
Drug dependency (including alcohol)  
Medication related  
Sleep disturbance  
Common geriatric conditions (pain, infection, constipation) |  
| **Screening tool** | Clinical interview with cognitive (Mini-Cog) and functional (ADL/IADL) assessment | Clinical interview with cognitive (Mini-Cog) and functional (ADL/IADL) assessment | Confusion Assessment Method (CAM) |
| **Further evaluation** |  
- Reassess periodically and with major changes in condition or when considering changes to treatment plan  
- Consider consultation with a clinician experienced in cognitive evaluation |  
- Consult with a clinician experienced in cognitive evaluation and treatment  
- Neuropsychological testing may be indicated  
- Evaluation: B12, TSH, brain imaging |  
- Evaluate and treat all potential causes of delirium  
- Consider consultation with clinicians experienced in cognitive evaluation and treatment |

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

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ASSESSMENT OF ADHERENCE

Assess risk of nonadherence whenever considering a treatment regimen that will include an oral agent. Although older age per se is not a consistent risk factor for nonadherence, several factors may increase the potential for nonadherence among older adults:

• Deceased propensity of older adults to ask questions about benefits and risks of treatments
• Increased likelihood of side effects adversely affecting comorbidities
• Increased likelihood of prior experience with medication side effects
• Increased likelihood of drug-drug interactions
• Increased likelihood of acquisition barriers, including out-of-pocket costs, mobility/transportation difficulties, and lack of synchronized refill dates
• Increased risk of cognitive impairment

Strategies to minimize nonadherence

When initiating therapy:

• Ask patient to bring in prescribed, over-the-counter medications and supplements to review
• In collaboration with other medical providers, reduce regimen complexity, if possible
• Take into consideration cost of the medication including insurance coverage and out-of-pocket cost
• Consult with pharmacist to synchronize medication refills whenever possible
• Prepare the patient regarding anticipated side effects to avoid inappropriate medication discontinuation
• Ensure that the patient/family understands the benefits/rationale for the medication and the risks of not taking it
• Provide written instructions to patient/caregiver for taking the medication at the sixth grade level. Have patient/caregiver repeat back his/her understanding of how to take the medication, common side effects, and “when to worry” and “what to do if worried”
• Engage family/other caregivers and interdisciplinary team in the process

At each follow-up visit:

• Ask patient to bring in prescribed, over-the-counter medications and supplements to review
• Provide additional cues or reminders (eg, calendars, pill boxes, other reminder techniques)
• Reinforce benefits and ask about side effects: if tolerable, stay the course; if intolerable, select an alternative
• Assess adherence in a nonjudgmental way: “How many pills did you take during the past week?” “How did you take them in relation to meals?” (if applicable)
• Ask the patient if there are any barriers to acquiring the medication; refer to case manager or pharmacist as applicable

4 Confirm ability to read and comprehend written instructions (eg, vision, literacy).
INSOMNIA

The American Geriatrics Society (AGS) provides recommendations for the diagnosis, evaluation, and management of insomnia.

- Benzodiazepines or other sedative-hypnotics should not be used as first-line treatment for insomnia in older adults.
- Nonpharmacologic methods such as cognitive behavioral therapy and lifestyle modifications are preferred.
- Patient should be cautioned that most over-the-counter sleep medications contain antihistamines and should not be used in older adults.
- If pharmacologic therapy is to be used, it is recommended for short-term use only with the lowest dose that is effective. The risks and benefits of the therapy should be discussed.

Please note that if zolpidem is considered, the FDA has advised that the recommended dose of zolpidem for women should be lowered from 10 to 5 mg for immediate-release products and from 12.5 to 6.25 mg for extended-release products.

- Patient information regarding optimizing sleep is available through the National Institute on Aging.

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PROCEDURE FOR FUNCTIONAL ASSESSMENT SCREENING IN ELDERLY PERSONS

<table>
<thead>
<tr>
<th>Target Area</th>
<th>Assessment Procedure</th>
<th>Abnormal Result</th>
<th>Suggested Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vision</td>
<td>Test each eye with Jaeger card while patient wears corrective lenses (if applicable)</td>
<td>Inability to read &gt;20/40</td>
<td>Refer to ophthalmologist</td>
</tr>
<tr>
<td>Hearing</td>
<td>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</td>
<td>Inability to answer question</td>
<td>Examine auditory canals for cerumen and clean if necessary. Repeat test; if still abnormal in either ear, refer for audiometry and possible prosthesis.</td>
</tr>
<tr>
<td>Arm</td>
<td>Proximal: “Touch the back of your head with both hands.” Distal: “Pick up the spoon”</td>
<td>Inability to do task</td>
<td>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.</td>
</tr>
<tr>
<td>Leg</td>
<td>Observe the patient after asking “Rise from your chair, walk 10 ft, return, and sit down”*</td>
<td>Inability to walk or transfer out of chair</td>
<td>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.</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>Ask patient: “Do you ever lose your urine and get wet?” Yes</td>
<td>Ascertain frequency and amount. Search for remediable causes including local irritations, polyuric states, and medications. Consider urologic referral.</td>
<td></td>
</tr>
<tr>
<td>Nutrition</td>
<td>Weigh the patient; measure height Weight is below acceptable range for height</td>
<td>Do appropriate medical evaluation. Consider dietician referral.</td>
<td></td>
</tr>
<tr>
<td>Mental status</td>
<td>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”†</td>
<td>Inability to recall all 3 objects after 1 min</td>
<td>Administer Folstein mini-mental status examination. If score is &lt; 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.</td>
</tr>
<tr>
<td>Depression</td>
<td>Ask patient: “Do you often feel sad or depressed?” Yes</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>ADL-IADL</td>
<td>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</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>Home environment</td>
<td>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</td>
<td>Evaluate home safety and institute appropriate countermeasures.</td>
<td></td>
</tr>
<tr>
<td>Social support</td>
<td>Ask patient: “Who would be able to help you in case of illness or emergency?” …</td>
<td>List identified persons in the medical record. Become familiar with available resources for the elderly in the community. Consider social worker referral.</td>
<td></td>
</tr>
</tbody>
</table>

ADL, activities of daily living; IADL, instrumental activities of daily living.
*This test is similar to the “Timed Up and Go” (TUG) test, except that the TUG test is calculated as the time in seconds it takes a patient to stand up from a chair (without using his or her arms), walk 10 feet straight ahead, turn back, and return to the chair and sit down. The patient may use an assistive device, such as a cane or walker, but may not have assistance from another person. A normal TUG test score is less than 13 seconds.
†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.
challenge of managing older patients with cancer 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. These NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Senior Adult Oncology address specific issues related to the management of cancer in older adults, including screening and comprehensive geriatric assessment (CGA), assessing the risks and benefits of treatment, preventing or decreasing complications from therapy, managing disease-specific issues, and managing patients deemed to be at high risk for toxicity from standard treatment.

CGA

Older patients can be classified into 3 categories: 1) young old patients are 65 to 75 years of age; 2) old patients are 76 to 85 years of age; and 3) oldest old patients are older than 85 years of age. Chronologic age by itself is not reliable in estimating life expectancy, functional reserve, or the risk of treatment complications. Although it is not possible for a physician to predict the exact life expectancy of an individual patient, providing an estimate of whether a patient is likely to live longer or shorter than an average person of similar age is possible.

Life expectancy at a given age can be estimated using life table data as suggested by Walter and Covinsky. 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 et al developed and validated a potentially useful tool for clinicians to estimate the 4-year mortality risk. Patients can be stratified into 3 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. Carey et al 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.

CGA is a multidisciplinary, in-depth evaluation to assess life expectancy and risk of morbidity and mortality in older patients. CGA includes assessment tools to predict the functional age of older patients with cancer based on functional status, comorbidities that may interfere with cancer treatment, polypharmacy, nutritional status, cognitive function, psychological status, socioeconomic issues, and geriatric syndromes.

Functional Status

Functional status in older patients with cancer can be evaluated using self-reported or performance-based measures (see SAO-C 1 of 2, page 93). Self-reported measures include the individual’s ability to complete activities of daily living (ADLs) and instrumental activities of daily living (IADLs). ADLs encompass basic self-care skills required to maintain independence at home, and IADLs encompass complex skills that are necessary for maintaining independence in the community. The need for assistance with IADLs has been associated with decreased treatment tolerance and poorer survival in older patients with cancer. Physical performance-based measures such as gait speed (also known as walking speed) and the Timed Up and Go (TUG) test are also used to assess functional status in older patients (see SAO-D, page 94).

Gait speed has been used to assess functional status and health outcomes in older adults. Recent reports have also identified gait speed as an indicator of survival and mortality in older adults. In a pooled analysis of individual data from 9 large cohort studies that included more than 30,000 participants (≥65 years) living in the community, Studenski et al reported that gait speed was associated with survival in older adults. In this analysis, with 0.8 meter per second as the cutoff, gait speed faster than 1.0 meter per second suggested a better-than-average life expectancy and gait speed above 1.2 meters per second suggested exceptional life expectancy. White et al reported that decline in gait speed (ranked as slow, moderate, and fast) could predict mortality in well-functioning older adults. A fast decline in gait speed was associated with a 90% greater risk of mortality than a slow decline.

The predictive value of gait speed has also been evaluated in older patients with cancer. In the Health, Ageing and Body Composition study that included 429 older patients with cancer, faster gait speed (time taken to cover a 20-meter course) was associated with lower risk of death (hazard ratio, 0.89) in patients with metastatic cancer and lower 2-year progression to death or disability in patients with nonmetastatic cancer. Gait speed could be helpful in identifying older patients with a longer
expected life expectancy and who may be candidates for preventive interventions that are associated with long-term benefit.

The TUG test is a quick screening test to assess mobility and overall motor function in older adults. The TUG test score is calculated as the time in seconds it takes a patient to get up from an armchair without using his or her arms, walk 10 feet forward at his or her usual pace, turn around, walk back to the chair, and then sit down again. The patient may use an assistive device, such as a cane or walker, but may not have assistance from another person. The TUG test score has been shown to predict the risk of falls in older adults. In a preliminary prospective study, the TUG test was also associated with good sensitivity and specificity in the assessment of falls in older patients with cancer.

Comorbidities
Older adults have an increased prevalence of comorbidities, which can impact cancer prognosis and treatment tolerance. Cardiovascular problems including congestive heart failure (CHF), diabetes, renal insufficiency, dementia, depression, anemia, chronic infections, osteoporosis, decubitus or pressure ulcers, and prior cancer diagnosis and treatment are some of the frequently encountered comorbid conditions in older patients with cancer (see SAO-2, page 85).

Specific comorbidities have been shown to have an impact on prognosis and treatment outcome in patients with cancer. For example, in a series of 5077 men (median age, 69.5 years) with localized or locally advanced prostate cancer, neoadjuvant hormonal therapy was significantly associated with an increased risk of all-cause mortality (26.3% vs 11.2%) among men with a history of coronary artery disease, CHF, or myocardial infarction after a median follow-up of 5.1 years. In a randomized adjuvant chemotherapy trial of 3759 patients with high-risk stage II and stage III colon cancer, patients with diabetes mellitus experienced a significantly higher rate of overall mortality and cancer recurrence. At 5 years, the disease-free survival (DFS; 48% vs 59%), overall survival (OS; 57% vs 66%), and relapse-free survival (RFS; 56% vs 64%) rates were significantly worse for patients with diabetes compared with patients without diabetes. In the SEER-Medicare database analysis of older patients (≥66 years) diagnosed with stages I to III breast cancer, those with diabetes had an increased rate of hospitalization for any chemotherapy toxicity and higher all-cause mortality.

In older patients with cancer, comorbidity may modify the disease course (see SAO-C 1 of 2, page 92). The interaction of cancer treatment with comorbidity may impact functional status or worsen the comorbidity. Cancer treatment may be too risky due to the type and severity of comorbidity. Furthermore, comorbidity may influence life expectancy (independent of cancer). The effect of comorbidity on life expectancy should be evaluated before initiation of treatment.

The number and severity of comorbidities could be assessed with any of the following indices commonly used to determine the risk of mortality associated with comorbidity in older patients: adult comorbidity evaluation-27 (ACE-27) index, the Charlson Comorbidity Index (CCI), the Cumulative Illness Rating Scale (CIRS), and the Older Americans Resources and Services (OARS) Multidimensional Functional Assessment Questionnaire. ACE-27, CCI, and CIRS have also been used to determine treatment tolerance in older patients with cancer. In a study of 310 older patients (≥70 years) with head and neck cancer, comorbidity as measured by the ACE-27 index was an indicator of OS. In a randomized trial that compared vinorelbine alone or in combination with gemcitabine in older patients with locally advanced non–small cell lung cancer (NSCLC), a CCI greater than 2 was associated with a higher risk of early treatment suspension (82% vs 30%, respectively). In a phase III trial comparing platinum-doublet therapy as first-line treatment in patients with advanced-stage NSCLC, patients with severe comorbidities (as measured by CIRS) benefited from and tolerated platinum-doublet chemotherapy as well as patients with no comorbidities. However, the former group had a higher risk of neutropenic fever and death from neutropenic infections.

More generally, a useful collection of tools to estimate the general mortality risk in the older adult can be found online at www.eprognosis.org. Life expectancy calculators available at this website could be used to determine anticipated life expectancy (independent of the cancer) and in clinical decision-making to assess whether the cancer is likely to shorten the patient’s life expectancy or whether the patient is likely to become symptomatic from cancer during the
Polypharmacy can be defined in various ways, including the use of an increased number of medications (5 or more), more than is clinically indicated; the use of potentially inappropriate medications; medication underuse; and medication duplication. Although polypharmacy can be an issue across all age groups, it can be a more serious problem in older patients due to the presence of increased comorbid conditions treated with one or more drugs. In this patient population, the use of drugs for the management of cancer-related symptoms or side effects can result in polypharmacy.

The use of multiple medications can lead to increased incidences of adverse drug reactions (which can lead to functional decline and geriatric syndromes), drug-drug interactions, and nonadherence. Among patients with cancer receiving systemic anticancer therapy for solid tumors, one or more drug-drug interactions were observed in 27% of patients, which increased to 31% among patients with cancer receiving palliative care only. Older patients, those with comorbid conditions, brain tumor patients, and those taking many medications are at greater risk of drug interactions.

Alterations in pharmacokinetics and pharmacodynamics of drug metabolism in the older population can also contribute to adverse drug interactions. Most of the commonly prescribed medications such as opioids, antidepressants, antibiotics, and antipsychotics, and anticancer drugs induce or inhibit cytochrome P-450 enzymes. In a retrospective analysis, Popa et al assessed the impact of polypharmacy on toxicity from chemotherapy in 290 older patients (>70 years). The results of this study demonstrated that cytochrome P-450 inhibition may contribute to nonhematologic toxicities, whereas hematologic toxicities may be associated with protein-binding interactions. The role of protein binding and cytochrome P-450 inhibition should be further explored.

The use of one or more potentially inappropriate medications among older patients has also been documented in several studies. In one study, the use of inappropriate medications increased from 29% to 48% among patients with cancer in the palliative care setting. In a more recent study of 500 older patients with cancer (≥65 years) starting a new chemotherapy regimen, polypharmacy (≥5 drugs) was observed in 48% of patients and the use of potentially inappropriate medications was seen in 11% to 18% of patients. Although polypharmacy did not increase the risk of chemotherapy-related toxicity in this cohort, it was associated with a higher frequency of hospitalization and early discontinuation of chemotherapy.

Evaluation of Polypharmacy: The guidelines recommend that medication review (prescription and over-the-counter medications, vitamins, and supplements) for duplication and appropriate use be done at every visit (see SAO-C, page 85). Beers criteria and the medication appropriateness index (MAI) are 2 of the most common approaches used to evaluate potentially inappropriate medication use in older patients. The screening tool of older persons’ prescriptions (STOPP) and the screening tool to alert doctors to right treatment (START) criteria have been recently developed to evaluate drug interactions, medication duplication, and medication underuse.

Beers Criteria: The Beers’ Criteria identify inappropriate medications that have potential risks that outweigh potential benefits based on the risk of toxicity and the presence of potential drug-disease interaction in older patients with cancer. The criteria are appropriate for persons older than 65 years of age and provide a rating of severity for adverse outcomes and a descriptive summary of the prescribing information associated with the medication. The updated 2003 Beers Criteria have been used to evaluate polypharmacy in older patients with cancer both in an oncology-specific acute care unit (oncology-acute care for elders [OACE]; n=47 with a median age of 73.5 years) and in the outpatient setting (n=154 with a median age of 74 years). The Beers Criteria-based polypharmacy was observed in 21% and 11% of patients, respectively. Both of these studies had implemented medication review and pharmacist-based interventions to improve the appropriateness of prescribing. In the OACE study, 53% had a subsequent alteration in their medication regimen and 28% had a potentially inappropriate medication discontinued, after implementation of recommendations by the OACE team. In the outpatient study, after geriatric management evaluation, 50% of patients required specific interventions, and the use of
potentially inappropriate medication was identified in 11% of patients.\(^5\)

The Beers’ Criteria were updated by the American Geriatrics Society (AGS) in 2012 to improve monitoring of drug use, e-prescribing, interventions to decrease adverse events in older adults, and patient outcomes.\(^6\) In the updated criteria, medications that are used in older adults are divided into 3 categories: 1) potentially inappropriate medications to avoid in older adults; 2) potentially inappropriate medications to avoid in older adults with certain diseases and syndromes that the listed drugs can exacerbate; and 3) medications to be used with caution in older adults.

MAI: MAI was developed to measure appropriate prescribing based on a 10-item list and a 3-point rating scale.\(^67\) Samsa et al\(^68\) subsequently modified the MAI to include a single summated MAI score per medication that demonstrated acceptable reliability in assessing medication appropriateness among 1644 medications prescribed to 208 older veterans from the same clinic. This modified MAI appears to be a valid and relatively reliable measure to detect medication appropriateness and inappropriateness in the community pharmacy setting and in ambulatory older patients on multiple medications.\(^59,70\) MAI scores were significantly lower for medications with a high potential for adverse effects compared with those with a low potential (1.8 vs 2.9).\(^69\) Higher MAI scores were also associated with lower self-reported health scores in older adults.\(^71\) MAI has not been evaluated extensively in older patients with cancer.

STOPP/START Criteria: STOPP/START criteria were established using the Delphi consensus process by an 18-member expert panel from the academic centers of Ireland and the United Kingdom.\(^72\) The STOPP criteria is composed of 65 indicators for potentially inappropriate prescribing, including drug–drug and drug-disease interactions, therapeutic duplication, and drugs that increase the risks of geriatric syndromes, whereas the START criteria incorporate 22 evidence-based indicators to identify prescribing omissions in older people.\(^73,74\) In a randomized trial of 400 hospitalized patients (≥65 years), unnecessary polypharmacy, the use of drugs at incorrect doses, and potential drug-drug and drug-disease interactions were significantly lower in the group assigned to screening with STOPP/START criteria with recommendations provided to their attending physicians compared with the control group assigned to routine pharmaceutical care.\(^75\) Significant improvements in prescribing appropriateness were sustained for 6 months after discharge.

Nutritional Status
Nutritional deficiency or malnutrition is a common and serious condition in older patients. Although some malnutrition is attributable to the underlying illness, in most patients it is due to inadequate intake of calories. The Mini-Nutritional Assessment (MNA) has been designed and validated to provide a single, rapid assessment of nutritional status in older patients in the outpatient settings (see SAO-C, page 93).\(^76,77\) MNA is composed of 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\(^78\) have developed a shortened version of MNA, which also has good diagnostic accuracy. Special attention should also be devoted to vitamin D deficiency since that may be related to osteoporosis and fractures.\(^79\)

Cognitive Function
Older patients with cancer who are cognitively impaired have an increased risk of functional dependence, a higher incidence of depression, and a greater risk of death. Cognitive function is also predictive of medication nonadherence across diagnoses, regardless of the complexity of regimen.\(^80\) Cognitively impaired patients should be cared for by an experienced multidisciplinary geriatric oncology team along with good supportive care throughout the treatment.\(^81\) In addition, the association between cognitive impairment and the ability to weigh the risks and benefits of cancer treatment decisions needs to be considered.

The use of certain classes of medications (anticholinergics, antipsychotics, benzodiazepines, corticosteroids, and opioids) has also been associated with cognitive impairment in older adults.\(^82–84\)

Antipsychotic drugs are also associated with higher mortality rates in patients with dementia.\(^85–87\) Hilmer et al\(^88\) 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 older adults. Special considerations for over- or undertreatment, duration of therapy, and dosage should be in place with the use of these classes of medications.

For patients with suspected impaired cognitive
function that could potentially interfere with their decision-making capacity, the guidelines recommend consultation with a clinician experienced in cognitive evaluation (geriatrician, neurologist, geriatric psychiatrist, or neuropsychologist) or initiation of further evaluation to determine the appropriate diagnosis (e.g., mild cognitive impairment, dementia, delirium). In addition to the clinical observation by the medical team, any concerns reported by the patient or the patient’s family suggestive of an impaired cognitive function should also trigger further evaluation. The NCCN Guidelines recommend periodic reassessment of cognitive function or when considering changes to treatment plan for all patients including those with no cognitive impairment (see SAO-E, page 95).

See “Geriatric Syndromes” below for the assessment of dementia and delirium in older patients with cancer.

Socioeconomic Issues

Social ties have been identified as significant predictors of mortality in older adults. In a study of 2835 women diagnosed with breast cancer, socially isolated women had an elevated risk of mortality after a diagnosis of breast cancer. An evaluation of social support is an integral part of geriatric assessment. The patient’s treatment goals should be discussed with them. In addition, the patient’s living conditions, presence, and adequacy of caregiver and financial status should also be taken into consideration. Consultation with a social worker should be encouraged. Consultation with a financial expert to discuss the cost and coverage options of treatment would also be beneficial.

Geriatric Syndromes

Dementia, delirium, depression, distress, osteoporosis, falls, fatigue, and frailty are some of the most common syndromes in older patients with cancer. Dementia and delirium are 2 of the most common causes of cognitive impairment. Older patients with cancer experience a higher prevalence of geriatric syndromes than those without cancer. In an analysis of a national sample of 12,480 community-based elders, 60.3% of patients with cancer reported one or more geriatric syndromes compared with 53.2% of those without cancer. In this cohort, the prevalence of hearing trouble, urinary incontinence, falls, depression, and osteoporosis were significantly higher in patients with cancer than those without cancer.

Dementia

Dementia is a progressive condition characterized by impairment of memory and at least one other cognitive function impairment (e.g., aphasia, apraxia, agnosia, executive function loss) that would interfere with the ability to perform daily functions independently. Dementia is often present in older patients as a comorbid condition. In a SEER database analysis, older patients with colon cancer (≥67 years) and dementia were less likely to receive invasive diagnostic methods or therapies with curative intent. Preexisting dementia was also associated with high mortality, mostly from noncancer causes, in patients 68 years or older diagnosed with breast, colon, or prostate cancer. Mild cognitive impairment is an intermediate state between normal cognition and dementia. It is characterized by subjective memory impairment, preserved general cognitive function, and intact ability to perform daily functions.

Blessed Orientation-Memory-Concentration (BOMC) test, Mini-Mental State Exam (MMSE), and the Montreal Cognitive Assessment (MoCA) have been used to screen for cognitive impairment in older adults. BOMC is a 6-item test that has been shown to discriminate among mild, moderate, and severe cognitive deficits. MMSE is an 11-item screening test that quantitatively assesses the severity of cognitive impairment and documents cognitive changes occurring over a period of time. However, MMSE is not adequate for mild cognitive impairment and does not predict future decline. MoCA is a brief screening tool with high sensitivity and specificity for detecting mild cognitive impairment in patients performing in the normal range on the MMSE. MoCA has been shown to be a superior prognostic indicator than the MMSE in patients with brain metastases. In a feasibility study of MoCA in patients with brain metastases, cognitive impairment was detected in 80% of the patients by the MoCA compared with 30% by the MMSE. Among the 28 patients with a normal MMSE, 71% had cognitive impairment according to the MoCA.

Clinical interview with cognitive and functional assessment to screen for mild cognitive impairment or dementia is recommended for all patients, because there is a strong correlation between decline in cognitive status and the loss of functional independence in older adults. The guidelines have included Mini-Cog as a screening tool for the assess-
ment of mild cognitive impairment and dementia in older patients with cancer. Mini-Cog is a 5-point test (consisting of a 3-word recall and clock drawing test) used for screening cognitive impairment in the older population.\textsuperscript{106,107} Assessment of cognitive function can also be confounded by fatigue, depression, anxiety, underlying brain tumors, endocrine dysfunction, nutritional deficiency, alcohol use, and sleep disturbances.\textsuperscript{108} Therefore, if dementia is suspected, further evaluation, including brain imaging neuropsychologic testing and evaluation for vitamin B\textsubscript{12} deficiency and thyroid dysfunction may be indicated. For patients with mild cognitive impairment, the guidelines recommend reassessment of cognitive function periodically or when considering changes to treatment plan.

**Delirium**

Delirium is an acute decline in attention and cognition over a short period of time (usually hours to days) and is characterized by the disturbance of consciousness with reduced ability to focus, sustain, or shift attention.\textsuperscript{109} It is an underrecognized problem in older adults and can contribute to poorer clinical outcome and functional decline, and can impair communication between the patient and physicians for patients with advanced cancer.\textsuperscript{110} Dementia is the leading factor for delirium and about two thirds of cases of delirium occur in older patients with dementia.\textsuperscript{109}

The Confusion Assessment Method (CAM) is a screening and diagnostic tool based on 4 important features of delirium: acute onset and fluctuating course, inattention, disorganized thinking, and altered level of consciousness.\textsuperscript{111,112} The Memorial Delirium Assessment Scale is a 10-item validated instrument developed for repeated use to quantify the severity of delirium symptoms in patients with advanced cancer.\textsuperscript{113} The Nursing Delirium Screening Scale is an observational 5-item scale and has been validated in the oncology inpatient setting and is associated with high sensitivity and specificity.\textsuperscript{114}

The Hospital Elder Life Program (HELP) includes interventions for the management of 6 risk factors for delirium (cognitive impairment, sleep deprivation, immobility, dehydration, vision or hearing impairment).\textsuperscript{115} In the Yale Delirium Prevention Trial (N=852), the HELP interventions resulted in a significant reduction in the development of delirium, total number of days with delirium, and the total number of delirium episodes in hospitalized patients 70 years or older.\textsuperscript{116}

The NCCN Guidelines have included CAM as a screening tool for delirium. Evaluation and treatment of all potential causes of delirium is recommended for all patients with delirium. Medications that can contribute to delirium should be used with caution in older patients with cancer.\textsuperscript{117–119}

**Depression**

The Geriatric Depression Scale (GDS) is a reliable and valid tool for screening for depression in older patients with no cognitive impairment and in patients with mild to moderate cognitive impairment.\textsuperscript{120} GDS was originally developed by Yesavage et al\textsuperscript{120} as a 30-item scale. Recently, shortened versions of GDS have been found equally accurate and less time consuming in screening for depression in older adults.\textsuperscript{121,122} Cancer-related fatigue and depression frequently occur together; therefore, patients reporting fatigue should probably be assessed for depression.\textsuperscript{123–125}

**Distress**

Psychologic distress is common among patients with cancer. Hurria et al\textsuperscript{126} reported that significant distress was identified in 41% of patients 65 years or older with cancer, and poorer physical function was the best predictor of distress. Screening tools have been found effective and feasible in reliably identifying distress and the psychosocial needs of patients.\textsuperscript{127–129} The NCCN distress thermometer (DT) and the accompanying 36-item problem list is a well-known screening tool, specifically developed for patients with cancer by the NCCN Distress Management Panel.\textsuperscript{130,131} The NCCN DT 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.\textsuperscript{129} Patients can quickly fill out the NCCN DT screening tool in the waiting room, and the tool can alert the physician to potential problems. This tool identifies whether patients with cancer have problems in 5 different categories: practical, family, emotional, spiritual/religious, and physical. See the NCCN Guidelines for Distress Management (to view the most recent version of these guidelines, visit NCCN.org) for more information on the use of the NCCN DT as a screening tool in patients with cancer.

**Frailty**

Frailty is a biologic syndrome of decreased reserve and resistance to stressors, causing vulnerability to adverse effects.
outcomes. Frail patients are at risk for falling, disability, hospitalization, and death. Fried Frailty Criteria and the Balducci Frailty Criteria are the 2 most common measures used to identify frail patients. According to Fried Frailty Criteria, frailty is defined as the clinical syndrome with 3 or more of the following conditions: unintentional weight loss (≥10 lb in the past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and/or low physical activity. In a prospective, observational study of 5317 men and women (≥65 years), frailty status based on these criteria was found to be predictive of incident falls, worsening mobility or ADL function, incidence of hospitalization, and death.

Balducci Frailty Criteria are based on the components of CGA (dependence in ≥1 ADLs, ≥3 comorbid conditions, and ≥1 geriatric syndromes). These CGA frailty criteria have been found to be more useful in identifying frail patients with cancer. In a prospective study that compared the Balducci Frailty Criteria and the modified version of Fried Frailty Criteria in 176 patients (age 70–94 years) who underwent elective surgery for colorectal cancer, although both frailty measures were predictive of OS, Balducci Frailty Criteria were more useful than the modified version of Fried Frailty Criteria in predicting postoperative complications.

**Fatigue**

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% to 70%. In a study that evaluated the prevalence of common symptoms in patients with advanced cancer, fatigue was independently associated with chemotherapy, hemoglobin level, and other symptoms such as pain and depression. Patients perceive fatigue to be one of the most distressing symptoms associated with cancer and its treatment; fatigue is more distressing than pain or nausea and vomiting. In contrast to normal fatigue, cancer-related fatigue is refractory to sleep and rest, perhaps because patients with cancer often have aberrant sleep patterns. It is reasonable to expect that fatigue may precipitate functional dependence, especially in patients who are already dependent in IADLs.

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 adults. 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 that would enable patients to rate the severity of their fatigue on a scale of 0 (no fatigue) to 10 (worst fatigue). See the NCCN Guidelines for Cancer-Related Fatigue (to view the most recent version of these guidelines, visit NCCN.org).

**Falls**

Falls are one of most common geriatric syndromes. Risk factors include arthritis; depressive symptoms; orthostasis; impairments in muscle strength, cognition, vision, balance, or gait; and the use of 4 or more prescription medications. The use of inappropriate medications (especially hypnotics, sedatives, antidepressants, long-acting benzodiazepines and other inappropriate psychotropics, and medications with anticholinergic properties) is associated with an increased risk of falls in older adults (≥65 years). Furthermore, cancer diagnosis (especially in the first 6 months after diagnosis) and chemotherapy are also associated with a high risk of falls. In a prospective study of 185 patients with advanced cancer, more than 50% of patients experienced falls associated with a high risk of physical injury, regardless of age; the incidences of falls were 53% among patients younger than 65 years and 49% among those 65 years or older. Median time to fall was 96 days. In a multivariate analysis, the diagnosis of primary brain tumor or brain metastasis, number of falls in the preceding 3 months, severity of depression, benzodiazepine dose, and cancer-related pain were identified as independent risk factors. Another recent study also reported that the risk of falls increases with each cycle of chemotherapy and that patients treated with taxane-based chemotherapy may be at greater risk of falls than those treated with platinum-based chemotherapy.

The AGS/British Geriatrics Society Clinical Practice Guideline for Prevention of Falls in Older Persons recommends a multifactorial risk assessment followed by multicomponent interventions to address the identified risks and prevent falls in patients 75 years or older with 2 or more falls in the past 12 months or difficulty with walking or balance or gait difficulties. Recommended interventions include...
minimizing the number of medications; providing a tailored exercise program to improve strength, balance, gait, and coordination; treating vision impairment (including cataracts); managing postural hypotension, heart rate, and rhythm abnormalities and foot and footwear problems; supplementing with vitamin D; modifying the home environment; and providing education and necessary information.150

Multifactorial risk assessment and management, exercise, vitamin D supplementation, withdrawal of psychotropic medications, and environmental modifications have been shown to be effective in reducing the risk and/or rate of falls in older patients.151–156 The guidelines recommend assessment of history of falls, balance, and gait difficulties for all patients (see SAO-D, page 94). Assessment of gait using the TUG test, evaluation for physical or occupational therapy, vitamin D supplementation (in patients with low levels of vitamin D), or referral to geriatrics or a primary care physician can be considered for patients who have experienced a fall in the last 6 months or who are afraid of falling.

Osteoporosis
Osteoporosis and its associated increased risk of fracture is a major risk factor in patients with cancer, 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. The diagnosis of osteoporosis is based on assessment of bone density by a dual energy x-ray absorptiometry scan. Management of bone health has become an integral part of comprehensive cancer care. Older patients should be made aware of the impact of cancer therapies on bone health and should adhere to treatment recommendations for maintaining bone health.157 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.158

and emotional function, nutritional status, polypharmacy, and geriatric syndromes.134 Ingram et al159 used a self-administered CGA including demographics, comorbid conditions, functional status, pain, financial well-being, social support, emotional state, spiritual well-being, and quality of life to characterize older patients with cancer. Repetto et al160 demonstrated that CGA adds substantial information on the functional assessment of older patients with cancer (≥65 years). Among patients with a good performance status, 13% had 2 or more comorbidities; 9.3% and 37.7% had ADL or IADL limitations, respectively.

CGA components (comorbid conditions, functional status, cognitive function, geriatric syndromes, and nutritional status) have been associated with the type of cancer treatment and survival in older patients with cancer.24–26,161–165 For example, in women aged 65 years or older diagnosed with stage I to III primary breast cancer, the all-cause and breast cancer-specific death rate at 5 and 10 years was consistently approximately 2 times higher in women with 3 or more cancer-specific CGA deficits, regardless of age and stage of disease.161 In another prospective study of 375 consecutive older patients with cancer (ELCAPA study), in a multivariate analysis, a lower ADL score and malnutrition were independently associated with cancer treatment changes.162 In a recent prospective multicenter study of 348 previously untreated patients with cancer older than 70 years, Soubeyran et al163 identified poor nutritional status, impaired mobility, and advanced tumors as risk factors predictive of early death (<6 months) after initiation of chemotherapy. In a phase III study (FFCD 2001-02), impairment in functional status and cognitive function (as assessed by IADL and MMSE, respectively) were predictive of severe chemotherapy toxicity and hospitalization in older patients with metastatic colorectal cancer.164 Similarly, among older patients receiving induction chemotherapy for acute myeloid leukemia (AML), OS was significantly shorter for patients with impaired cognitive and physical function.165 CGA has also been reported to be an efficient method to identify older patients with diffuse large B-cell lymphoma who can benefit from anthracycline-based chemoimmunotherapy.26,135,166

Although CGA is helpful for physicians to develop a coordinated plan for cancer treatment and to guide appropriate interventions to the patient’s
problems, it can be time consuming and may not be practical for all patients. Some investigators have developed a brief but comprehensive geriatric assessment specific for older patients with cancer, while others have reported a 2-step approach using frailty screening tools to identify older patients who would benefit from a CGA.167,168

The cancer-specific geriatric assessment (CSGA) developed by Hurria et al167 includes assessment of older patients with cancer across 7 domains (functional status, comorbidity, polypharmacy, cognitive function, psychological status, social functioning and support, and nutritional status) using validated measures. The feasibility of CSGA was demonstrated in a pilot study of 43 patients with cancer (median age, 74 years), most of whom had advanced-stage disease. This brief geriatric assessment is largely self-administered and can be completed by most older patients without assistance. Recent results from the CALGB 360401 study also demonstrated the feasibility of including CSGA in future cooperative group clinical trials.169 A multicenter study involving 500 older patients (median age, 73 years) with cancer also showed that CSGA is useful for predicting treatment-related toxicity in older patients with solid tumors.170

The Senior Adult Oncology Program 2 (SAOP2) screening tool developed by Extermann171 is aimed at identifying older patients who would benefit from a multidisciplinary evaluation by a geriatric oncology team. The SAOP2 screening tool includes assessment of older patients with cancer across the following domains using validated measures: self-rated health, cognitive function, nutritional status, comorbidity, ECOG performance status, and functional status.

Abbreviated CGA (aCGA),172,173 Barber questionnaire,174 Fried Frailty Criteria,133,175 Geriatric 8 (G-8),176-178 Groningen Frailty Index,173 Triage Risk Screening Tool (TRST),178 Vulnerable Elders Survey (VES-13),177,179-182 and Lachs’ screening test183 have been used to determine if a CGA would be beneficial for older patients with cancer. G-8 and aCGA were developed specifically for older patients with cancer. In a recent systematic review, Hamaker et al168 assessed the sensitivity and specificity of frailty screening methods that could potentially be useful in the selection of patients for CGA. G-8 and TRST had the highest sensitivity (87% and 92%, respectively) and aCGA had the highest specificity (97%) for predicting frailty on CGA. Although all of the screening tools included the assessment of functional status, the assessment of other domains such as psychosocial status, nutritional status, comorbidities, and polypharmacy varied widely. For example, aCGA, Fried Frailty Criteria, and the VES-13 had a stronger predictive value for impairment of functional status (ADLs and IADLs) and G-8 had a strong predictive value for nutritional status but not for other geriatric conditions. As a result, none of the screening tools were successful in identifying impairments across all of the domains included in the CGA. Given the lack of data supporting the efficacy of any one screening tool for predicting outcome of a CGA, it would be beneficial to assess all older patients with a CGA before starting therapy.

Approach to Decision-Making in Older Patients With Cancer

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. After initial screening and CGA, patients with a low risk of dying or suffering from cancer during their lifetime can receive symptom management and supportive care as detailed in the appropriate NCCN Guidelines for Supportive Care (to view the most recent version of these guidelines, visit NCCN.org). Patients in the moderate- or high-risk group can be further evaluated to assess their functional dependency, decision-making capacity, overall goals, and desire for proposed treatment (see SAO-1, page 84).184,185

A patient’s decision-making capacity is generally evaluated based on the patient’s ability to understand the relevant information about the diagnosis and proposed diagnostic tests or treatment; appreciate his or her underlying values and current medical situation; use reason to make a decision; and communicate his or her choice. Sessums et al184 recently evaluated a variety of instruments used to assess medical decision-making capacity in adult patients without any mental illness and concluded that Aid to Capacity Evaluation (ACE) is the best available instrument to assist physicians in making assessments about a patient’s medical decision-making capacity. Irrespective of age, a person who is function-
ally independent without serious comorbidities and has the decision-making capacity should be a good candidate for most forms of cancer treatment. In patients without decision-making capacity, the guidelines recommend considering consultation from an ethics committee or social worker. Additional information can be obtained from the patient’s proxy, advanced directive, health care power of attorney, or clinician’s documentation.

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 (available online at NCCN.org). Patients who are dependent in some IADLs, with or without severe comorbidities, are at increased risk of treatment complications. For these patients with intermediate functional impairment who have milder problems (such as dependence in one or more IADLs, milder comorbidity, depression, minor memory disorder, mild dementia, and inadequate caregiver), treatment may still be administered with special individualized precautions.4

The potential benefits of cancer treatment include prolonged survival, maintenance, improvement of quality of life and function, and palliation of symptoms. For patients who are able to tolerate curative treatment, options include surgery, radiation therapy (RT), chemotherapy, and targeted therapies. Symptom management and supportive care as detailed in the appropriate NCCN Guidelines for Supportive Care (available online at NCCN.org) are recommended for all patients.

Surgery
In general, age is not a primary consideration for surgical risk, although the physiologic status of the patient needs to be assessed (see SAO-3, page 86). Performance status and comorbidities are more important factors than age when considering surgical treatment options for older adults.186 The American College of Surgeons and the AGS have provided general guidelines for the preoperative assessment of older patients undergoing surgery. These guidelines could also be applied to older patients with cancer undergoing surgery.119

The Surgical Task Force report from SIOG (International Society of Geriatric Oncology) reported that in many malignancies (breast, gastric, and liver), surgical outcomes in older patients with cancer were not significantly different from their younger counterparts.187 Preoperative Assessment of Cancer in the Elderly (PACE) was developed to determine the suitability of older patients for surgical intervention.188 PACE incorporates CGA, brief fatigue inventory, performance status, and American Society of Anesthesiologists (ASA) grade. In an international prospective study, 460 consecutive older patients completed PACE before surgery.190 In a multivariate analysis, moderate-to-severe fatigue, a dependent IADL, and an abnormal performance status were identified as the most important independent predictors of postoperative complications. Disability assessed by ADLs, IADLs, and performance status were associated with an extended hospital stay.

Patients should be made aware that emergency surgery carries increased risk of complications. After surgery, physical or occupational therapy should be considered to expedite the patient’s return to their preoperative functional level. Impaired cognitive function is also a risk factor for postoperative complications, prolonged hospital stay, and 6-month overall postoperative morbidity.191,192 Older age is also a risk factor for postoperative delirium. The HELP115,116 and NICE guidelines193 provide recommendations for the management of delirium in hospitalized patients 70 years or older.

RT
RT (external-beam or brachytherapy) can be offered either in the curative or in the palliative setting. Hypofractionated RT may be an alternative treatment option in patients who are unable to tolerate conventional dose RT.195 Available data from the literature indicate that RT is highly effective and well tolerated and that age is not a limiting factor in older patients with cancer.196–198 However, concurrent chemoradiation, should be used with extreme caution; dose modification of chemotherapy may be necessary to reduce toxic side effects. Nutritional support and pain control for RT-induced mucositis are recommended for patients receiving RT (see SAO-3, page 86).

Chemotherapy
Several retrospective studies have reported that the toxicity of chemotherapy is not more severe or prolonged in persons older than 70 years.199,203 However, the results of these studies cannot be generalized for the following reasons:
In a study of 83 older patients (≥65 years), Extermann et al. identified advanced age (≥65 years), comorbidities (e.g., symptoms of depression at baseline), functional dependence, and polypharmacy (>6 different medications per day) as independent predictors of severe toxicity and OS. Hurria et al. developed a scoring algorithm for predicting chemotherapy toxicity in older patients with cancer. The following factors were predictive of grade 3 to 5 chemotherapy toxicity: 1) age 72 years or older; 2) cancer type (gastrointestinal or genitourinary); 3) standard dosing of chemotherapy; 4) polychemotherapy; 5) hemoglobin (male: <11g/dL; female: <10g/dL); 6) creatinine clearance less than 34 mL/min (Jelliffe formula using ideal weight); 7) hearing impairment described as fair or worse; 8) one or more falls in last 6 months; 9) limited in walking one block; 10) the need for assistance with taking medications; and 11) decreased social activities because of physical or emotional health. Extermann et al. developed the chemotherapy risk assessment scale for high-age patients score, which could be useful in predicting significant differences in the risk of severe toxicity in older patients with cancer starting a new chemotherapy. In this model, diastolic blood pressure, IADLs, lactate dehydrogenase, and type of therapy were the best predictors of hematologic toxicity. Performance status, cognitive function, nutritional status, and type of therapy were the best predictors of nonhematologic toxicity.

**Side Effects of Chemotherapy:** In older patients undergoing chemotherapy, the most common complications include myelosuppression resulting in neu-
Adherence to Therapy

Adherence to the prescribed regimen, especially oral therapy, is essential to derive maximal clinical benefit. Although older age per se is not a consistent risk factor for nonadherence, older adults are at an increased risk for nonadherence for a variety of reasons, including cognitive impairment, increased number of comorbid conditions, polypharmacy, higher risk of side effects adversely affecting comorbidities, increased likelihood of drug interactions, limited insurance coverage, social isolation, and inadequate social support.

Discontinuation and nonadherence to adjuvant hormonal therapy is well documented in women with early-stage breast cancer. In studies that have evaluated adherence to adjuvant hormonal therapy among older women (≥55 years) diagnosed with early-stage breast cancer, the reported rates of nonadherence or discontinuation range from 15% to 49%. In a cohort of 961 women (≥65 years) diagnosed with early-stage estrogen receptor-positive or indeterminate breast cancer, Owusu et al. reported a discontinuation rate of 49% before the completion of 5 years. Women aged 75 years or older, those with an increase in CCI, and those with an increase in the number of cardiopulmonary comorbidities at 3 years from diagnosis, those with an indeterminate estrogen receptor status, and those who had received breast-conserving surgery without RT were at higher risk of discontinuation. Women with estrogen receptor-negative and node-positive disease, those who report severe initial side effects (depression, nausea, visual complaints, and vaginal bleeding), and women with neutral or negative beliefs about the value of hormonal therapy are also more likely to discontinue therapy.

Adherence to adjuvant chemotherapy has also been evaluated in older patients with early-stage breast cancer. In the randomized study (CALGB 49907) that evaluated adjuvant chemotherapy with oral capecitabine versus standard chemotherapy in 161 women (≥65 years) with early-stage breast cancer, 25% of the patients took fewer than 80% of the planned doses. Nonadherence was more likely among women with node-negative disease and mas-
Although nonadherence to adjuvant chemotherapy was not associated with shorter RFS in the CALGB 49907 study (may be due to limited sample size), other studies have reported inferior clinical outcomes in patients with nonadherence to cancer therapy. Among 8769 women treated with adjuvant hormone therapy for stage I to III breast cancer, Hershman et al identified early discontinuation and nonadherence to adjuvant hormonal therapy as independent predictors of increased mortality. At a median follow-up of 4 years, the estimated 10-year survival rates were 80.7% and 73.6%, respectively, for women who continued hormonal therapy and those who discontinued therapy (P < .001). For those who continued, the 10-year survival rate was higher for women with adherence to therapy than for those with nonadherence (81.7% and 77.8%, respectively; P < .001). In the ADAGIO study, nonadherence was associated with poorer response to imatinib in patients with CML; nonadherence rates were significantly higher for patients with suboptimal response compared with those with optimal response to imatinib (23% and 7%, respectively). Marin et al also identified adherence as the only independent predictor for achieving complete molecular response on standard-dose imatinib in patients with CML. Poor adherence to imatinib therapy has also been identified as the most important factor contributing to cytogenetic relapse and imatinib failure.

Treatment-related adverse events, complexity of regimens, and poor understanding of the need for treatment and the consequences of nonadherence are some of the common barriers to adherence. In a multicenter, prospective, open-label randomized trial of exemestane versus letrozole (n = 503), 32.4% discontinued initial therapy within 2 years because of adverse effects, and the median time to treatment discontinuation was 6 months. In a recent survey of women taking oral hormonal therapy for breast cancer, prior knowledge about the impact of adherence on clinical outcomes and better management of treatment-related side effects were indicated as the most important factors for increasing compliance.

In older patients with cancer, assessment of risk factors for nonadherence is recommended when considering a treatment regimen that will include an oral agent (see SAO-F, page 97). Close monitoring of patient adherence, reducing regimen complexity (if possible), interventions designed to educate older patients about the risks and benefits of oral therapy and the importance of adherence to therapy, adequate and appropriate management of side effects, and scheduling follow-up at regular intervals to review the side effects are some of the strategies that may be helpful to minimize nonadherence.

**Disease-Specific Issues**

Because the biologic characteristics of certain cancers are different in older patients compared with their younger counterparts and partly because of older adults’ decreased tolerance of treatment, chemotherapy should be individualized based on the nature of the disease and the performance status of the patient.

Disease-specific issues related to age in hematologic malignancies are discussed in the next section. See the discussion section of the complete guidelines at NCCN.org for the disease-specific issues related to age in other cancer types.

**Hematologic Malignancies**

**Acute Lymphoblastic Leukemia:** Acute lymphoblastic leukemia (ALL) in older patients is characterized by a lower incidence of T-cell ALL and the presence of unfavorable chromosomal abnormalities, both of which have been identified as poor prognostic factors. It is strongly recommended that older patients with ALL be treated in a specialized center.

In older patients, intensive multiagent chemotherapy regimens have been associated poor OS, in spite of favorable response rates after induction therapy. In an analysis of 268 patients (≥60 years) with newly diagnosed ALL, induction therapy with vincristine, doxorubicin, and dexamethasone (VAD) induced an overall complete response (CR) in 65% of patients. However, the 3-year OS rate was less than 10%. In a multicenter prospective study that evaluated age-adapted induction chemotherapy followed by maintenance therapy with interferon and chemotherapy, 85% of patients 55 years or older had a CR after completion of induction therapy with a median OS, and DFS was only 14 months. The inferior outcomes have been attributed to treatment-
related mortality (7.5%) during induction and more-resistant disease. A recent randomized phase II trial (GRAALL-SA1) showed that with the use of pegylated doxorubicin in combination with vincristine and dexamethasone, pegylated doxorubicin did not result in any survival benefit over doxorubicin, despite its better toxicity profile (lower risk of cardiotoxicity and myelosuppression), due to a higher rate of induction failure (17% vs 3%; P=.10) and a higher cumulative incidence of relapse (52% vs 32%) at 2 years.236

More recently, O’Brien et al237 reported that dose-intensive induction therapy with the hyper-CVAD regimen induced CR rates of 84% in patients 60 years or older, with an improved 5-year OS rate (20% compared with 9% on regimens that were used before hyper-CVAD) and decreased incidence of disease resistance. However, this regimen was also associated with higher treatment-related mortality (10% vs 2%) during induction and significantly higher incidence of death (34% vs 7%; P<.001) from infections associated with myelosuppression among older patients.

Philadelphia-chromosome (Ph) is the most frequent cytogenetic abnormality in older patients with ALL. Ph-chromosome results from the reciprocal translocation t(9;22) that fuses the BCR gene on chromosome 22 and the ABL gene located on chromosome 9. BCR-ABL tyrosine kinase inhibitors (imatinib and dasatinib) in combination with steroids have been evaluated as induction therapy in older patients with Ph-positive ALL.236,239 In a phase II study of older patients with Ph-positive ALL (n=30; ≥60 years), induction therapy with imatinib and steroids induced complete remissions and prolonged survival without additional chemotherapy.238 Median survival from diagnosis was 20 months. In another phase II study of older patients with Ph-positive ALL (n=30; ≥60 years), induction therapy with imatinib and steroids induced complete remissions and prolonged survival without additional chemotherapy.238 Median survival from diagnosis was 20 months. In another phase II study (n=55; 12 patients were older than 60 years), induction therapy with dasatinib and steroids and intrathecal chemotherapy induced complete remission rates in all patients.239 At 20 months, the OS and DFS rates were 69% and 51%, respectively. In a randomized trial of 55 older patients, induction therapy with imatinib alone resulted in a significantly higher complete remission rate (96% vs 50%; P=.001) with lower toxicity compared with induction chemotherapy.240 Severe adverse events were significantly more frequent with induction chemotherapy (90% vs 39%; P=.005). The OS was not significantly different between the groups. The use of imatinib and steroids as consolidation therapy following induction chemotherapy has also resulted in improved outcomes (compared with historical controls) in older patients with Ph-positive ALL.241

Among patients with CD20-positive and Ph-negative ALL, the benefit of adding rituximab to chemotherapy has been confined only to younger patients. In a study of 282 adolescents and patients with CD20-positive and Ph-negative ALL treated with a modified hyper-CVAD and rituximab, the 3-year complete remission duration was 67% for younger patients compared with 45% for patients 60 years or older.242 The 3-year OS rates were 78% and 45%, respectively.

**AML:** AML in older patients is associated with a poor prognosis. Increasing age, FLT3 internal tandem duplications, unfavorable cytogenetics, increasing white blood cell count, poorer performance status, and the presence of secondary AML are considered poor prognostic indicators in this group of patients.243,244 A retrospective analysis of 968 patients with AML showed a marked increase in the proportion of patients with unfavorable cytogenetics (35% in patients <56 years to 51% in patients >75 years), prevalence of multidrug resistance (33% in patients <56 years compared with 57% in patients >75 years), and treatment-related mortality (especially in patients with poor performance status) within 30 days after induction therapy (82% among patients >75 years).245

In patients 60 years or older, although anthracycline-based induction chemotherapy regimens have resulted in CR rates ranging from 39% to 63%, median OS and DFS have remained poor (7–12 months).246 Despite these poor outcomes, standard intensive treatment has been shown to improve early death and long-term survival rates compared with palliative treatment in most patients with AML up to 75 to 80 years of age.247,248

Induction chemotherapy should be considered for older patients with good performance status and no comorbidities. The optimal chemotherapy regimen is unknown. In a randomized trial (1314 patients older than 56 years) that compared 3 different induction regimens, DAT (daunorubicin, cytarabine, and thioguanine), ADE (cytarabine, daunorubicin and etoposide), and MAC (mitoxantrone and cytarabine), the remission rates in the DAT arm...
were significantly better than in the ADE (62% vs 50%; \(P = 0.02\)) or MAC (62% vs 55%; \(P = 0.04\)) arms, but there were no differences in the 5-year OS rates between the 3 regimens (2% vs 8% vs 10%, respectively).\(^{249}\) The remission or survival rates were also not improved by the addition of granulocyte colony-stimulating factor. In another study of 362 older patients with previously untreated AML (139 patients ≥70 years of age) randomized to receive daunorubicin, idarubicin, or mitoxantrone with a standard dose of cytarabine as induction therapy, no difference in efficacy was seen among the 3 regimens in terms of CR rate, OS, and DFS.\(^{250}\) Conversely, an exploratory analysis of a randomized phase III trial that compared induction chemotherapy with mitoxantrone and etoposide (ME) versus daunorubicin and cytarabine (AD) showed that the use of etoposide with an anthracycline resulted in poor survival rates (11% and 19%, respectively, for ME and AD regimens) in patients with untreated AML older than 55 years of age, although no significant difference in CR rate was seen between the 2 regimens (34% and 43%, respectively, for patients treated with ME and AD). These findings suggest that etoposide should be used in combination with an anthracycline for patients who are considered candidates for induction chemotherapy.\(^{251}\)

Induction therapy with intensified anthracycline doses and cytarabine has not been consistently associated with improved outcomes in older patients.\(^{252–256}\) For example, the LRF AML14 trial did not show any difference in CR rate or OS for patients treated with daunorubicin (50 vs 35 mg/m\(^2\)) and cytarabine (200 vs 400 mg/m\(^2\)) at 2 different dose levels.\(^{251}\) In contrast to these findings, Lowenberg et al\(^{254}\) showed that, in patients older than 60 years, dose escalation of daunorubicin (90 mg/m\(^2\)) resulted in a higher response rate than the conventional dose (45 mg/m\(^2\)), without any additional toxic effects. The CR rate was 64% and 54%, respectively (\(P = 0.002\)) but there was no difference in OS rates. The subgroup analysis showed a potential benefit for dose escalation of daunorubicin in patients 60 to 65 years of age (especially those with core binding factor [CBF] AML) in terms of CR (51% in the conventional-dose group vs 73% in the escalated-dose group), the 2-year DFS (14% vs 29%, respectively), and 2-year OS rates (23% vs 38%, respectively). The results from Acute Leukemia French Association (ALFA) trials (ALFA-9801 and ALFA-9803) also showed that although the use of idarubicin in combination with cytarabine resulted in higher CR rates than daunorubicin, it did not translate into a benefit in OS.\(^{252,253}\) In a more recent report, a combined analysis of these two trials showed that induction therapy with idarubicin was associated with a significantly higher cure rate than daunorubicin (16.6% and 9.8%, respectively; \(P = 0.018\)) in patients 50 years or older.\(^{256}\) In addition to younger age and favorable-risk AML, idarubicin treatment was also identified as a predictor of higher cure rate in multivariate analysis (\(P = 0.04\)), although it did not have any influence on OS (\(P = 11\)).\(^{256}\)

Standard induction chemotherapy is associated with a 10% to 20% risk of death in patients older than 56 years. Prediction tools are available to assist in counseling older patients regarding the safety and efficacy of standard induction chemotherapy. The probability of obtaining a CR and the risk of treatment-related mortality can be calculated using a Web-based tool: http://www.aml-score.org/.\(^{257}\) In view of the seriousness of the complications of AML treatment, older patients with AML should be treated according to the NCCN Guidelines for AML in centers skilled in the management and supportive care of those patients (to view the most recent version of these guidelines, visit NCCN.org).

**Multiple Myeloma:** High-dose therapy followed by autologous stem cell transplantation (HDT/ASCT) is the initial treatment for younger patients. However, the role of this approach in older patients has not yet been established in randomized trials because most of these trials included patients younger than 65 years. There is also lack of consensus on what constitutes transplant eligibility in older patients. Recent reports (mostly from retrospective studies) suggest that ASCT may be beneficial for selected older patients with good performance status and no severe comorbidities.\(^{258–260}\) Initial evaluation should determine whether the patient is a potential candidate for HDT/ASCT. An older patient’s eligibility for transplant should be based on the assessment of their physiologic rather than chronologic age, with specific attention to comorbidities, functional status, and adequate cardiac, pulmonary, renal, and hepatic function. Melphalan-based chemotherapy should be avoided in transplant candidates. Early referral to a transplant physician should be considered if uncertain whether the patient is transplant-eligible before exposure to alkylating agents.
Immunomodulator-Based Combination Therapy: In randomized studies, the addition of thalidomide to the combination of melphalan and prednisone (MP) was associated with significantly superior response rates, progression-free survival (PFS), time-to-treatment progression, and RFS in older patients with newly diagnosed multiple myeloma.\textsuperscript{261–268} However, OS benefit was reported only in 2 of these studies. In the IFM 99-06 trial, which compared melphalan, prednisone, and thalidomide (MPT); MP; and reduced-intensity ASCT; median OS was 51.6, 33.2, and 38.3 months, respectively. The MPT regimen was associated with a significantly better OS than the MP regimen (P=.0006) and reduced-intensity ASCT (P=.027).\textsuperscript{261} In the IFM 01/01 trial, median OS was 44 and 29 months, respectively (P=.028), for older patients (≥75 years) treated with MPT and MP.\textsuperscript{264} MPT was associated with significant toxicity (constipation, fatigue, deep vein thrombosis [DVT], neuropathy, cytopenias, and infection).\textsuperscript{268}

In a double-blind, multicenter, randomized study, induction therapy with melphalan, prednisone, and lenalidomide followed by lenalidomide maintenance (MPR-R) significantly prolonged PFS in patients 65 years or older with newly diagnosed multiple myeloma that were ineligible for HDT/ASCT.\textsuperscript{269} At a median follow-up of 30 months, the median PFS was significantly longer with MPR-R (31 months) than with MPR (14 months; P<.001) or MP (13 months; P=.001). The greatest PFS benefit was observed in patients 65 to 75 years of age.\textsuperscript{269} MPR-R was also associated with higher response rate than MPR or MP (77%, 68%, and 50%, respectively). The results of a landmark analysis showed that MPR-R resulted in a 66% reduction in the rate of progression that was age-independent.

Bortezomib-Based Combination Therapy: Bortezomib-based combinations have been evaluated as initial therapy and maintenance therapy in older patients with untreated multiple myeloma. Induction therapy with bortezomib, melphalan, and prednisone (VMP) was superior to MP alone in patients (median age, 71 years) with newly diagnosed multiple myeloma who were ineligible for HDT/ASCT, and the survival benefit was seen across all age groups.\textsuperscript{270,271} However, the rates of adverse events (peripheral neuropathy, cytopenias, and fatigue) were higher among patients in the VMP group than in the MP group. The subgroup analyses of the VISTA trial showed that VMP resulted in longer OS among patients younger than 75 years compared with those 75 years or older (3-year OS rates were 74.1% and 55.5%, respectively; P=.011).\textsuperscript{271}

In the Spanish randomized trial that evaluated induction therapy with VMP or bortezomib, thalidomide, and prednisone (VTP) followed by maintenance therapy with bortezomib with thalidomide or prednisone in 260 older patients, VTP and VMP resulted in similar response rates (partial response rates were 81% and 80%, respectively) and OS, with different side-effect profiles in the induction phase.\textsuperscript{272} Incidences of infection were higher in the VMP group and VTP was associated with higher incidences of cardiac events. In the maintenance setting, CR rates were higher with bortezomib and thalidomide (46%) compared with bortezomib and prednisone (39%).\textsuperscript{272} In the updated report, the median PFS and the 5-year OS rate were also superior for bortezomib and thalidomide (39 months and 69%, respectively) compared with bortezomib and prednisone (32 months and 50%, respectively), but the differences were not statistically significant.\textsuperscript{273} The achievement of CR was associated with a significantly longer PFS (P<.001) and 5-year OS (P<.001). However, peripheral neuropathy was higher with bortezomib and thalidomide (9%) compared with bortezomib and prednisone (3%).

In another phase III study, the 4-drug combination of bortezomib, melphalan, prednisone, and thalidomide (VMPT) followed by maintenance with bortezomib and thalidomide (VT) was associated with higher response rates and PFS compared with VMP alone but did not result in an improvement in OS.\textsuperscript{274} The 3-year OS rates were 89% and 87%, respectively, for VMPT followed by VT and with VMP (P=.77). VMPT followed by VT was also associated with higher grade 3 or 4 toxicities (neutropenia and cardiologic and thromboembolic events). An updated analysis of this study (with a median follow-up of 47.2 months) showed that the VMPT-VT regimen significantly prolonged OS compared with VMP, especially in patients younger than 75 years (5-year OS rates were 67.8% and 49.9%, respectively; P=.01).\textsuperscript{275} The VMPT-VT regimen also reduced the risk of death by 37% in patients 67 to 75 years of age.

In a phase II study, a sequential approach incorporating bortezomib-based induction therapy (bortezomib, doxorubicin, and dexamethasone) and ASCT
followed by maintenance therapy with lenalidomide improved overall response rates in older patients with newly diagnosed multiple myeloma. These findings have to be confirmed in randomized studies.276

Dexamethasone-Based Combination Therapy: Dexamethasone-based regimens are associated with increased mortality and severe hematologic toxicities compared with MP in older patients with newly diagnosed multiple myeloma who are not eligible for HDT/ASCT.277,278 In a large randomized trial (IFM 95-01) comparing MP with dexamethasone-based regimens (dexamethasone alone or in combination with melphalan or interferon), although no difference was seen in OS among the 4 treatment groups, the response rate was significantly higher in patients receiving dexamethasone and melphalan. The PFS was significantly better for patients receiving MP and melphalan and dexamethasone; however, the toxicities associated with dexamethasone-based regimens (severe pyogenic infections in the melphalan-dexamethasone arm; hemorrhage, severe diabetes, and gastrointestinal and psychiatric complications in the dexamethasone arms) were significantly higher than with MP.277

The results of a recent randomized trial suggest the low-dose dexamethasone used in combination with lenalidomide is associated with better short-term OS and lower toxicity than high-dose dexamethasone and lenalidomide in patients with newly diagnosed myeloma.278 DVT, infection including pneumonia, and fatigue were the most common grade 3 or 4 toxicities.

Deep Vein Thrombosis Prophylaxis: The incidence of venous and arterial thrombosis increases with the use of thalidomide or lenalidomide in combination with chemotherapy or dexamethasone. In a phase III randomized trial, aspirin and fixed low-dose warfarin showed similar safety and efficacy in reducing thromboembolic complications compared with low-molecular-weight heparin (LMWH) in patients with myeloma treated with thalidomide-based regimen, whereas in older patients LMWH was more effective than warfarin.279 DVT prophylaxis with LMWH is recommended for older patients receiving regimens containing thalidomide or lenalidomide.

Myelodysplastic Syndromes: Myelodysplastic syndromes (MDS) are a diverse group of clonal hematologic disorders characterized by ineffective hematopoiesis subsequently leading to cytopenias and potential transformation to AML. In randomized phase III trials, DNA methyl transferase inhibitors such as azacitidine and decitabine have been shown to improve quality of life by decreasing the risk of AML transformation as well as transfusion dependence compared with conventional regimens or best supportive care in patients with high-risk MDS.280–284

The subgroup analysis of the AZA-001 trial demonstrated that azacitidine significantly improved OS compared with conventional care, with no increased risk of toxicity in older patients (≥75 years) with intermediate- or high-risk MDS.285 The 2-year OS rates were 55% and 15%, respectively (P<.001). In a study of 282 patients with high-risk MDS, Itzykson et al286 identified previous treatment with low-dose cytosine arabinoside, bone marrow blasts greater than 15%, and abnormal or complex karyotype as predictors of lower response rates; performance status 2 or greater, intermediate- and poor-risk cytogenetics, presence of circulating blasts, and red blood cell transfusion dependency 4 units/8 weeks or more were independent predictors of poorer OS. For patients with higher-risk MDS, azacitidine is given 7 days in a row. This schedule may be challenging for older patients due to logistic or transportation problems. In a phase II study, azacitidine schedule of 5-2-2 (5 days on, 2 days off, 2 days on) did not seem to negatively impact the response rate or duration of response in patients 65 years or older.287

A recent report from the Spanish Registry of MDS also demonstrated the equal efficacy of 3 different schedules of azacitidine (5-0-0, 5-2-2, and 7 days) in older patients (107 patients; ≥75 years) with low-intermediate risk and intermediate high-risk MDS. Transfusion independence was achieved in 40% of patients. With a median follow-up of 14 months, the median OS was 18 months and the probability of OS at 2 years was 34%.288 A 5-day schedule is not recommended for patients with high-risk MDS. Azacitidine has also been shown to be a feasible and effective treatment for older patients (≥70 years) with low-risk MDS.289,290

In the 2 large studies that included predominantly older patients with low- and high-risk MDS, decitabine (5-day schedule given as 15 mg/m² every 8 hours for 3 days at a dose of 135 mg/m² per course) resulted in durable responses, hematologic, improvement and improved time to AML transformation or death.282,291 However, in a phase III study of 232 older patients with intermediate- or high-risk MDS ineligible for intensive chemotherapy, decitabine resulted
in improvement in PFS (6.6 vs 3.0 months; \( P = .004 \)) and AML transformation (22% vs 33% with best supportive care), but no significant difference was seen in OS (10.1 vs 8.5 months; \( P = .38 \)) and AML-free survival (8.8 vs 6.1 months; \( P = .24 \)) compared with best supportive care.\(^{283} \) Longer duration of MDS and prior therapy were predictive factors for achieving CR, whereas abnormalities of chromosomes 5 or 7, older age, and prior therapy were adverse prognostic factors for survival.\(^{283} \)

Lenalidomide has also been effective in transfusion-dependent patients with low-risk MDS with 5q deletions, resulting in the reduction of transfusion requirements and reversal cytologic and cytogenetic abnormalities.\(^{282,283} \) The drug also has been shown to improve transfusion independence in patients with low-risk MDS without deletion 5q.\(^{284} \) Although the median age of patients included in these studies is early 70s, few data are available regarding the risks and benefits at the extremes of age.

### Summary

Cancer is the leading cause of death in women and men aged 60 to 79 years. The biologic characteristics of certain cancers are different in older patients compared with their younger counterparts, and older patients also have decreased tolerance to chemotherapy. Nevertheless, advanced age alone should not be the only criteria to preclude effective cancer treatment that could improve quality of life or lead to a survival benefit in older patients. Treatment should be individualized based on the nature of the disease, the physiologic status of the patient, and the patient’s preferences.

Chronicologic age is not reliable in estimating life expectancy, functional reserve, or the risk of treatment complications. The best guide as to whether cancer treatment is appropriate may be provided by careful assessment of the older patient. CGA can be used to assess life expectancy and risk of morbidity from cancer in older patients. CGA in turn can enable physicians to develop a coordinated plan for cancer treatment as well as guide interventions tailored to the patient’s problems.

### References


NCCN Clinical Practice Guidelines in Oncology
Senior Adult Oncology, Version 2.2014


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The NCCN Guidelines Staff have no conflicts to disclose.