National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Older Adult Oncology

Version 2.2017 — May 1, 2017

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Older Adult Oncology

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NCCN Guidelines Panel Disclosures

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‡ Hematology oncology
§ Radiation oncology
₪ Geriatric medicine
Þ Internal medicine, including family practice and preventive management
ξ Bone marrow transplantation
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NCCN Guidelines Panel Disclosures

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

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

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

See NCCN Categories of Evidence and Consensus.

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NCCN Guidelines Version 2.2017 Updates Older Adult Oncology

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Updates in Version 2.2017 of the NCCN Guidelines for Older Adult Oncology from Version 1.2017 include:

MS-1: The discussion section was updated to reflect the changes in the algorithm.

Updates in Version 1.2017 of the NCCN Guidelines for Older Adult Oncology from Version 2.2016 include:

OAO-1

- Global Change: The footnotes have been reflowed throughout the guidelines.

OAO-2

- "Does the patient have risk factors for adverse outcomes from cancer treatment?" now links to comorbidity assessment (*See OAO-D*)

Assessment of Risk Factors:

- "Treat as recommended in disease-specific treatment guidelines (NCCN Guidelines for Treatment of Cancer by Site) See Disease-Specific Issues Related to Age (OAO-C) *and considerations for older adults undergoing cancer treatments* (OAO-3)"

OAO-3

- Title of page modified: "~~Special~~ *Considerations for* ~~Patients Able to Tolerate~~ *Older Adults Undergoing Cancer Treatments*" (Also for OAO-4)
- Systemic therapy: *Updated the JCO reference for Cancer and Aging Research Group*

OAO-4

- Neurotoxicity, omitted: "Consider alternative regimens with non-neurotoxic drugs"
- Falls, modified: "*Periodic* assessment of history of falls, balance, and gait difficulties is recommended for all patients *as fall risk may change over time"*
- Added: *"The use of early and preventative use of durable medical equipment and in-home safety evaluations is recommended for patients with neurotoxicities at high risk for falls."*
- Modified: Cardiac toxicity: "Caution with use of anthracyclines; consider alternative treatment *dosing schedule or* treatment *as appropriate per disease site*. See NCCN Guidelines for Treatment of Cancer by Site."
- Renal toxicity, modified: "~~Calculate creatinine clearance to assess renal function~~ and ~~Adjust dose for glomerular filtration rate to reduce systemic toxicity~~ *Serum creatinine is not a good indicator of renal function in older adults. Calculation of creatinine clearance is recommended to assess renal function and adjust dose to reduce systemic toxicity."*

OAO-B

- *"Optimizing Communication with Older Adults"* is new to the guidelines.

OAO-C (3 of 32)

Disease-Specific Issues Related to Age

Acute Myeloid Leukemia:

- 2nd bullet, 2nd and 3rd sentence modified: "...however, a post-hoc analysis showed a potential benefit to the higher dose of daunorubicin in patients ~~older than~~ *age 60*–65 years, especially in those with CBF-AML. *However,* ~~*doses*~~ *in clinical practice* ~~*of*~~ *daunorubicin are typically given at 60–90 mg/m² as data show no difference between these two doses.* ~~*Alternatively*~~ *Idarubicin 12 mg/m² is a valid alternative*."
- Removed: "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. Therefore, if standard induction chemotherapy (off protocol) is given, an ARA-C-containing regimen should be utilized"

Footnotes:

- Removed footnote "6": "Anderson JE, Kopecky KJ, Willman CL, et al. Outcome after induction chemotherapy for older patients with acute myeloid leukemia is not improved with mitoxantrone and etoposide compared to cytarabine and daunorubicin: a Southwest Oncology Group study. Blood 2002;100:3869-3876."
- Added footnote "8": *"Burnett AK, Russell NH, Hills RK, et al. A randomized comparison of daunorubicin 90 mg/m² vs 60 mg/m² in AML induction: results from the UK NCRI AML 17 trial in 1206 patients. Blood 2015 125(25):3878-3885."*

OAO-C (8 of 32)

Disease-Specific Issues Related to Age

Central Nervous System Cancers:

- Glioblastoma has been modified to "*Glioblastoma Multiforme (GBM)*"

Surgery:

- First sentence has been modified: "Patients older than 70 years with ~~glioblastoma~~ *GBM* who are treated surgically with gross total resection achieve a greater *overall survival* (OS) than those who are treated with lesser resection."

Adjuvant therapy:

- Radiation therapy has been changed to "*RT*" throughout.
- 1st bullet, 3rd sentence has been modified: "Typical fractionation schedules are 34 Gy/10 fractions, ~~or~~ 40~~.05~~ Gy/15 fractions, *or 25 Gy/5 fractions* with a new corresponding reference."

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Updates in Version 1.2017 of the NCCN Guidelines for Older Adult Oncology from Version 2.2016 include:

OAO-C (10 of 32)
Disease-Specific Issues Related to Age
- Title modified: "Chronic ~~Myelogenous~~ *Myeloid* Leukemia"

OAO-C (12 of 32)
Disease-Specific Issues Related to Age
Colon Cancer:
- 5-FU changed to *fluorouracil* throughout the page (Also for Rectal Cancer).

OAO-C (23 of 32)
Disease-Specific Issues Related to Age
Myelodysplastic Syndromes:
Allogeneic Hematopoietic ~~Stem~~ Cell Transplantation
- "Among 372 patients aged 60 to 75 years with a variety of hematologic malignancies (eg, AML, MDS, CLL, lymphoma, multiple myeloma) enrolled in prospective allogeneic ~~stem~~ hematopoietic cell transplant (HCT)..."
- "There are a lack of prospective data regarding ~~transplant~~ allogeneic HCT in older adults with MDS; however, retrospective reviews demonstrate that older patients with MDS who were selected to undergo allogeneic ~~stem cell transplant~~ HCT...In a retrospective analysis of 514 patients with de novo MDS (ages 60–70 years), reduced-intensity allogeneic HCT ~~stem cell transplants were~~ was not associated with an improved life..."

OAO-D (1 of 7) Comprehensive Geriatric Assessment
- Collaboration with the Oncologist in the Care of an Older Patient with Cancer: the following is new to the page:
  - *"Older adults may benefit from a referral to a Geriatrician for risk stratification prior to cancer treatment, to develop a coordinated plan of care with the oncologist and/or to manage geriatric syndromes that could jeopardize outcomes of cancer treatment. The geriatrician thus may be able to assist the oncologist in optimizing the management of the non-cancer aspects of the patient's care which in turn may enable more effective delivery of direct cancer care. Consider consultation to a Geriatrician for the following:*
- *Cognitive impairment*
  - *Dementia/Delirium*
  - *Decision-making capacity evaluation*
  - *Life expectancy, advance care planning, guardianship*
- *Functional or physical impairment, mobility issues, or disability*
  - *Falls evaluation and/or advice on falls prevention"*
  - *"Promote independent living or supportive living*
- *Multimorbidity including vision and hearing impairments*
- *Polypharmacy evaluation*
- *When considering a high-risk procedure, such as:*
  - ~~Patient at high risk for~~ Chemotherapy and radiotherapy ~~toxicity~~
  - ~~Stem~~ *Hematopoietic cell transplant*
  - *Complex surgeries (example: cystectomy)*
- *Presence of geriatric syndromes such as*
  - Pressure ulcers, urinary incontinence, depression, osteoporosis, neglect or abuse, failure to thrive, or sarcopenia; frailty
- *Weight loss (>7 lbs in last 3 months) and anorexia"*

OAO-D (2 of 7) Comprehensive Geriatric Assessment
Functional status
- Modified: "Activities of Daily Living (ADL) - *Self-feeding*, ~~Eating~~..."
- Falls and/or unstable gait
  - In patients who are at risk, such as those 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 *by evaluating gait speed or* using Timed Up and Go (TUG) test (Also for OAO-E)

OAO-D (3 of 7) Comprehensive Geriatric Assessment
Comorbidities
- *"Methods to assess comorbidities: (Charleson Comorbidities Index, CIRS, and OARS)"* is new to the page

OAO-D (5 of 7) Comprehensive Geriatric Assessment
Comorbidities
- *Care Process for Older Adults with Cancer* is a new table in the guidelines.

OAO-F (2 of 2) Assessment of Cognitive Function
Mild Cognitive Impairment
- Screening tool: Modified: "Clinical interview with cognitive (*Mini-Cog*) and functional (ADL/IADL) assessment (*See OAO-D*)." (Also for Dementia)
- Further Evaluation, 2nd bullet modified: "*If screening is abnormal* ~~Consider~~ consult~~ation~~ with a clinician experienced in cognitive evaluation." (Also for Delirium)

References
- "3": "*If you have concerns about decision-making capacity see (OAO-1)"* corresponds to the title of the page.

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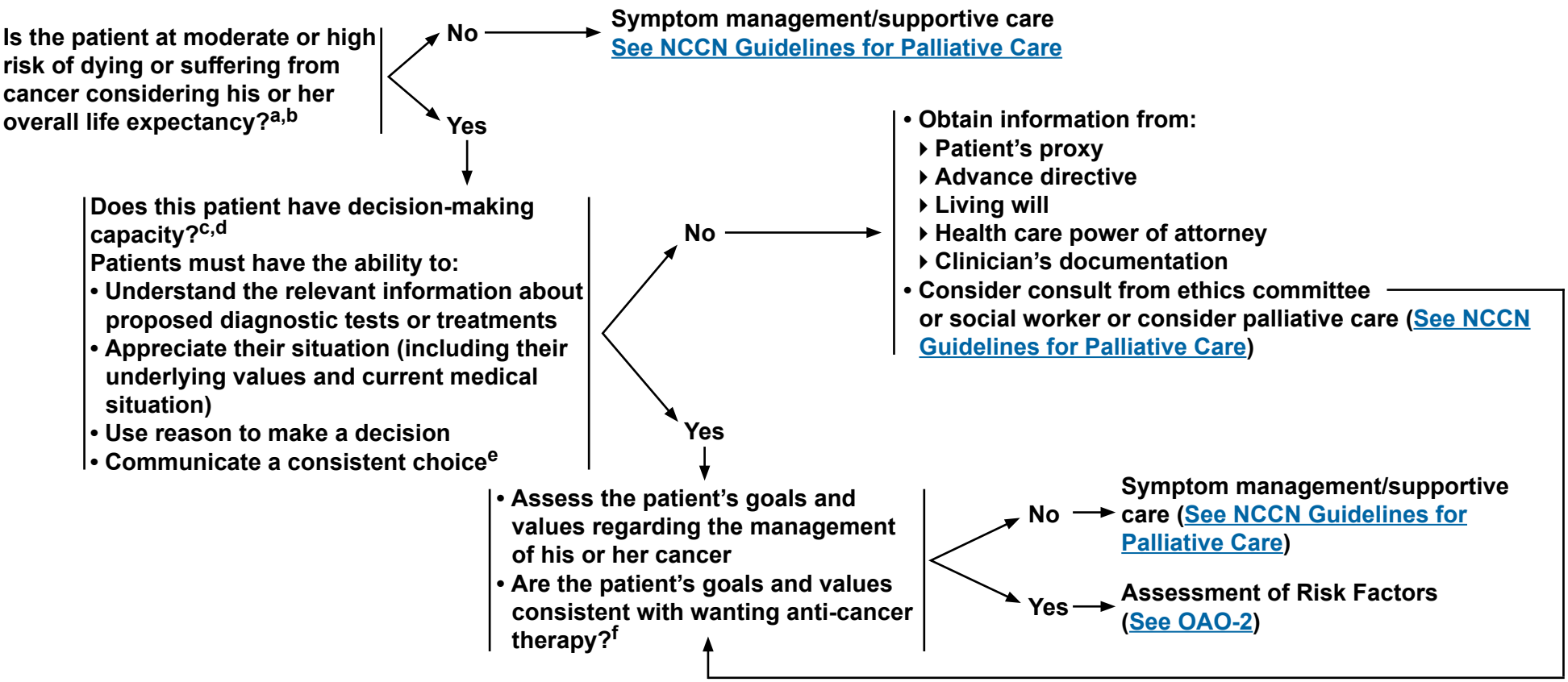
APPROACH TO DECISION MAKING IN THE OLDER ADULT[e]



[a]Life expectancy calculators are available at www.eprognosis.com. Note that these calculators are used to determine anticipated life expectancy (independent of the cancer). They could be utilized in clinical decision-making to weigh whether the cancer is likely to shorten the patient's life expectancy or whether the patient is likely to become symptomatic from cancer during his or her anticipated life expectancy. Note that these calculators should be used in conjunction with clinical judgment.

[b]See histograms for age-specific life expectancy (OAO-A).

[c]Sessums LL, Zembrzuska H, Jackson JL. Does this patient have medical decision-making capacity? JAMA 2011;306(4):420-427. Copyright © (2012) American Medical Association. All rights reserved.

[d]McKoy JM, Burhenn PS, Browner IS, et al. Assessing cognitive function and capacity in older adults with cancer. J Natl Compr Canc Netw 2014;12(1):138-144.

[e]See Optimizing Communication with Older Adults (OAO-B)

[f]Harrington SE, Smith TJ. The role of chemotherapy at the end of life: when is enough, enough? JAMA 2008;299:2667-2678.

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ASSESSMENT OF RISK FACTORS[g]

Does the patient have risk factors for adverse outcomes from cancer treatment? (See OAO-D)

- **Comorbidities[g]**
  - **cardiovascular disease[h]**
  - **renal insufficiency[i]**
  - **neuropathy**
  - **anemia**
  - **osteoporosis**
    - ◊ See NCCN Bone Health Task Force
  - **liver disease**
  - **diabetes**
  - **lung disease**
  - **hearing or vision loss**
  - **prior cancer diagnosis and treatment**
  - **chronic infections**
  - **decubitus or pressure ulcers**
- **Geriatric syndromes[g]**
  - **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**

No → **Treat as recommended in disease-specific treatment guidelines (See NCCN Guidelines for Treatment of Cancer by Site) See Disease-Specific Issues Related to Age (OAO-C) and Considerations for Older Adults Undergoing Cancer Treatments (OAO-3)**

Yes → **Are the risk factors modifiable?**

No → **Are there alternate treatment options that would reduce toxicity to an acceptable level?**

No → **See NCCN Guidelines for Supportive Care**

Yes → **See Considerations for Older Adults Undergoing Cancer Treatments (OAO-3) and (OAO-4) and see NCCN Guidelines for Supportive Care**

Yes → **Treat risk factors** → **See Considerations for Older Adults Undergoing Cancer Treatments (OAO-3) and (OAO-4) and see NCCN Guidelines for Supportive Care**

[g] See Comprehensive Geriatric Assessment (OAO-D).
[h] Older age has been associated with increased risk for congestive heart failure (CHF) in patients receiving cytotoxic and targeted therapies.
[i] The panel recommends calculation of creatinine clearance to assess renal function for all patients.

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CONSIDERATIONS FOR OLDER ADULTS UNDERGOING CANCER TREATMENTS[j,k]

Surgery

- 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.[1] These guidelines can be applied to older cancer patients undergoing surgery.
- There are data to suggest that an increased need for functional assistance pre-surgery (measured by ADL, IADL, and PS) predicts postoperative complications, extended hospital stay, and 6-month mortality in older patients undergoing cancer surgery.[2-4]
- Impaired cognitive status is a risk factor for postoperative complications, prolonged length of stay, and 6-month overall mortality postoperatively.[2,5]
- In patients undergoing general surgery
  http://site.acsnsqip.org/wp-content/uploads/2011/12/ACS-NSQIP-AGS-Geriatric-2012-Guidelines.pdf
  - Older age is a risk factor for postoperative delirium.[6]
  - Delirium is a risk factor for functional and cognitive decline.[7] See Assessment of Cognitive Function (OAO-F)
- Preventive measures exist for delirium
  - Yale Delirium Prevention Trial and Hospital Elder Life Program (HELP): http://www.hospitalelderlifeprogram.org/
  - National Institute for Health and Clinical Excellence (NICE) Guideline for Prevention of Delirium: http://publications.nice.org.uk/delirium-cg103

Radiation 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.

Systemic therapy

- 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) and https://www.ncbi.nlm.nih.gov/pubmed/27185838

Diarrhea

- Rule out other medical causes of diarrhea before starting anti-diarrhea drugs
- Consider early aggressive rehydration
- Manage with octreotide if oral preparations are ineffective

Constipation

- See NCCN Guidelines for Palliative Care

Nausea/ vomiting

- See NCCN Guidelines for Antiemesis and NCCN Guidelines for Palliative Care

Systemic Therapy Continued on OAO-4

[j]Monitor the patient's functional status, comorbidities, social circumstances, pain, nutritional status, and distress.
[k]See Disease-Specific Issues Related to Age (OAO-C).

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CONSIDERATIONS FOR OLDER ADULTS UNDERGOING CANCER TREATMENTS[j,k]

Systemic Therapy

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

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
- 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
- Monitor for cognitive dysfunction See OAO-F

Falls
- Periodic assessment of history of falls, balance, and gait difficulties is recommended for all patients as fall risk may change over time[8] (See Comprehensive Geriatric Assessment OAO-D 1 of 7)
- The use of early and preventative use of durable medical equipment and in-home safety evaluations is recommended for patients with neurotoxicities at high risk for falls.

Cardiac toxicity
- Monitor for symptomatic or asymptomatic congestive heart failure (CHF)
  - Caution with use of anthracyclines; consider alternative treatment dosing schedule or treatment as appropriate per disease site. See NCCN Guidelines for Treatment of Cancer by Site.
  - Caution with use of trastuzumab (among patients with normal LVEF, risk factors for CHF include older age, receipt of an anthracycline-based regimen, baseline LVEF of 50%–54%, coronary artery disease, hypertension, and weekly trastuzumab administration).[9,10,11]

Renal toxicity
- Serum creatinine is not a good indicator of renal function in older adults. Calculation of creatinine clearance is recommended to assess renal function and adjust dose to reduce systemic toxicity.

Insomnia[l]
- Benzodiazepines or other sedative-hypnotics should not be used as first-line treatment for insomnia in older adults.[12]
- Non-pharmacologic methods such as cognitive behavioral therapy and lifestyle modifications are preferred.
- See NCCN Guidelines for Survivorship for Sleep Disorders

Systemic Therapy Continued on OAO-5

[j]Monitor the patient's functional status, comorbidities, social circumstances, pain, nutritional status, and distress.
[k]See Disease-Specific Issues Related to Age (OAO-C).
[l]See Insomnia (OAO-H).

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References

[1]Chow WB, Rosenthal RA, Merkow RP, et al. Optimal preoperative assessment of the geriatric surgical patient: a best practices guideline from the American College of Surgeons National Surgical Quality Improvement Program and the American Geriatrics Society. J Am Coll Surg 2012;215(4):453-66.
[2]Fukuse T, Satoda N, Hijiya K, et al. Importance of a comprehensive geriatric assessment in prediction of complications following thoracic surgery in elderly patients. Chest 2005;127(3):886-91.
[3]Audisio RA, et al. Shall we operate? Preoperative assessment in elderly cancer patients (PACE) can help. A SIOG surgical task force prospective study. Crit Rev Oncol Hematol 2008;65(2):156-63.
[4]Robinson TN, Eiseman B, Wallace JI, et al. Redefining geriatric preoperative assessment using frailty, disability and co-morbidity. Ann Surg 2009;250(3):449-55.
[5]Robinson TN, Wu DS, Pointer LF, et al. Preoperative cognitive dysfunction is related to adverse postoperative outcomes in the elderly. J Am Coll Surg 2012;215(1):12-7; discussion 17-8.
[6]Marcantonio ER, Goldman L, Mangione CM, et al. A clinical prediction rule for delirium after elective non-cardiac surgery. JAMA 1994;271(2):134-9.
[7]Inouye SK, Westendorp R, Saczynski JS. Delirium in elderly people. Lancet 2014;383(9920):911-922.
[8]Tinetti ME. Clinical practice. Preventing falls in elderly persons. N Engl J Med 2003;348:42-49.
[9]Piccart-Gebhart M, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005;353:1659-1672.
[10]Romond E, Perez E, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005;353(16):1673-1684.
[11]Chavez-MacGregor M, Zhang N, Buchholz TA, et al. Trastuzumab-related cardiotoxicity among older patients with breast cancer. J Clin Oncol 2013;31:4222-4228.
[12]American Geriatrics Society: Five things Physicians and Patients Should Question (http://www.choosingwisley.org/doctor-patient-lists/american-geriatrics-society/).

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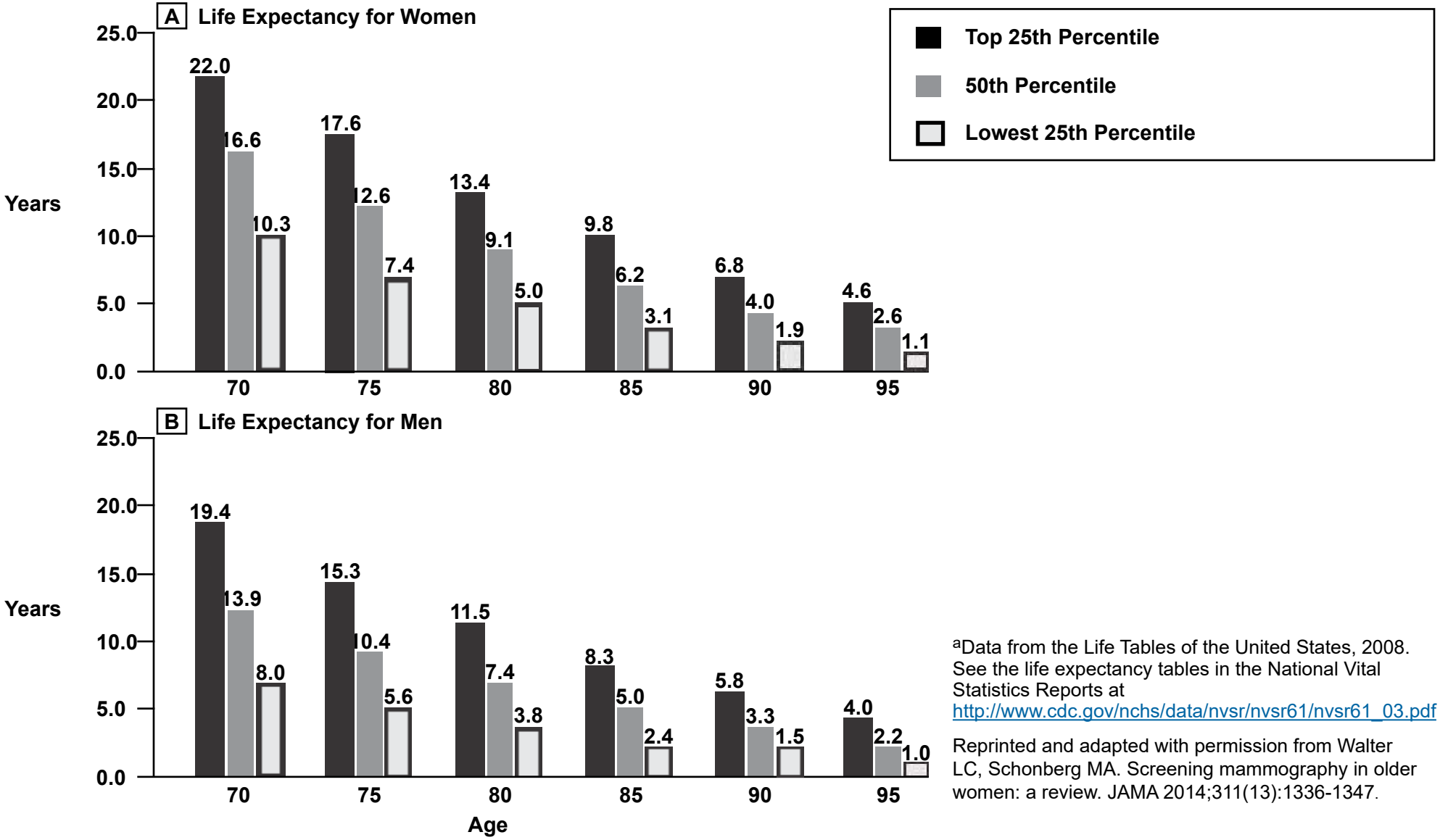
UPPER, MIDDLE, AND LOWER QUARTILES OF LIFE EXPECTANCY FOR WOMEN AND MEN AT SELECTED AGES[a]



[a]Data from the Life Tables of the United States, 2008. See the life expectancy tables in the National Vital Statistics Reports at http://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_03.pdf

Reprinted and adapted with permission from Walter LC, Schonberg MA. Screening mammography in older women: a review. JAMA 2014;311(13):1336-1347.

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OPTIMIZING COMMUNICATION WITH OLDER ADULTS[a]

General:
Optimize vision – glasses if needed
Optimize hearing – hearing aid, amplifying device (eg, pocket talker)
Avoid jargon (eg, instead of "benign" use "not cancer" or instead of "metastasized" use "the cancer has spread")

Written materials:
Write materials at the 5th grade level
Use a large font (14 pt or larger)
Use pictures that enhance the text
Use black ink on white paper to optimize contrast

Oral communication:
Ask the patient how best to communicate, and if hearing is better in one ear or the other
Have the patient sit with his/her back to a wall (to help reflect sound)
Speak toward the better ear and use a lower-pitched voice
Face the patient when speaking, speak slowly and distinctly; don't shout
Rephrase rather than repeat
Pause at the end of phrases or ideas
After each key concept, topic, or instruction, stop and ask, "What questions do you have?"
For major concepts (prognosis, expected side effects, outcomes of treatment, and informed consent) always use the "teach back" or "teach goal" method, by querying the patient for understanding. Use questions such as: "I just gave you a lot of information and that can be confusing or a lot to absorb at once. Can you tell me in your own words what this chemotherapy will do for you/how you will take your medicine, etc?"
Use a black board/white board or written materials to reinforce key concepts

[a]With permission from Reuben DB, Herr KA, Pacala JT, et al. Geriatrics At Your Fingertips: 2016, 18th Edition. New York: The American Geriatrics Society; 2016.

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DISEASE-SPECIFIC ISSUES RELATED TO AGE

This section of the guidelines includes data that are specific to the care of older adults with the following cancer types. See NCCN Guidelines for Treatment of Cancer by Site (www.nccn.org) for further details regarding specific treatment options.

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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 Acute Lymphoblastic Leukemia

- **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 Acute Lymphoblastic Leukemia Studies

- **Hyper CVAD in older patients with ALL results in higher CR rates and OS (compared to historical regimens); however, there is a higher risk of myelosuppression-related deaths. Of note, the dose of Ara-C was reduced to 1 gm/m^2 in patients >60 years.[5]**
- **A randomized phase II study of pegylated liposomal doxorubicin vs. continuous infusion doxorubicin in patients older than 55 years with ALL demonstrated no benefit to pegylated liposomal doxorubicin vs. continuous infusion doxorubicin.[6]**
- **The benefit of adding rituximab to chemotherapy in older adults with Ph(-) CD20-positive ALL has not been demonstrated.[7]**

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*For comparison of efficacy and toxicity of various targeted therapies between younger and older patients, see Gonsalves W, Ganti AK. Targeted anti-cancer therapy in the elderly. Crit Rev Oncol Hematol 2011;78:227-242.

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DISEASE-SPECIFIC ISSUES RELATED TO AGE

Acute Myeloid Leukemia

See NCCN Guidelines for 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 therapy-related AML or AML arising from prior myelodysplasia or chemotherapy or radiation. Prediction tools are available to assist in counseling older adults regarding the safety and efficacy of standard induction chemotherapy.[1-4] Standard induction chemotherapy is associated with a 10%–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 utilizing a web-based tool[5]: http://www.aml-score.org/.**
- **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.[6] 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 mg/m² 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 age 60–65 years, especially in those with CBF-AML.[7] However, in clinical practice daunorubicin is typically given at 60–90 mg/m² as data show no difference between these two doses.[8] Idarubicin 12 mg/m² is a valid alternative.**

[1]Goldstone AH, Burnett AK, Wheatley K, et al. Attempts to improve treatment outcomes in acute myeloid leukemia (AML) in older patients: the results of the United Kingdom Medical Research Council AML11 trial. Blood 2001;98:1302-1311.
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DISEASE-SPECIFIC ISSUES RELATED TO AGE

Bladder Cancer

See NCCN Guidelines for Bladder Cancer

- **BCG treatment for superficial bladder carcinoma has decreased efficacy in the very old (older than 80 years).[1,2]**
- **Age alone should not be a criterion for decisions regarding cystectomy, radiation therapy, and chemotherapy in older patients.[3,4]**
- **The improvement in disease-specific survival from neoadjuvant chemotherapy is preserved with age.[4]**
- **Older patients in RTOG protocols appear to have similar response rates and disease-specific survival compared to younger patients following curative intent selective bladder preservation.[5]**
- **Older age does not appear to be associated with worse late pelvic toxicity after curative intent selective bladder preservation.[6]**
- See NCCN Guidelines for Bladder Cancer

[1]Joudi FN, Smith BJ, O'Donnell MA, Konety BR. The impact of age on the response of patients with superficial bladder cancer to intravesical immunotherapy. J Urol 2006;175:1634-1639.
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DISEASE-SPECIFIC ISSUES RELATED TO AGE

Breast Cancer*

See NCCN Guidelines for Breast Cancer

- Multiple studies have shown that older women often do not receive "standard of care" treatment, and do not do as well as younger women with the same stage of breast cancer.
- Women older than 75 years receive less aggressive treatment and have higher mortality from early-stage breast cancer than younger women.[1-3] Biologic as well as chronologic age should be considered in selecting treatments for older women with breast cancer.

Surgery:

- Women who do not undergo axillary lymph node (ALN) dissection, sentinel lymph node (SLN) biopsy, or ALN irradiation may be at increased risk for ipsilateral lymph node recurrence, especially if they fail to undergo standard adjuvant systemic therapy.
- In the absence of definitive data demonstrating superior survival from the performance of ALN dissection,[4-6] in patients 65 years or older with no palpable axillary lymph nodes, performance of ALN dissection or SLN dissection may be considered optional for the following patients:
  - patients with particularly favorable tumors
  - patients for whom the selection of adjuvant systemic therapy is unlikely to be affected
  - older patients or for patients with serious comorbid conditions (See NCCN Guidelines for Breast Cancer)

Radiation Therapy:

- In patients 70 years or older, omission of radiation therapy can be considered for patients with stage I estrogen receptor-positive breast cancer who undergo a lumpectomy with negative margins and who are likely to complete 5 years of endocrine therapy. Omission of radiation therapy has been associated with a modest increased risk of local recurrence (4% vs. 1% at 5 years; 10% vs. 2% at 10 years); however, there has been no difference in OS or distant metastatic disease.[7,8]

Primary Endocrine Therapy:

- At the current time, primary endocrine therapy should be reserved for patients who are not surgical candidates (including predicted life expectancy to less than 5 years).[9]

Adjuvant Therapy:

- A select group of older adults is enrolled in clinical trials. A review of CALGB studies for node-positive breast cancer demonstrated that only 8% (542/6487) of patients enrolled in cooperative group trials were 65 years and older and only 2% (159/6487) of patients were 70 years or older.[10]
- Older adults (65 years or older) with breast cancer enrolled in cooperative group trials of adjuvant chemotherapy derive similar benefits (disease-free survival and OS) compared to younger patients. However, older patients have an increased risk of side effects and treatment-related mortality.[11]
- In the adjuvant treatment of breast cancer, single-agent capecitabine is inferior to either cyclophosphamide, methotrexate, and fluorouracil (CMF) or doxorubicin and cyclophosphamide (AC) in patients 65 years or older. Unplanned subset analysis suggested that the greatest difference was seen in women with hormone-receptor-negative tumors.[11]
- The results of the randomized phase III trial (ELDA) showed that weekly docetaxel did not improve disease-free survival compared to CMF as adjuvant treatment for older women (65–79 years) with early breast cancer. Docetaxel was associated with severe nonhematologic toxicity and worse quality of life.[12]

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Continue

DISEASE-SPECIFIC ISSUES RELATED TO AGE

Metastatic Disease:

- **A randomized, double-blind, placebo-controlled phase III study investigating the efficacy and safety of pertuzumab, trastuzumab, and docetaxel compared with placebo, trastuzumab, and docetaxel in patients with HER2-positive first-line metastatic breast cancer showed that the combined use of pertuzumab, trastuzumab, and docetaxel resulted in superior progression-free survival (PFS) in older patients. Patients ≥65 years treated with pertuzumab, trastuzumab, and docetaxel experienced diarrhea, neutropenia, and dysgeusia more frequently compared to patients age ≥65 years treated with placebo, trastuzumab, and docetaxel. Patients ≥65 years (in comparison with those <65 years) were more likely to experience diarrhea, decreased appetite, vomiting, fatigue, asthenia, and dysgeusia. In contrast, older adults were less likely to experience neutropenia and febrile neutropenia; however, older adults were more likely to have dose reductions and a lower number of median cycles of docetaxel, possibly explaining these findings.[13]**
- **A randomized, double-blind, placebo-controlled phase III study investigating the efficacy and safety of everolimus with exemestane versus exemestane plus placebo in patients with HER2-negative, hormone receptor positive breast cancer showed that treatment with everolimus plus exemestane was associated with an improvement in PFS regardless of patient age. Treatment with everolimus plus exemestane (compared to exemestane plus placebo) was associated with increased risk of stomatitis, pneumonitis, infection, rash, and hyperglycemia. Older adults had a similar adverse event profile compared to younger adults; however, older adults were more likely to experience on-treatment death. Cautious monitoring and appropriate dose reductions or interruptions for adverse event management are recommended during treatment with everolimus.[14]**
- **A recently published population-based retrospective study of patients 66 years and older who were diagnosed with stage I-III breast cancer and have been treated with trastuzumab demonstrate a CHF rate of almost 30%, which is substantially higher than the rate reported in the clinical trials. Among patients treated with trastuzumab, the rate of CHF was associated with weekly administration of trastuzumab, older age, hypertension, anthracycline use, increases in comorbidities (based on the Charlson comorbidity scale), coronary artery disease, and patients who are non-Hispanic black. Patients who did not receive trastuzumab were more likely to receive anthracycline-based treatment.[15]**

Surveillance:

- **Decisions about mammograms for older breast cancer survivors should incorporate discussions with patients about their risk of developing a recurrent or new breast cancer, the potential benefits of mammography in improving outcomes, the potential harms of mammography (including false positives and overdiagnosis/overtreatment), and patients' values and preferences.[16]**

  Some key points include:

  - **Breast cancer survivors continue to have an increased risk of recurrence or new primaries that is higher than the general population (the risk is about 4%–5% over 5 years).**
  - **Regular mammograms may be helpful in finding these cancers early and improving outcomes, but mammograms also have harms, including false positives, unnecessary biopsies, and finding cancers that never would have become clinically significant in a woman's lifetime (overdiagnosis).**
- **There likely is no benefit to regular mammograms for older women with a life expectancy of less than 5 years. In this group, the harms of mammographic screening among asymptomatic women probably outweigh any potential benefits that the patient might experience.**

Continue

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Breast Cancer*

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*For comparison of efficacy and toxicity of various targeted therapies between younger and older patients, see Gonsalves W, Ganti AK. Targeted anti-cancer therapy in the elderly. Crit Rev Oncol Hematol 2011;78:227-242.

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DISEASE-SPECIFIC ISSUES RELATED TO AGE

Central Nervous System Cancers*

See NCCN Guidelines for Central Nervous System Cancers

Glioblastoma Multiforme (GBM)

Surgery:

- Patients older than 70 years with GBM who are treated surgically with gross total resection achieve a greater overall survival (OS) than those who are treated with lesser resection. Just as in younger patients, it is difficult to be certain that this is a direct effect of the surgical procedure or a result of selection bias.[1,2]

Adjuvant Therapy:

- Postsurgical radiation therapy (RT) alone is effective in improving outcomes in patients older than 70 years with GBM, and shorter course regimens are reasonable to consider. Hypofractionated accelerated course RT (with the goal of completing the treatment in 2–3 weeks) is a reasonable treatment option for older patients. Typical fractionation schedules are 34 Gy/10 fractions, 40 Gy/15 fractions,[3,4] or 25 Gy/5 fractions.[5]
- For anaplastic astrocytomas and GBM in patients older than 64 years, temozolomide alone is non-inferior to RT alone. Temozolomide alone produces improved event-free survival over radiation alone in tumors with a methylated promoter for the methylguanine methyltransferase (*MGMT*) gene (in an unplanned subset analysis).[6] In patients with GBM who are older than 70 years, hypofractionated RT alone over two weeks OR temozolomide alone each produce an OS benefit compared to standard fractionated RT over six weeks. This study also confirms the predictive benefit of MGMT promoter methylation status with temozolomide use.[7]
- The addition of temozolomide concurrently with RT followed by at least 6 months of adjuvant temozolomide improves survival in patients between 60 and 70 years of age.[8]
- Hypofractionated accelerated course RT with concurrent and adjuvant temozolomide is safe in older patients, and may have comparable survival and less toxicity to standard fractionated RT with concurrent and adjuvant temozolomide.[9,10] Hypofractionated accelerated course RT with concurrent and adjuvant temozolomide has been shown to be superior to hypofractionated accelerated course RT in a randomized controlled trial of patients with newly diagnosed GBM ≥65 years of age.[11]

Recurrent Disease:

- In recurrent glioblastoma, bevacizumab likely improves quality of life (and possibly OS) in patients 55 years and older.[12]

Primary Central Nervous System Lymphoma:

- Patients older than 60 years with primary central nervous system lymphoma should be treated primarily with chemotherapy, saving radiation for palliative therapy.[13,14]

Continue

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DISEASE-SPECIFIC ISSUES RELATED TO AGE
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Central Nervous System Cancers*

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DISEASE-SPECIFIC ISSUES RELATED TO AGE

Chronic Myeloid Leukemia*

See NCCN Guidelines for Chronic Myeloid Leukemia

Imatinib

- There are limited prospective data regarding the use of imatinib in older adults with chronic myeloid leukemia (CML). The available data suggest that the approach to treatment should be similar across the age spectrum, and that dose adjustments should be based on toxicity, not age.[1-5]

Dasatinib

- Dasatinib 140 mg may be associated with greater risk of toxicity in older adults.[6]
- Underlying pulmonary disease may be associated with an increased risk of pleural effusion in older adults with chronic phase CML.[7]

Nilotinib

- Underlying cardiovascular disease risk factors appear to be associated with an increased risk of cardiovascular adverse events, including peripheral artery occlusion and myocardial infarction, during treatment with nilotinib.[8]
- Treatment with nilotinib is associated with metabolic effects, including hyperglycemia and hyperlipidemia.[9,10]
- The clinician should check a fasting lipid profile and glucose levels prior to initiation of therapy and consider serial monitoring while on nilotinib.[11] See NCCN Guidelines for Chronic Myeloid Leukemia.

Bosutinib

- In subgroup analysis, the efficacy of bosutinib appeared similar in older and younger adults, but older adults were at greater risk for grade 3 or 4 adverse events (particularly diarrhea) and treatment discontinuation due to adverse events.[12]

Ponatinib

- In a phase II trial of ponatinib, age >65 years was associated with a lower rate of major cytogenetic response (40% vs. 62% in 45–64 years age group, *P* = .0016); [13] older age and cardiovascular risk factors were associated with higher likelihood of arterial thrombotic events.[14]

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Continue

DISEASE-SPECIFIC ISSUES RELATED TO AGE
(References)

Chronic Myeloid Leukemia*

See NCCN Guidelines for Chronic Myeloid Leukemia

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*For comparison of efficacy and toxicity of various targeted therapies between younger and older patients, see Gonsalves W, Ganti AK. Targeted anti-cancer therapy in the elderly. Crit Rev Oncol Hematol 2011;78:227-242.

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DISEASE-SPECIFIC ISSUES RELATED TO AGE

Colon Cancer*

See NCCN Guidelines for Colon Cancer

Surgery:

- Age alone should not be a contraindication for curative surgery in early-stage colon cancer and in resectable metastatic colon cancer. Careful preoperative planning and non-emergent surgery are more likely to result in optimal outcomes.[1-5]

Adjuvant Therapy:

- Older adults derive the same relative benefit as younger patients (in terms of disease-free survival and OS) with fluorouracil-based therapy for adjuvant treatment. Older adults are at increased risk for hematologic toxicities.[6]
- The relative benefit from adjuvant treatment is similar across age groups; however, the absolute benefit of chemotherapy may be smaller due to competing causes of death.
- Pooled data from adjuvant studies did not show a benefit in disease-free or OS for the addition of oxaliplatin to fluorouracil-based therapy in patients older than 70 years. Other analyses of patients 75 years and older show a limited magnitude of benefit for oxaliplatin over non-oxaliplatin-based regimens. Due to the lack of prospective data, adjuvant, oxaliplatin-based therapy in adults 70 years and older should be considered on an individual basis.[7,8,9]

Metastatic Disease:

- Older adults derive the same relative benefit as younger patients (in terms of disease-free survival and OS) with fluorouracil-based therapy for metastatic treatment. Older adults are at increased risk for hematologic toxicities.[10]
- Stop-and-go or maintenance monotherapy strategies during combination chemotherapy may be desirable for older patients to minimize toxicity.[11]
- A prospective study evaluated treatment options for patients not eligible for standard combination chemotherapy. The addition of dose-reduced oxaliplatin to fluorouracil or capecitabine failed to demonstrate significant improvement in PFS. The same study showed a higher rate of grade 3 toxicity with capecitabine compared with fluorouracil without improvement in quality of life.[12]
- Retrospective analyses suggest acceptable toxicity profiles with anti-EGFR antibodies in older patients, although data are limited. Similar benefits with anti-EGFR antibodies are seen in young and older patients.[13,14]
- Among patients age 70 years and older with metastatic colorectal cancer receiving first-line treatment, the addition of bevacuzimab to capecitabine in comparison to capecitabine alone, is associated with improved PFS. Patients receiving bevacizumab were at increased risk for grade 3 or higher thromboembolic events and any grade bleeding or hypertension. Exclusion criteria included clinically significant cardiovascular disease or a history of thromboembolic event in the past 6 months.[15]
- Pooled analysis of large clinical trials has demonstrated the feasibility of treating older adults with metastatic colon cancer with the combination FOLFOX or FOLFIRI with similar toxicity and efficacy to that seen in younger patients.[16,17]

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Continue

DISEASE-SPECIFIC ISSUES RELATED TO AGE
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Colon Cancer*

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DISEASE-SPECIFIC ISSUES RELATED TO AGE

Rectal Cancer

See NCCN Guidelines for Rectal Cancer

- **There are conflicting results from retrospective studies regarding the tolerance to neoadjuvant fluorouracil-based chemotherapy and radiation among older patients with locally advanced rectal cancer. However, since the standard of care for locally advanced rectal cancer is neoadjuvant chemotherapy and radiation, medically fit older patients should be considered for this treatment approach, or for participation in clinical trials targeting older patients with this disease.[1,2]**

- **A pooled analysis from 22 clinical trials with over 8,000 rectal cancer patients demonstrated reduction in risk of local recurrence and death from rectal cancer with perioperative radiotherapy regardless of patient age. However, the risk of death from non-cancer-related causes was increased in the older patient population.[3]**

- **Available data demonstrate that postoperative chemotherapy and radiation in fit older patients with stage III rectal cancer improves OS.[4]**

- **Large retrospective series demonstrate underuse of sphincter-preserving surgeries with increasing age, with a mild increase in postoperative mortality rates among older patients.[5-8]**

- **The available data regarding rectal cancer in older adults are primarily retrospective in nature, and are mostly evaluated treatment regimens that are not considered the standard of care today. Multidisciplinary evaluation and optimization of comorbidities is important for optimal patient outcomes in rectal cancer management.**

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DISEASE-SPECIFIC ISSUES RELATED TO AGE

See NCCN Guidelines for Head and Neck Cancers

Head and Neck Cancers*

Primary Surgical Approach to Localized/Locally Advanced Head and Neck Cancers:

- **Surgery: Older adults with head and neck cancer appear to have similar efficacy with surgery but higher complication rates, which increase with comorbidities.[1,2]**
- **Postoperative chemoradiation: In the adjuvant therapy of resected squamous cell carcinoma of the head and neck (SCCHN), too few patients older than 70 years have been evaluated to support or reject the addition of cisplatin to radiation therapy.[3,4]**

Definitive Radiation for Localized/Locally Advanced Head and Neck Cancers:

- **Radiation:**
  - **Patients older than 70 years with SCCHN who are treated with radiation therapy experience similar OS in comparison to younger patients.**
  - **Older adults are at increased risk for acute mucosal toxicities; however, there were no significant differences in late toxicities seen in older patients compared to those younger than 70 years (median of 3 years follow-up).[5]**
- **Chemotherapy/Radiation:**
  - **Regarding primary therapy for head and neck cancer, there are not enough data in patients older than 70 years to draw firm conclusions regarding a survival advantage of adding concurrent chemotherapy to radiation therapy.[6]**
  - **Concurrent chemotherapy with radiation and cisplatin improves laryngeal sparing over radiation alone in patients with localized T2 and T3 laryngeal cancer in patients both older and younger than 60 years.[7]**
  - **Retrospective studies suggest an increase in severe late toxicity with chemotherapy concurrent with radiation therapy in older patients.[8,9]**
  - **There is limited evidence for or against the benefit of cetuximab in combination with radiation therapy to treat locally advanced SCCHN in patients older than 64 years.[10] Available evidence in patients older than 64 years does not allow one to draw firm conclusions regarding a survival benefit of adding concurrent cetuximab to radiation.**
- **Induction Therapy: Few patients older than 70 years have been included in induction chemotherapy trials. There are limited data on the efficacy and toxicity of such an approach in this subset of patients.[11,12]**

Chemotherapy for Recurrent/Metastatic Disease:

- **Retrospective studies suggest an increase in toxicity with chemotherapy in older adults with recurrent/metastatic head and neck cancer.[13]**
- **There is limited evidence for or against the benefit of adding cetuximab to chemotherapy in treating recurrent or metastatic SCCHN in patients older than 64 years.[14]**

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Continue

DISEASE-SPECIFIC ISSUES RELATED TO AGE
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Head and Neck Cancers*

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*For comparison of efficacy and toxicity of various targeted therapies between younger and older patients, see Gonsalves W, Ganti AK. Targeted anti-cancer therapy in the elderly. Crit Rev Oncol Hematol 2011;78:227-242.

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DISEASE-SPECIFIC ISSUES RELATED TO AGE

Hepatocellular Carcinoma

See NCCN Guidelines for Hepatobiliary Cancers

Liver Resection, Liver Transplantation, and Locoregional Therapy

- **Published data (primarily retrospective) demonstrate age-related differences in patterns of care; however, there was no major difference in outcomes between well-selected older adults and younger patients with hepatocellular carcinoma (HCC).[1-5]**
- **A few centers have successfully transplanted highly selected patients older than 70 years, but the data are inadequate to make a recommendation regarding liver transplantation in older adults with HCC.[1]**
- **Based on retrospective analyses, older patients may benefit from liver resection or transplantation for HCC, but they need to be carefully selected, as OS is lower than for younger patients.[6,7,8]**
- **Stereotactic body radiation therapy (SBRT)/stereotactic ablative radiotherapy (SABR) should be considered for older patients, particularly those with comorbidities or compromised performance status, who may not be suitable for liver resection or transplantation. Because it is noninvasive, the successful completion rate of SBRT/SABR is high.[9] Toxicity to treatment can be minimized by careful patient selection, appropriate radiation dosing, and optimized dosimetry to meet normal tissue constraints. Ideal patients are those with good liver function (Child Pugh Class A) and limited volume of disease.**

Systemic Therapy

In a retrospective analysis of patients with advanced HCC treated with single-agent sorafenib, grade 3 or 4 adverse events and survival outcomes were similar in patients ≥70 and <70 years; however, treatment with sorafenib was associated with increased incidence of grade 3 or 4 neutropenia, malaise, and mucositis in patients ≥70 years.[10]

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DISEASE-SPECIFIC ISSUES RELATED TO AGE

See NCCN Guidelines for Kidney Cancer

Kidney Cancer*

- **Sorafenib and sunitinib have similar efficacy in younger and older patients. Some adverse events, including fatigue, occur with increased frequency in older patients.[1–6]**
- **Everolimus has similar efficacy in older and younger adults; however, older adults are at increased risk for adverse events (most commonly stomatitis, anemia, and infection). The frequency of grade 3/4 for adverse events is low.[7]**
- **Interferon is not recommended for first-line treatment. It has increased toxicity in patients 65 years or older compared to temsirolimus, including asthenia, nausea, fever, and neutropenia.[3,8,9]**

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DISEASE-SPECIFIC ISSUES RELATED TO AGE

Melanoma

See NCCN Guidelines for Melanoma

Surgery and Radiation

The data regarding radiation and surgery for melanoma in older adults were reviewed. The presently available data suggest that no specific age-related recommendations can be made.

Advanced or Metastatic Melanoma

Systemic Therapy

Ipilimumab improves OS over vaccine therapy with gp100 in patients age >18 years with advanced melanoma. Pre-specified subset analysis suggests ipilimumab improves OS in patients age >65 years.[1]

A phase III trial demonstrated similar OS for temozolomide compared to dacarbazine for advanced melanoma. Pre-specified subset analysis suggests similar results in patients age >65 years.[2]

BRAF (V600 E or K)- mutated

Vemurafenib (BRAF kinase inhibitor) improves OS and PFS over dacarbazine in V600E mutated advanced melanoma. This is true for ages <65 and >65 years.[3]

Dabrafenib (BRAF kinase inhibitor) improves PFS over dacarbazine in patients aged 21–93 years. No age-specific subset analysis was performed. [4]

Trametinib (an oral selective MEK inhibitor)[5] improves OS and PFS in V600E melanoma in patients aged 21–85 years compared to chemotherapy (dacarbazine or paclitaxel). The combination of dabrafenib and trametinib improves PFS in patients aged 18–85 years in comparison to dabrafenib alone in advanced melanoma.[6] Although not statistically significant the magnitude of benefit seen in patients age >65 years was similar to that of younger patients.[5,6]

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DISEASE-SPECIFIC ISSUES RELATED TO AGE

Multiple Myeloma*

See NCCN Guidelines for 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 potentially a candidate for high-dose therapy and autologous stem cell transplantation, as melphalan should be avoided in transplant candidates. There is a lack of consensus on what constitutes transplant eligibility; determining whether a patient is eligible for transplant incorporates assessment of physiologic age rather than chronologic age, with attention to comorbidities, functional status, and adequate cardiac, pulmonary, renal, and hepatic function. Consider early referral to a transplant physician if uncertain whether the patient is transplant-eligible prior to 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.[1-9]**
- **MPT is associated with higher response rate and OS than transplant with intermediate-dose melphalan (MEL 100).[2]**
- **Melphalan, prednisone, and lenalidomide followed by lenalidomide maintenance (MPL-L) 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] Patients receiving MPL-L had clinically important improvements in more health-related quality-of-life domains than patients treated with MP.[11]**
- **Continuous lenalidomide and dexamethasone improves PFS and is associated with superior health-related quality of life compared with MPT.[12,13]**

Venous Thromboembolism (VTE) Prophylaxis:

- **In older patients receiving immunomodulator-based regimen, VTE prophylaxis is recommended.[14]**

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Continue

DISEASE-SPECIFIC ISSUES RELATED TO AGE

Multiple Myeloma*

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 (ie, peripheral neuropathy, cytopenias, fatigue). The survival benefit is maintained across age groups.[15,16,17]**
- **In a randomized trial of VMP vs. VTP (bortezomib, thalidomide, and prednisone) there were similar response rates and OS but differing side effect profiles (VMP [ie, hematologic toxicity, infection] and VTP [cardiac complications]). Rates of neuropathy were similar in both groups. VMP was associated with better OS.[18,19]**
- **VMPT (bortezomib, melphalan, prednisone, and thalidomide) followed by maintenance VT (bortezomib and thalidomide) vs. VMP is associated with a higher response rate. Weekly bortezomib is associated with a decreased rate of peripheral neuropathy without a decrement in response.[20] An updated analysis showed that VMPT-VT regimen significantly prolonged OS compared to VMP, especially in patients younger than 75 years.[21]**

High-Dose Dexamethasone is Excessively Toxic in Older Adults:

- **High-dose dexamethasone is associated with an increased risk of mortality and severe hematologic toxicities in comparison to MP.[22]**
- **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).[23]**

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Continue

DISEASE-SPECIFIC ISSUES RELATED TO AGE
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Multiple Myeloma*

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*For comparison of efficacy and toxicity of various targeted therapies between younger and older patients, see Gonsalves W, Ganti AK. Targeted anti-cancer therapy in the elderly. Crit Rev Oncol Hematol 2011;78:227-242.

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DISEASE-SPECIFIC ISSUES RELATED TO AGE

Myelodysplastic Syndromes

See NCCN Guidelines for Myelodysplastic Syndromes

- Azacytidine 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 and ≥75 years of age. Predictors of a better response include a bone marrow blast count <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 azacytidine 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 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 older 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 azacytidine.
- 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, there are little data 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]

Allogeneic Hematopoietic Cell Transplantation:

- Among 372 patients aged 60 to 75 years with a variety of hematologic malignancies (eg, AML, MDS, CLL, lymphoma, multiple myeloma) enrolled in prospective allogeneic hematopoietic cell transplant (HCT) trials using nonmyeloablative conditioning, patient age was not associated with non-relapse mortality, OS, and PFS. Therefore, comorbidities and disease status, rather than age alone, should be considered in determining eligibility for allogeneic stem cell transplantation. There are very limited data in patients age >75 years.[11]
- There are a lack of prospective data regarding allogeneic HCT in older adults with MDS; however, retrospective reviews demonstrate that older patients with MDS who were selected to undergo allogeneic HCT with reduced intensity regimens had no increase in transplant-related mortality.[12,13] In a retrospective analysis of 514 patients with de novo MDS (ages 60–70 years), reduced-intensity allogeneic HCT was not associated with an improved life expectancy for patients with low/intermediate-1 IPSS MDS as compared to nontransplant therapies, while there was a potential improvement in life expectancy for those patients with intermediate-2 or high-risk IPSS MDS.[14]

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DISEASE-SPECIFIC ISSUES RELATED TO AGE
(References)

Myelodysplastic Syndromes

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DISEASE-SPECIFIC ISSUES RELATED TO AGE

Non-Small Cell Lung Cancer*

See NCCN Guidelines for Non-Small Cell Lung Cancer

Surgery[1-6]

- **Few prospective studies exist.**
- **Retrospective analyses demonstrate that older patients who are selected for surgery tolerate it well.**
- **There is caution with pneumonectomy in older adults.**

Stereotactic Body Radiation Therapy (SBRT)/Stereotactic Ablative Radiotherapy (SABR)[7-9]

- **SABR (also known as SBRT) is recommended for patients who are medically inoperable or who refuse to have surgery after thoracic surgery evaluation. SABR has achieved primary tumor control rates and OS, comparable to lobectomy and higher than 3D-CRT in prospective and population-based comparisons in medically inoperable or older patients.**[7,8] **(See NCCN Guidelines for Non-Small Cell Lung Cancer)**
- **The outcomes in terms of high tumor control and low toxicity are similar in older patients to those reported in younger patients.**[9]

Adjuvant Chemotherapy[10-11]

- **The benefits of adjuvant chemotherapy are similar with age.**

Locally Advanced Disease[12-16]

- **Combined modality therapy: While efficacy is maintained, older adults (especially those with a KPS <90) are more likely to have side effects (ie, esophagitis, pneumonitis, myelosuppression).**

Advanced Disease[17-27]

- **As in younger patients, chemotherapy is associated with improved quality of life in comparison to best supportive care.**
- **Emerging data are confirming the survival benefit of doublet chemotherapy in comparison to single-agent treatment.**
- **A retrospective subset analysis of ECOG 4599 and a recent SEER-Medicare analysis both suggest that older patients may not benefit from the addition of bevacizumab to carboplatin-paclitaxel.**

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Continue

Non-Small Cell Lung Cancer* (continued)

DISEASE-SPECIFIC ISSUES RELATED TO AGE (References)

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DISEASE-SPECIFIC ISSUES RELATED TO AGE

Mesothelioma

See NCCN Guidelines for Malignant Pleural Mesothelioma

- **There are limited data regarding the surgical management of mesothelioma in older adults. Single-institution retrospective analyses demonstrate that older age is a negative prognostic factor.[1, 2]**
- **In a retrospective analysis of 178 patients, using pooled data from two phase II trials of pemetrexed and carboplatin as first-line therapy, patients ≥70 years (n = 48) had slightly worse hematologic toxicity, but outcomes and other toxicities were the same as for younger patients.[3]**

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DISEASE-SPECIFIC ISSUES RELATED TO AGE

Small Cell Lung Cancer

See NCCN Guidelines for Small Cell Lung Cancer

- **Available data suggest that older adults derive benefit from standard doses of combination systemic chemotherapy (platinum and etoposide); however, toxicity related to bone marrow suppression is higher.[1,2]**
- **Attenuated doses of chemotherapy are associated with inferior outcomes and should be avoided if possible.[1]**
- **Cisplatin and carboplatin appear to have similar efficacy in the first-line treatment of small cell lung cancer. However, toxicity profiles are different, with carboplatin having a higher hematologic toxicity and cisplatin having a higher non-hematologic toxicity.[3]**
- **Age-related subset analyses of cisplatin + etoposide and concurrent external beam radiation therapy demonstrate similar response rates between older and younger patients, but older adults are at risk for increased toxicity (ie, myelosuppression, esophagitis, pneumonitis) and increased rate of treatment-related deaths (1% vs. 3% in NCCTG; 1% vs. 10% in INT 0096). Despite this, OS appears to be similar in both age groups.[4,5]**

Prophylactic Cranial Irradiation

- **Patients 70 years and older with extensive stage and response to chemotherapy may benefit from prophylactic cranial irradiation (PCI), with improved OS.[6] Other studies have also suggested a benefit from PCI in patients with limited stage and good response after chemotherapy, without differences in risk reduction by age. However, PCI is associated with more adverse events and increased neurotoxicity in older patients compared to younger patients.[7,8] PCI is not recommended in patients with poor performance status or impaired neurocognitive functioning.**

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DISEASE-SPECIFIC ISSUES RELATED TO AGE

Ovarian Cancer

See NCCN Guidelines for Ovarian Cancer

Overview:

- There are limited prospective data regarding the treatment of older adults with newly diagnosed ovarian cancer. Four studies from the SEER database and one study from a Geneva registry offer a unique look at older patients diagnosed with ovarian cancer.[1]
- Women older than 70 years with ovarian cancer had a 3-fold increased risk of death, more aggressive tumors, and more advanced stages at diagnosis, and received less standard chemotherapy and surgery. The 5-year, disease-specific survival was only 18% for women older than 70 years, compared to 53% for the younger cohort.[2]
- Women older than 65 years with ovarian cancer receive less chemotherapy and are less likely to complete a planned course of chemotherapy, particularly if >2 comorbid conditions are present. Predictors of no adjuvant chemotherapy include being older than 70 years, >2 comorbid conditions, and Hispanic race. Age is not significantly associated with hospitalizations or the use of other health services for women who received chemotherapy.[3]
- There are regional variations in the receipt of ovarian cancer-directed surgery and chemotherapy in the United States. A wide range of care is offered to older patients depending on geographic location. Cancer-directed surgery varied from 53% to 83%, and chemotherapy use varied from 48% to 93%. Improving access to high-quality surgery may have the greatest impact on improving outcomes in older patients.[4]
- For women at the end of life, hospice services were received by 60% of women older than 65 years during their last 6 months of life; African-American women and those of lower socioeconomic status are less likely to be offered these palliative services.[5]

Primary Chemotherapy:

- A review (N = 620 patients, age ≥70; N = 3066 patients, age <70) of women enrolled in the phase III clinical trial of adjuvant combination platinum therapy (GOG 182) reported that age (≥70 years) was associated with lower completion rates of the prescribed 8 cycles of chemotherapy (72% vs. 82%), shorter survival (37 vs. 45 months), and increased toxicity (particularly cytopenias and neuropathy). The analysis calls for more age-specific prospective studies.[6]
- A multicenter prospective study (N = 83 patients, age ≥70) of older patients with newly diagnosed stage 3 or 4 ovarian cancer who received a platinum-based regimen demonstrated that geriatric assessment variables identified patients at risk for severe toxicity and poorer OS. ECOG PS ≥2, depression, and loss of autonomy were associated with severe toxicity. Advanced stage, depression, and increased comorbidity were associated with poorer OS.[7]
- A small prospective phase II study (N = 26 patients, median age 77) of older patients with a high degree of comorbidity (54% had 2 or more comorbidities) and functional dependence (30% needed assistance with activities of daily living [ADL] and 74% needed assistance with instrumental ADL [IADL]) evaluated the feasibility and toxicity of carboplatin (AUC 2) and paclitaxel (60 mg/m^2) given on a weekly schedule. Sixty-five percent of patients completed 6 cycles of therapy with a low overall toxicity rate.[8]
- A very small prospective U.S. phase II study (N = 12; median age 82) of older patients receiving standard doses of carboplatin/paclitaxel demonstrated that 50% of patients discontinued therapy before completing the prescribed 6 cycles.[9]

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Continue

DISEASE-SPECIFIC ISSUES RELATED TO AGE

Ovarian Cancer

See NCCN Guidelines for Ovarian Cancer

- A retrospective review of a phase III study evaluating standard doses of cisplatin or carboplatin with paclitaxel every 3 weeks demonstrated that older patients (age ≥70; N = 103 [13% of the study population]) had similar toxicity (except for febrile neutropenia; 5% age ≥70 vs. <1% in those age <70), although they also had lower chemotherapy completion rates. The rate of neuropathy and impact on quality of life were not significantly different for older vs. younger patients.[10]

Intraperitoneal Chemotherapy:

- There are limited data regarding the feasibility of intraperitoneal (IP) chemotherapy in older adults. A retrospective study (109 patients [23 patients (21%) age ≥70]) demonstrated that older adults were less likely to complete the planned number of IP chemotherapy cycles; however, there was no significant association between age and IP chemotherapy toxicity or dose adjustments. Age alone should not limit access to IP chemotherapy.[11]
- A single-institution, retrospective review (N = 100; age ≥65) demonstrated that IP chemotherapy can be safely administered to select older patients with adequate supportive care and dose modifications.[12]

Prognostic Factors:

- A review of the Gynecologic Oncology Group (GOG) database demonstrated 4 significant adverse prognostic factors for the outcome of patients with stage III ovarian cancer treated with surgery and platinum-taxane chemotherapy. These included: mucinous or clear cell histology, PS >0, macroscopic disease at surgery, and increasing age (HR 1.12 for death). In women older than 70 years of age (14% total), 77% were able to complete all 6 planned cycles of chemotherapy.[13]
- A prospective review of ovarian cancer therapeutic GOG trials demonstrated that, compared to a younger cohort, patients 65 years and older were less likely to enroll on protocols (26% vs. 35%) due to ineligibility, refusal, or investigator decision. Further efforts to improve enrollment and design age-specific studies at the GOG are underway.[14]

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Continue

DISEASE-SPECIFIC ISSUES RELATED TO AGE

Ovarian Cancer References

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DISEASE-SPECIFIC ISSUES RELATED TO AGE

Prostate Cancer

See NCCN Guidelines for Prostate Cancer

- **For treatment of clinically localized or locally advanced prostate cancer, see the NCCN Guidelines for Prostate Cancer.**
- **In men of advanced age with high-risk prostate cancer and moderate-to-severe comorbidity, shorter course (4–6 months) of androgen deprivation therapy (ADT) with RT can be considered over longer course (28–36 months).[1-4]**
- **There are no significant age-related differences in docetaxel efficacy in patients with castration-recurrent prostate cancer. Every-3-week dosing remains the preferred method for fit older patients who should be monitored closely for toxicity. Growth factor support should be considered in patients 65 years or older to decrease the risk of neutropenic complications.[5,6,7] See the NCCN Guidelines for Myeloid Growth Factors.**
- **There are no age-related differences in cabazitaxel efficacy in patients with castration-recurrent prostate cancer. Growth factor support is strongly recommended in patients 65 years or older to decrease the risk of neutropenic complications in older patients[8,9] See the NCCN Guidelines for Myeloid Growth Factors.**
- **ADT is associated with an increased risk of fracture. Attention to bone health is warranted.[10] ADT significantly decreases muscle mass, and treatment-related sarcopenia appears to contribute to frailty and increased risk of falls in older men.[11,12] See the NCCN Guidelines for Prostate Cancer.**
- **In older adults, newer hormonal therapies can potentially replace or delay the usage of cytotoxic chemotherapy and may be used in patients who would otherwise be ineligible for chemotherapy.**

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COMPREHENSIVE GERIATRIC ASSESSMENT

Reasons to Perform Comprehensive Geriatric Assessment (CGA)[1,2]

- CGA is a systematic procedure to appraise objective health, including multiple comorbidities and functional status, which interfere with cancer prognosis and treatment choices in older adults.
- CGA can reveal/detect reversible geriatric problems not found by routine oncology care.
- CGA can predict toxicity/adverse effects from cancer treatment or decrease in quality of life (QOL), enabling more targeted use of supportive care measures.
- CGA has important prognostic information that can be helpful in estimating life expectancy, which is of paramount importance when making treatment decisions.
- CGA can influence/improve treatment decisions.
- CGA allows targeted intervention, which can improve QOL and adherence to therapy.

Collaboration with the Oncologist in the Care of an Older Patient with Cancer

Older adults may benefit from a referral to a Geriatrician for risk stratification prior to cancer treatment, to develop a coordinated plan of care with the oncologist and/or to manage geriatric syndromes that could jeopardize outcomes of cancer treatment. The geriatrician thus may be able to assist the oncologist in optimizing the management of the non-cancer aspects of the patient's care which in turn may enable more effective delivery of direct cancer care. Consider consultation to a geriatrician for the following:

- Cognitive impairment
  - Dementia/Delirium
  - Decision-making capacity evaluation
  - Life expectancy, advance care planning, guardianship
- Functional or physical impairment, mobility issues, or disability
  - Falls evaluation and/or advice on falls prevention
  - Promote independent living or supportive living
- Multimorbidity including vision and hearing impairments
- Polypharmacy evaluation
- When considering a high-risk procedure, such as:
  - Chemotherapy and radiotherapy
  - Hematopoietic cell transplant
  - Complex surgeries (eg, cystectomy)
- Presence of geriatric syndromes such as:
  - Pressure ulcers, urinary incontinence, depression, osteoporosis, neglect or abuse, failure to thrive, or sarcopenia; frailty
- Weight loss (>7 lbs in last 3 months) and anorexia

See References (OAO-D 6 of 7)

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COMPREHENSIVE GERIATRIC ASSESSMENT

Functional Status

- Activities of daily living (ADL) - Self-feeding, 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
- Physical performance status
- Visual function and/or hearing impairment
- Falls and/or unstable gait
  - Falls are more common in older adults with cancer than those without cancer
  - Factors that have been prospectively associated with increased risk of subsequent falls in older adults with cancer include: prior falls, benzodiazepine use, cancer pain, and neurotoxic chemotherapy
  - In patients who are at risk, such as those 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 by evaluating gait speed[3] or using Timed Up and Go (TUG) test: See OAO-E
    - ◊ Exercise promotion including PT or OT evaluation, as needed
    - ◊ Checking and replacing vitamin D levels
    - ◊ Referral to geriatrics or primary care physician
    - ◊ Home safety evaluation and home modifications as indicated
    - ◊ Medication review for at-risk medications (eg, benzodiazepines, hypnotics) See Medications Commonly Used for Supportive Care that Are of Concern in Older Patients (OAO-I)

Socioeconomic Issues See OAO-2
Psychosocial Distress See NCCN Guidelines for Distress Management

See References (OAO-D 6 of 7)

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COMPREHENSIVE GERIATRIC ASSESSMENT

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.
  - Methods to assess comorbidities: (Charleson Comorbidities Index[4], CIRS[5], OARS[6])

Cognitive Function (See Assessment of Cognitive Function OAO-F)

- Dementia
  - Mini-Mental State Examination (MMSE)[7,8]
  - Montreal Cognitive Assessment (MoCA)[9] (http://www.mocatest.org/)
- Depression
  - Geriatric Depression Scale (GDS)[10,11]
  - See NCCN Guidelines for Distress Management
- Delirium
  - Confusion Assessment Method and/or Memorial Delirium Assessment Scale[12,13]
  - See NCCN Guidelines for Palliative Care and NCCN Guidelines for Distress Management

Nutritional Status

- Patients with cancer tend to be at risk for severe malnutrition that is under diagnosed.[14]
- Poor nutritional status is associated with increased mortality and poor chemotherapy tolerance.[15,16,17,18]
- Malnutrition among hospitalized patients with cancer is associated with increased length of stay.[14]
  - Practical consideration to guide further nutritional assessment of at-risk patients includes:
    - ◊ Unintentional weight loss of greater than 5%[19]
    - ◊ Body mass index (BMI) of 22 or below[20]
    - ◊ Weighing less than 80% of ideal body weight[21]
    - ◊ Practical suggestions to optimize nutrition among patients with cancer can be found in the guide to nutritional intervention from NCI Nutrition in Cancer Care (PDQ) http://www.cancer.gov/cancertopics/pdq/supportivecare/nutrition/HealthProfessional/page4

See References (OAO-D 6 of 7)

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COMPREHENSIVE GERIATRIC ASSESSMENT

Polypharmacy

- Reconcile medications at every visit, including prescription and over-the-counter medications, vitamins, and supplements.[22,23,24]
- Review medications periodically as indicated to identify medication-related problems.[22,25] Medication review may be indicated with any initiation or change in oncologic treatment, change in comorbid disease management, or change in clinical condition, and at other times as determined by the clinical team and during transition of care. See Medication Review (below).
- Carefully review indications, duration of therapy, and dosage when using these medications or classes of medications that are not recommended for older adults. See Medications Commonly Used for Supportive Care that Are of Concern in Older Patients (OAO-I).
- Evaluate adherence to therapy (See OAO-G)

Medication Review[26]

- Does every medication match a known medical problem or chronic condition?
  - Any deficiencies?[27,28,29,30,31]
  - Any duplications?
- Are the dosages appropriate for each medication for the patient's age, renal function, or liver function?
- Are there potential drug-drug or drug-disease interactions or other adverse effects of the medication?
  - Drug interactions:[32]
    - http://medicine.iupui.edu/clinpharm/ddis/
    - http://www.mskcc.org/cancer-care/integrative-medicine/about-herbs-botanicals-other-products
- Are there any high-risk/low-benefit or inappropriate medications?
  - Beers criteria:[33]
    - http://geriatricscareonline.org/toc/american-geriatrics-society-updated-beers-criteria-for-potentially-inappropriate-medication-use-in-older-adults/CL001
  - STOPP criteria[28,29,30,31]
  - Medication Appropriateness Index[34]
- Could a medication-related problem be responsible for current compliants or presenting problems?
- Can the regimen be simplified?
- Are there any less expensive alternative medications that are of equal utility?

See References (OAO-D 6 of 7)

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COMPREHENSIVE GERIATRIC ASSESSMENT
CARE PROCESS FOR OLDER ADULTS WITH CANCER

Impairment in any domain may consider the following:

Domain Impaired	Potential Interventions
Functional Status (See OAO-D 2 of 7)	**Physical therapy referral** **Occupational therapy referral** **Home safety evaluation/Home health care** **Evaluate fall risk** **Promote exercise**
Cognition/Memory (See OAO-D 3 of 7 and OAO-F)	**Involve caregiver** **Assess/minimize potentially inappropriate medications (See OAO-I)** **Delirium prevention** **Assess capacity and ability to consent to treatment (See OAO-1)** **Identify health care proxy/collaborative decision maker** **Cognitive testing/neuropsychology referral**
Social Support/Caregiver Burden	**Transportation assistance** **Home health care** **Home safety evaluation** **Support groups** **Refer to psychiatry/psychology** **Spiritual care**
Psychological status: anxiety/depression	**Complementary (non-pharmacological) modalities such as guided imagery, meditation, relaxation, acupuncture, etc.** **Counseling** **Refer to psychiatry/psychology** **Start medications to treat anxiety/depression** **Support programs** **Spiritual care**
Nutrition (See OAO-D 3 of 7)	**Nutrition consult** **Make specific dietary recommendations** **Oral care** **Supplemental nutrition** **Physical/Occupational therapy if function related**

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See References (OAO-D 6 of 7)

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COMPREHENSIVE GERIATRIC ASSESSMENT
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COMPREHENSIVE GERIATRIC ASSESSMENT
(References)

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[22]Reconcilation and review of medications, and medication changes in particular, should ideally occur in the context of a patient's oncologic treatment and with the input from other physicians involved in the patient's care. The extent to which a patient's oncologic care occurs in a shared model of care with primary care providers will guide the extent of involvement of a primary care physician in medication management questions.

[23]Reconcilation refers to the process of developing an accurate list of medications a patient is taking in order to communicate and make care decisions about medication therapy.

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ASSESSMENT OF GAIT AND TREATMENT RECOMMENDATIONS

Assessment of gait by evaluating gait speed or using 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	TREATMENT RECOMMENDATIONS
Assess proximal muscle strength	• Diagnose and treat underlying causes • Consider physical therapy evaluation
Mobility aids assessment	• Assess for type, condition, usage technique, and fit of mobility aid • Consider referral for occupational/physical therapy evaluation
Check orthostatic blood pressure	• Diagnose and treat underlying causes • Review medications • Address salt intake, adequate hydration, and compensatory strategies (eg, elevating head of bed, rising slowly, using pressure stockings)
Ask about changes in vision	• Diagnose and treat underlying cause of vision changes • Consider referral to opthalmologist • Consider neurologic evaluation
Assess for neurological changes	• Evaluate if cancer or cancer treatment-related and modify treatment if possible • Consider neurologic evaluation
Review medications	• See “Polypharmacy” (OAO-D, 4 of 7) and “Medication Review” (OAO-D, 4 of 7)
Environmental hazards	• Consider home safety evaluation • Educate patients to reduce risk (http://www.cdc.gov/HomeandRecreationalSafety/Falls/CheckListForSafety.html)
Footwear assessment	• Assess type, condition, and fit of shoes • Perform foot exam

[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.

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ASSESSMENT OF COGNITIVE FUNCTION[1,2]

WHEN TO ASSESS FOR COGNITIVE FUNCTION	RECOMMENDATIONS
Would impaired cognitive function affect the planning or delivery of care? (eg, impact life expectancy or risk/benefit, impact adherence to treatment plan)	No (to all) → Reassess periodically or when considering treatment plan changes
Is the medical team concerned about decision-making capacity? See OAO-1	Yes (to any) → Consult with a clinician experienced in cognitive evaluation (ie, geriatrician, neurologist, geriatric psychiatrist, neuropsychologist, occupational therapist) OR Initiate the evaluation yourself See OAO-F (2 of 2)
Does the patient have a history of recent delirium or late onset of depression?	
Does the medical team suspect impaired cognitive function?	
Has the patient or patient's family suggested that the patient has impaired cognitive function?	

[1]Cordell CB, Borson S, Boustani M, et al. Medicare Detection of Cognitive Impairment Workgroup. Alzheimer's Association recommendations for operationalizing the detection of cognitive impairment during the Medicare Annual Wellness visit in a primary care setting. Alzheimers Dement 2013;9(2):141-150.
[2]Simpson JR. DSM-5 and neurocognitive disorders. J Am Acad Psychiatry Law 2014;42:159-64.

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ASSESSMENT OF COGNITIVE FUNCTION[1,2,3]

	Mild Cognitive Impairment	Dementia	Delirium
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: • Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains • Interference with ability to perform daily functions (ADL/IADL) (See OAO-D)	Disturbance in attention and awareness: • 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 (confounding factors)	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 (See OAO-D)	Clinical interview with cognitive (Mini-Cog) and functional (ADL/IADL) assessment (See OAO-D)	Confusion Assessment Method (CAM) https://www.healthcare.uiowa.edu/igec/tools/cognitive/CAM.pdf
Further Evaluation	• Reassess periodically and with major changes in condition or when considering changes to treatment plan • If screening is abnormal consult 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 • If screening is abnormal consult with a clinician experienced in cognitive evaluation

[1]Cordell CB, Borson S, Boustani M, et al. Medicare Detection of Cognitive Impairment Workgroup. Alzheimer's Association recommendations for operationalizing the detection of cognitive impairment during the Medicare Annual Wellness visit in a primary care setting. Alzheimers Dement 2013;9(2):141-150.
[2]Simpson JR. DSM-5 and neurocognitive disorders. J Am Acad Psychiatry Law 2014;42:159-64.
[3]If you have concerns about decision-making capacity see (OAO-1).

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ASSESSMENT OF ADHERENCE

Assess risk of non-adherence whenever considering a treatment regimen that will include an oral agent

Although older age per se is not a consistent risk factor for non-adherence, several factors may increase the potential for non-adherence among older adults:

- **Deceased propensity of older adults to ask questions about benefits and risks of treatments**
- **Increased numbers of comorbidities and associated medications leading to regimen complexity**
- **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 non-adherence

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[1]**
- **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 [2,3]**
- **Provide written instructions to patient/caregiver for taking the medication at the sixth grade level.[4] 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 non-judgmental 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.**
- **If patient agrees, also check with primary caregiver or family member regarding medication adherence and explore any challenges.**

[1]Agarwal S, et al. Does synchronizing initiation of therapy affect adherence to concomitant use of antihypertensive and lipid-lowering therapy? Am J Ther 2009;16(2):119-126.
[2]Steiner JF. Rethinking adherence. Ann Inter Med 2012;157:580-585.
[3]Viswanathan M, Golin CE, Jones CD, et al. Interventions to improve adherence to self-administered medications for chronic diseases in the United States: A systematic review. Ann Intern Med 2012;157:785-795.
[4]Confirm ability to read and comprehend written instructions (eg, vision, literacy).

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INSOMNIA

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.[a]**
- **Non-pharmacologic methods such as sleep hygiene, 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 utilized, 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.[b]**
- **Please note that if zolpidem is considered, the FDA has advised that the recommended dose of zolpidem for women should be lowered from 10 mg to 5 mg for immediate-release products and from 12.5 mg to 6.25 mg for extended-release products.[c]**
- **Patient information regarding optimizing sleep is available through the National Institute on Aging.[d]**

[a]See American Geriatrics Society: Five Things Physicians and Patients Should Question (http://www.choosingwisely.org/doctor-patient-lists/american-geriatrics-society/).
[b]See AGS Geriatrics Evaluation and Management Tools (Geriatrics E&M Tools): http://www.americangeriatrics.org.
[c]See http://www.fda.gov/Drugs/DrugSafety/ucm334033.htm.
[d]See http://www.nia.nih.gov/health/publication/good-nights-sleep.

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MEDICATIONS COMMONLY USED FOR SUPPORTIVE CARE THAT ARE OF CONCERN IN OLDER PATIENTS

Therapeutic Class/ Medication(s)	Negative Effects	Condition the Drug May Adversely Affect	Recommendation	Alternative(s)
Corticosteroids (oral):[1,2,3,13,14] • hydrocortisone • methylprednisolone • prednisone • prednisolone • dexamethasone	• Can result in weight gain, muscle weakness, agitation, hyperglycemia, Cushing syndrome • Increases risk of gastrointestinal bleeding, fractures, infection, and thromboembolism	Delirium Diabetes Osteoporosis Insomnia	• When used for supportive care, carefully consider the dose and duration of therapy • Use the lowest possible dose ideally for short-term therapy (1–3 weeks) • Short-term use as an adjuvant for pain or antiemetic, for spinal cord compression, increased intracranial pressure, and bowel obstruction is appropriate (when benefit outweighs risk)	When risk outweighs benefit: • For pain, consider other adjuvant pain medications (eg, gabapentin,[a] SNRI antidepressants,[b] lamotrigine,[a] tramadol, topical lidocaine, as indicated by type of pain and response) • For nausea, consider alternative antiemetics (eg, serotonin antagonists, aprepitant)·
Benzodiazepines:[4,5,13,14] • alprazolam • estazolam • lorazepam • oxazepam • temazepam • triazolam • clorazepate • chlordiazepoxide • clonazepam • diazepam • flurazepam • quazepam	• Older adults have increased sensitivity to benzodiazepines and slower metabolism for benzodiazepines • Can increase the risk of falls, cognitive impairment, and motor vehicle accidents	Falls Fractures Cognitive impairment Delirium	• Avoid for treatment of insomnia, agitation, or delirium • Potentially appropriate for seizures, rapid eye movement sleep disorders, benzodiazepine withdrawal, alcohol withdrawal, severe generalized anxiety disorders, and end-of-life care. • Reduce dose and/or lengthen the dosing interval when using for supportive care during chemotherapy administration	• For anxiety, consider buspirone, SSRIs,[a] or SNRIs.[a] • For sleep, use sleep hygiene education, sleep restriction or sleep compression,[c] or cognitive behavioral therapy. See “Insomnia” (OAO-H). • For nausea, consider an alternative agent

[a]Unlabeled use.
[b]Not all medications in this class are labeled for this use.
[c]Sleep compression is an incremental decrease of time spent in bed.

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Therapeutic Class/ Medication(s)	Negative Effects	Condition the Drug May Adversely Affect	Recommendation	Alternative(s)
First-generation antihistamines: [4,5,13,14] • diphenhydramine • hydroxyzine • promethazine • brompheniramine • carbinoxamine • clemastine • cyproheptadine • dexbrompheniramine • dexchlorpheniramine • doxylamine • triprolidine	• Highly anticholinergic; increased risk of confusion, dry mouth, constipation, and other anticholinergic toxicities. • Clearance reduced with advanced age. • Tolerance develops when used as hypnotic	Delirium Cognitive impairment Urinary retention	•Use only for supportive care when convincing benefit exists • Appropriate for acute treatment of severe allergic reactions	• For allergic rhinitis, use second-generation antihistamines (cetirizine, desloratadine, fexofenadine, levocetirizine), intranasal corticosteroids, intranasal antihistamines, intranasal anticholinergics, or leukotriene inhibitors • For pruritis, use second-generation antihistamines • For sleep, use sleep hygiene education, sleep restriction or sleep compression, or cognitive behavioral therapy See “Insomnia” (OAO-H)
Antiemetic, prokinetic: [4,5] • metoclopramide	• May cause extrapyramidal effects; risk greater in frail older adults	Parkinson’s disease	•Avoid, unless use for patients with gastroparesis • If benefit outweighs risk, use the lowest dose possible, and avoid exceeding 5 mg	• Consider serotonin antagonists (ie, dolasetron, granisetron, ondansetron, palonosetron, tropisetron), short-term corticosteroids (ie, dexamethasone, prednisone), or other antiemetics
Histamine-2 receptor blockers: [4] • famotidine • ranitidine • cimetidine	• Can induce or worsen delirium in older adults	Delirium Cognitive impairment Dementia	• Avoid in patients at risk for delirium	• Proton-pump inhibitors (eg, omeprazole, esomeprazole, pantoprazole, lansoprazole)

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Therapeutic Class/ Medication(s)	Negative Effects	Condition the Drug May Adversely Affect	Recommendation	Alternative(s)
Phenothiazine antiemetic: [4] • prochlorperazine	• Can worsen Parkinsonian symptoms	Parkinson's disease	• Avoid in patients with Parkinson's disease	• Use other antiemetics (serotonin antagonist such as ondansetron, dexamethasone, aprepitant)
Antipsychotics: [4,5,7,8,9,10,13,14] • chlorpromazine • fluphenazine • haloperidol • loxapine • molindone • perphenazine • pimozide • promazine • thioridazine • thiothixene • trifluoperazine • triflupromazine • aripiprazole • asenapine • clozapine • iloperidone • lurasidone • olanzapine • paliperidone • quetiapine • risperidone • ziprasidone	• Some agents have high anticholinergic effects (especially chlorpromazine, clozapine, loxapine, olanzapine, thioridazine, and trifluoperazine). • Increases the risk of cerebrovascular accident. • Increased mortality risk in patients with dementia. • Can cause hyperglycemia. • Increases the risk of falls and fractures, especially in patients with baseline high risk. • Concern for QT prolongation, especially in combination with serotonin antagonists, antidepressants, and in patients with underlying cardiac diseases.	Dementia (black box FDA warning for increased mortality risk) Falls Fractures	• In the presence of psychosis and danger to self/others, use low-dose non-anticholinergic agent for the shortest duration possible. • May be appropriate for short duration treatment of refractory chemotherapy-induced nausea and vomiting. • May be appropriate for short-term management of delirium. • With concern for QT prolongation, start at the lowest dose with slow uptitration. Consider baseline EKG before initiation of therapy	• For delirium, short-term use (no more than 5 days) of one of the following at low dose: - Haloperidol[a] (0.25–1 mg PO up to q 8 hours) - Olanzapine[a] (2.5–5 mg PO daily) - Risperidone[a] (0.25–0.5 mg PO daily) - For patients with parkinsonism, quetiapine[a] (12.5–25 PO daily or q 12 h) • If using an antipsychotic, attempt to reduce, taper, or stop other antipsychotics and/or drugs acting on the central nervous system that can worsen the risk of falls or cognitive decline. • For nausea, could consider other antiemetics (serotonin antagonists such as ondansetron, dexamethasone, or aprepitant) if risk outweighs the benefit of using an antipsychotic. • Monitor for extrapyramidal symptoms; tools such as the Abnormal Involuntary Movement Scale are useful.

[a]Unlabeled use.

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Therapeutic Class/ Medication(s)	Negative Effects	Condition the Drug May Adversely Affect	Recommendation	Alternative(s)
Non-benzodiazepine sedative hypnotics: [4,5] • zolpidem • eszopiclone • zaleplon	• Similar adverse effects to benzodiazepines with minimal improvement in sleep latency and duration	Delirium Falls Fractures	• Use no more than 2 to 3 days per week for up to 90 days. • Avoid chronic use. • If zolpidem is used, the dose in women should not exceed 5 mg	• Use sleep hygiene education, sleep restriction or compression, or cognitive behavioral therapy. In the right setting, if pharmacologic therapy is deemed necessary, agents such as trazodone,[a] mirtazapine,[a] melatonin,[a] ramelteon, or other medications could be considered, keeping in mind the risks and benefits of each individual therapy. See "Insomnia" (OAO-H).
SSRI antidepressants: [4,5,11,12,13,14] • fluoxetine • paroxetine • sertraline • fluvoxamine • citalopram • escitalopram	• Can produce ataxia, impair psychomotor function, increase risk of syncope, and increase risk of falls. • May exacerbate hyponatremia, particularly in older persons. • May increase risk of GI bleeding, particularly in patients taking NSAIDs, aspirin, heparin, warfarin, or other antithrombotic therapy. • Can increase the QT interval.	Falls Syndrome of inappropriate antidiuretic hormone secretion (SIADH) Prolonged QT syndrome	• Consider sertraline or citalopram as first-line due to a lower propensity for interactions. • Review the need for continued treatment for depression at least 6 months after remission of the episode, based on number of prior episodes, residual symptoms, current medical problems, and psychosocial difficulties. • Consider stopping by gradually reducing the dose over a 4-week period in patients who no longer need antidepressants. • Avoid in patients with falls, unless alternatives are not available.	• For patients with falls, consider SNRIs (eg, venlafaxine, desvenlafaxine, duloxetine) or bupriopion. • Consider the use of a gastroprotective medication (proton pump inhibitors such as omeprazole, esomeprazole, or misoprostol) if SSRIs must be combined with NSAIDs, aspirin, or antiplatelet agents. • For patients taking warfarin, heparin, or anticoagulants, consider mirtazapine • Consider complementary or alternative therapy (eg, CBT)

[a]Unlabeled use.

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Therapeutic Class/ Medication(s)	Negative Effects	Condition the Drug May Adversely Affect	Recommendation	Alternative(s)
SSRI antidepressants (cont'd)			• Avoid in patients with SIADH. • Avoid paroxetine (and possibly fluoxetine) in patients taking tamoxifen. • Consider baseline EKG before initiation of therapy.	
Antiepileptic drugs (AEDs):[15,16] • phenobarbital • primidone • phenytoin • carbamazepine	• Induce multiple cytochrome P450 enzymes, resulting in clinically significant drug interactions	Presence of multiple comorbid conditions Falls	• Avoid for newly diagnosed epilepsy in persons ≥60 years of age not currently on antiepileptic therapy, unless at least two other AEDs have been unsuccessful in stopping seizures or have intolerable adverse effects	• Examples of multiple AEDs that do not induce cytochrome P450 enzymes: lamotrigine, levetiracetam, tiagabine, and topiramate

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[2]Sturdza A, Millar BA, Bana N, et al. The use and toxicity of steroids in the management of patients with brain metastases. Support Care Cancer 2008;16:1041-8.

[3]AGS Panel on Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons. J Amer Geriatr Soc 2009;57:1331-46.

[4]The American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2012; 60:616-31.

[5]HEDIS: Health Care Effectiveness Data and Information Set, at http://www.ncqa.org/HEDISQualityMeasurement.aspx.

[6]Malik I, Moid I, Khan Z, Hussain M. Prospective randomized comparison of tropisetron with and without dexamethasone against high-dose metoclopramide in prophylaxis of acute and delayed cisplatin-induced nausea and vomiting. Am J Clin Oncol 1999;22:126-30.

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[15]Pugh MJ, Berlowitz DR, Rao JK, et al. The quality of care for adults with epilepsy: an initial glimpse using the QUIET measure. BMC Health Serv Res 2011;11:1.

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Discussion

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Table of Contents

Overview

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.[2] It is estimated that by 2030 approximately 70% of all cancers will be diagnosed in adults aged ≥65 years.[3] Aging in the U.S. population and greater life expectancy mean that cancer in older adults is becoming an increasingly common problem. Furthermore, older patients with cancer are under-represented in clinical trials for new cancer therapies.[4] Therefore, less evidence-based information exists to guide the treatment of these patients.

The 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. There are unique issues to consider when caring for an older adult with cancer. The biologic characteristics of certain cancers and their responsiveness to therapy are different in older patients compared to their younger counterparts.[5] In addition, older patients also have decreased tolerance to anticancer therapy. Nevertheless, advanced age alone should not be the only criterion to preclude effective treatment that could improve quality of life (QOL) or lead to a survival benefit in older patients.[6,7] 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.[8-10] However, there have been few studies that have addressed patients at the extremes of age or those with poor performance status.

Together, these age-related issues form the basis for the development of guidelines that address special considerations in older patients with cancer. Proper selection of patients is the key to administering effective and safe cancer treatment. Treatment that diminishes QOL with no significant survival benefit should be avoided. 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. The NCCN Guidelines for Older 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, and managing patients deemed to be at high risk for toxicity from standard treatment.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for Older Adult Oncology, a literature search was performed to obtain key literature in Older Adult Oncology published between October 2015 and October 2016, using the following search terms: older patients and cancer, treatment, allogeneic stem cell transplantation, adherence, comprehensive geriatric assessment, toxicity and chemotherapy, polypharmacy, comorbidities, functional status, cognitive status, nutritional status, falls, frailty, geriatric syndromes, delirium, dementia, depression, and distress. In addition, key literature published between October 2015 and October 2016 specific to the treatment of older patients with the cancer types included in the *Disease-Specific Issues Related to Age* section of the NCCN Guidelines for Older Adult Oncology was also obtained. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[11]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article

types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 93 citations and their potential relevance was examined. The data from key PubMed articles selected by the panel for review during the Guidelines update meeting as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN webpage.

Comprehensive Geriatric Assessment

CGA is a multidisciplinary, in-depth evaluation to assess the objective health of a patient while assessing multiple domains, which affect cancer prognosis and treatment choices in older adults. 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.

CGA can reveal and/or detect reversible geriatric problems that are not found by routine oncology care, predict toxicity from cancer treatment enabling a more targeted use of supportive care measures that can improve QOL, compliance with adherence to therapy.[12-14] In addition, CGA can provide important prognostic information that can be helpful in estimating life expectancy, which is of paramount importance when making treatment decisions.

Older adults may benefit from a referral to a Geriatrician for risk stratification prior to their cancer treatment, to develop a coordinated plan of care with the oncologist and/or to manage geriatric syndromes that could jeopardize outcomes of cancer treatment. The geriatrician thus may be able to assist the oncologist in optimizing the management of the non-cancer aspects of the patient's care which in turn may enable more effective delivery of direct cancer care.

Functional Status

Functional status in older patients with cancer can be evaluated using self-reported or performance-based measures. Self-reported measures include the individual's ability to complete activities of daily living (ADLs) and instrumental activities of daily living (IADLs).[15,16] 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.[17-20] 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.

Gait speed has been used to assess functional status and health outcomes in older adults.[21,22] Recent reports have also identified gait speed as an indicator of survival and mortality in older adults.[23,24] 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.[23] In this analysis, with 0.8 meter/second as the cutoff, gait speed faster than 1.0 meter/second suggested a better-than-average life expectancy and gait speed above 1.2

meters/second suggested exceptional life expectancy. White et al reported that decline in gait speed (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.[24] The predictive value of gait speed has also been evaluated in older patients with cancer.[25] In the Health, Ageing and Body Composition study that included 429 older patients with cancer, faster gait speed (time taken to cover a 20-m course) was associated with lower risk of death (hazard ratio [HR] = .89) in patients with metastatic cancer and lower 2-year progression to death or disability in patients with non-metastatic cancer.[25] 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.[26,27] 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.[28,29] 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.[30] A TUG test score of 13 seconds or greater is associated with an increased risk of falls. For these patients, a comprehensive evaluation should be considered. See *Assessment of Gait and Treatment Recommendations* in the algorithm.

Comorbidities

Older adults have an increased prevalence of comorbidities that can impact cancer prognosis and treatment tolerance.[31,32] 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.

Specific comorbidities have been shown to have an impact on prognosis and treatment outcome in patients with cancer.[33-35] In a randomized adjuvant chemotherapy trial of 3,759 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%) were significantly worse for patients with diabetes compared with patients without diabetes.[33] In another 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.[34] In the SEER-Medicare database analysis of older patients (≥66 years) diagnosed with stages I-III breast cancer, those with diabetes had an increased rate of hospitalizations for any chemotherapy toxicity and higher all-cause mortality.[35]

In older patients with cancer, comorbidity may modify the disease course. 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). In one study that evaluated the association between comorbidity, toxicity, time to relapse, and OS in older women with good performance status receiving adjuvant chemotherapy for early-stage breast cancer, comorbidity was associated with shorter OS, but was not associated with increased treatment-related toxicity or relapse.[36] The effect of comorbidity on life expectancy should be evaluated prior to initiation of treatment.

Charlson Comorbidity Index (CCI),[37] the Cumulative Illness Rating Scale (CIRS),[38] and the Older Americans Resources and Services (OARS) Multidimensional Functional Assessment Questionnaire[39] are commonly used to determine the risk of mortality associated with comorbidity in older patients. CCI[40] and CIRS[41,42] 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.[43] 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 of greater than 2 was associated with a higher risk of early treatment suspension (82% vs. 30%, respectively).[40] 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.[41] However, the former group had a higher risk of neutropenic fever and death from neutropenic infections.

Cognitive Function

Older patients with cancer who are cognitively impaired have an increased risk of functional dependence, higher incidence of depression, and are at greater risk of death. Cognitive function is also predictive of medication nonadherence across diagnoses, regardless of the complexity of regimen.[44] Cognitively impaired patients should be cared for by an experienced multidisciplinary geriatric oncology team along with good supportive care throughout the treatment.[45] 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.[46-48] Antipsychotic drugs are also associated with higher mortality rates in patients with dementia.[49-51] Hilmer and colleagues have developed a drug burden index, which is a useful evidence-based tool for assessing the effect of medications on the physical and cognitive performance in older adults.[52] Special considerations for over- or under-use, 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 (eg, mild cognitive impairment, dementia, delirium).[53] 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 the section on *Geriatric Syndromes* for the assessment of dementia and delirium in older cancer patients.

Nutritional Status

Nutritional deficiency or malnutrition is a common and serious condition that is under diagnosed in older patients with cancer. Poor nutritional status is associated with an increased risk of severe hematologic toxicity, an increased mortality risk, poor chemotherapy tolerance and an increased length of stay among hospitalized patients with cancer.[54-57] While some of the malnutrition is attributed to the underlying illness, in most of the patients it is due to inadequate intake of calories. Nutritional parameters such as a body mass index (BMI) of less than or equal to 22 kg/m^2 and unintentional weight loss of greater than 5% in the previous 6 months would help to identify patients who are at risk for individualized or advanced intervention.[58] Special attention should also be devoted to vitamin D deficiency since that may be related to osteoporosis and fractures.[59]

Polypharmacy

Polypharmacy can be defined in various ways, including the use of increased number of medications (5 or more), more than is clinically indicated; the use of potentially inappropriate medications; medication underuse; and medication duplication.[60] 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.[61-63]

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 non-adherence.[64,65] 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 cancer patients receiving palliative care only.[66] Older patients, those with comorbid conditions, brain tumor patients, and those taking many medications are at greater risk of drug interactions.[66]

Alterations in pharmacokinetics and pharmacodynamics of drug metabolism in the older population can also contribute to adverse drug interactions.[67] Most of the commonly prescribed medications such as opioids, antidepressants, antibiotics, and antipsychotics as well as anticancer drugs induce or inhibit cytochrome P-450 enzymes. In a retrospective analysis of 244 older patients (≥70 years), Popa et al assessed the impact of potential drug interactions (PDIs) from polypharmacy and their association with chemotherapy tolerance.[68] The results of this study demonstrated that PDIs may contribute to severe non-hematologic toxicities whereas there was no association between PDIs and hematologic toxicities. Further research regarding PDIs and chemotherapy toxicity is warranted in order to develop interventions and optimize clinical outcomes in older patients receiving chemotherapy.

The use of one or more potentially inappropriate medications among older patients has also been documented in several studies.[69-71] In one study, the use of inappropriate medications increased from 29% to 48% among cancer patients in the palliative care setting.[70] 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.[71] While 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.[71] The use of potentially inappropriate medications (especially hypnotics, sedatives, antidepressants, long-acting benzodiazepines and other inappropriate psychotropics, and medications with anticholinergic properties) is also associated with an increased risk of falls in older adults (≥65 years).[72,73]

Evaluation of Polypharmacy

The guidelines recommend evaluation of adherence to therapy and periodic medication review to check for medication duplication, appropriate use, availability of less expensive alternative medications, and PDIs. Although the optimal polypharmacy cut-point for predicting clinically important adverse events in older people with cancer is unclear, the common definition of greater than or equal to 5 medications is reasonable for identifying patients for medication review.[74] Medication review may be indicated prior to initiation or change in treatment, change in comorbid disease management or in clinical condition, and at other times as determined by the clinical team and during transition of care. A careful review of the indication for treatment, duration of therapy, and dosage should be performed when using specific medications or classes of medications that are not recommended for older adults. See the section on *Medications Commonly Used for Supportive Care that are of Concern in Older Patients* in the algorithm for specific recommendations.

Beers criteria and the Medication Appropriateness Index (MAI) are two 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.[75,76] The criteria are appropriate for persons older than 65 years of age and provide a rating of severity for adverse outcomes as well as 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 73.5 years) and in the outpatient setting (n = 154 with a median age 74 years).[77,78] 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 recommendation by the OACE team.[77] In the outpatient study, 50% of patients required specific interventions and the use of potentially inappropriate medication was identified in 11% of patients, following geriatric management evaluation.[78]

The Beers' Criteria were recently 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.[79] In the updated criteria, medications that are used in older adults are divided into three 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.

Medication Appropriateness Index

MAI was developed to measure appropriate prescribing based on a 10-item list and a 3-point rating scale.[80] Samsa and colleagues 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.[81] This modified MAI appears to be a valid and relatively reliable measure to detect medication appropriateness and inappropriateness in the community pharmacy setting as well as in ambulatory older patients on multiple medications.[82,83] 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; $P < .001$).[82] Higher MAI scores were also associated with lower self-related health scores in older adults.[84] MAI has not been evaluated extensively in older patients with cancer.

STOPP/START Criteria

STOPP/START criteria were established using the Delphi consensus and an 18-member expert panel from the academic centers of Ireland and the United Kingdom.[85] The STOPP criteria is comprised 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.[86,87] 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 to the control group assigned to routine pharmaceutical care.[88] Significant improvements in prescribing appropriateness were sustained for 6 months after discharge.

Socioeconomic Issues

The lack of social ties has been identified as significant predictors of mortality in older adults.[89,90] In a study of 2,835 women diagnosed with breast cancer, socially isolated women had an elevated risk of mortality after a diagnosis of breast cancer.[91] 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. Furthermore, information should be sought as to whether the patient is a caregiver for someone else and whether cancer treatment may impact their ability to provide this care. 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

Falls, dementia, delirium, depression, distress, osteoporosis, fatigue, and frailty are some of the most common syndromes in older patients with cancer.[92] 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.[93] In this cohort, the

prevalence of hearing trouble, urinary incontinence, depression, and osteoporosis were significantly higher in patients with cancer than in those without cancer.

Falls

Falls are more common in older adults with a cancer diagnosis than those without cancer. Cancer diagnosis (especially in the first 6 months after diagnosis) and chemotherapy are also associated with a high risk of falls.[94-96] In a prospective study of 185 patients with advanced cancer, 93 (50.3%) patients experienced falls associated with a high risk of physical injury, regardless of age: 35 patients were less than 65 years of age and 58 patients were 65 years of age or older.[94] The median time to a fall was 96 days. In a multivariate analysis, the diagnosis of a 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.[94] Another recent study also reported that the risk of falls increases with each cycle of chemotherapy, and patients treated with taxane-based chemotherapy may be at a greater risk of falls than those treated with platinum-based chemotherapy.[95] In a recent study that evaluated the occurrence of falls in 937 older adults with cancer, during the follow-up of 2 to 3 months after cancer treatment decision, a fall was reported by 142 patients (17.6%), of whom 51.4% fell more than once. Fall history in the past 12 months, fatigue, ADL dependency, geriatric risk profile by G8, and living alone were identifed as independent predictors of 1 or fewer fall within 2 to 3 months after cancer treatment decision.[97] These findings suggest that falls are important problems in older cancer patients and geriatric assessment can identify patients at risk for falls.

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.[98-103] The guidelines recommend periodic assessment of history of falls, balance, and gait difficulties for all patients, as fall risk may change over time. The use of early and preventative use of durable medical equipment and in-home safety evaluations are recommended for patients with neurotoxicities at high risk for falls. Assessment of gait by evaluating gait speed[23] or 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 if they are afraid of falling.

Dementia

Dementia is a progressive condition characterized by impairment of memory and at least one other cognitive function (such as aphasia, apraxia, agnosia, or executive function) 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.[104] Preexisting dementia was also associated with high mortality, mostly from noncancer causes in patients ≥68 years diagnosed with breast, colon, or prostate cancer.[105] 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.[106]

The Mini-Mental State Exam (MMSE) and the Montreal Cognitive Assessment (MoCA) are recommended for the assessment of cognitive function in older adults.[107-109] 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.[107,108] 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.[109] MoCA has been shown to be a superior prognostic indicator to the MMSE in patients with brain metastases.[110,111] 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.[110] 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, since there is a strong correlation between decline in cognitive status and the loss of functional independence in older adults.[112] The guidelines have included Mini-Cog as a screening tool for the assessment of mild cognitive impairment and dementia in older patients with cancer. Mini-Cog is a 5-point test (consisting of a three-word recall and clock drawing test) used for screening cognitive impairment in the older population.[113,114] Assessment of cognitive function can also be confounded by fatigue, depression, anxiety, underlying brain tumors, endocrine dysfunction, nutritional deficiency, alcohol use, and sleep disturbances.[115] Therefore, if dementia is suspected, further evaluation including brain imaging, neuropsychological testing, and evaluation for vitamin B12 deficiency and thyroid dysfunction may be indicated. For patients with mild cognitive impairment, the guidelines recommend periodic reassessment of cognitive function or when considering changes to the 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.[116] It is an under-recognized problem in older adults and can contribute to poorer clinical outcomes, functional decline, and impaired communication between the patient and physicians in patients with advanced cancer.[117] Dementia is the leading factor for delirium and about two thirds of cases of delirium occur in older patients with dementia.[116]

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.[118,119] 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.[120] 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.[121]

The Hospital Elder Life Program (HELP) includes interventions for the management of 6 risk factors for delirium (ie, cognitive impairment, sleep deprivation, immobility, dehydration, vision or hearing impairment).[122] In the Yale Delirium Prevention Trial (852 patients), 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.[123]

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.[124-126]

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.[127] GDS was originally developed as a 30-item scale.[127] Recently, shortened versions of GDS have been found to be equally accurate and less time consuming in screening for depression in older adults.[128,129] Cancer-related fatigue and depression frequently occur together; therefore, patients reporting fatigue should probably be assessed for depression.[130-132]

Distress

Psychological distress is common among patients with cancer. Hurria and colleagues reported that significant distress was identified in 41% of patients ≥65 years with cancer and poorer physical function was the best predictor of distress.[133] Screening tools have been found to be effective and feasible in reliably identifying distress and the psychosocial needs of patients.[134-136] The NCCN Distress Thermometer (DT) and the accompanying 36-item problem list is a well-known screening tool, specifically developed for cancer patients by the NCCN Distress Management Panel.[137,138] 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.[136] Patients can quickly fill out this distress assessment tool in the waiting room and the tool can alert the physician to potential problems. This tool identifies whether patients with cancer have problems in five different categories: practical, family, emotional, spiritual/religious, and physical. See the NCCN Guidelines for Distress Management for more information on the use of DT as a screening tool in patients with cancer.

Fatigue

Cancer-related fatigue is a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning.[139] In advanced cancer, the prevalence of fatigue is greater than 50% to 70%.[140] 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.[141] 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.[142,143] In contrast to normal fatigue, cancer-related fatigue is refractory to sleep and rest, perhaps because patients with cancer have aberrant sleep patterns. It is reasonable to expect that fatigue may precipitate functional dependence, especially in patients who are already dependent in IADLs.[30,144,145]

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.

Frailty

Frailty is a biologic syndrome of decreased reserve and resistance to stressors, causing vulnerability to adverse outcomes.[146] Frail patients are at risk for falling, disability, hospitalization, and death. Fried Frailty Criteria and the Balducci Frailty Criteria are the two most common measures used to identify frail patients.[147,148]

According to Fried Frailty Criteria, frailty is defined as the clinical syndrome with three or more of the following conditions: unintentional weight loss (10 lb or more in the past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and/or low physical activity.[147] 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.[147]

The Balducci Frailty Criteria are based on the components of CGA (dependence in one or more ADLs, three or more comorbid conditions, and one or more geriatric syndromes).[148] These CGA-frailty criteria have been found to be more useful in identifying frail cancer patients. In a prospective study that compared the Balducci Frailty Criteria and the modified version of Fried Frailty Criteria in 176 patients (aged 70 to 94 years) who underwent elective surgery for colorectal cancer, although both frailty measures were predictive of OS, the Balducci Frailty Criteria were more useful than the modified version of the Fried Frailty Criteria in predicting postoperative complications.[149]

Osteoporosis

Osteoporosis and its associated increased risk of fracture is a major risk factor in cancer patients, especially in women receiving chemotherapy or hormonal therapy for breast cancer and in men receiving hormonal therapy for prostate cancer. Osteoporosis can be prevented with appropriate screening, lifestyle interventions, and therapy. The diagnosis of osteoporosis is based on assessment of bone density by a dual-energy x-ray absorptiometry (DEXA) 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.[150] The NCCN Task Force Report on Bone Health in Cancer Care discusses effective screening and therapeutic options for optimizing bone health in patients with cancer.[151]

Application of CGA for Older Patients with Cancer

The feasibility of CGA has been demonstrated in older patients with cancer[148,152,153] and the components of CGA (comorbid conditions, functional status, cognitive function, geriatric syndromes, polypharmacy, and nutritional status) have been associated with survival and chemotherapy toxicity.[18-20,154-160]

For example, in women ≥65 years diagnosed with stage I-III primary breast cancer, the all-cause and breast-cancer-specific death rate at 5 and 10 years was consistently approximately two times higher in women with 3 or more cancer-specific CGA deficits, regardless of age and stage of disease.[154] 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.[155] In a recent prospective multicenter study of 348 previously untreated cancer patients older than 70 years, poor nutritional status, impaired mobility, and advanced tumors were identified as risk factors predictive of early death (less than 6 months) after initiation of chemotherapy.[156] 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.[157] Similarly, among older patients receiving induction chemotherapy for acute myeloid leukemia (AML), OS was significantly shorter for patients with impaired cognitive and physical function.[158] CGA has also been reported to be an efficient method to identify older patients with diffuse large B-cell lymphoma (DLBCL) who can benefit from anthracycline-based chemoimmunotherapy.[20,161]

Although CGA is helpful for physicians to develop a coordinated plan for cancer treatment as well as 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.[162-164] The Cancer-Specific Geriatric Assessment (CSGA) developed by Hurria and colleagues includes the assessment of older cancer patients across seven domains (functional status, comorbidity, polypharmacy, cognitive function, psychological status, social functioning and support, and nutritional status) using validated measures.[162] The feasibility of CSGA was demonstrated in a pilot study of 43 patients with cancer (median age of 74 years), the majority of whom had advanced-stage disease. This brief geriatric assessment is largely self-administered and can be completed by the majority of older patients without assistance.[162] Results from the CALGB 360401 study also demonstrated the feasibility of including CSGA in future cooperative group clinical trials.[163] The Senior Adult Oncology Program 2 (SAOP2) screening tool developed by Extermann and colleagues is aimed at identifying older patients who would benefit from a multidisciplinary evaluation by a geriatric oncology team.[164] The SAOP2 screening tool includes the assessment of older cancer patients across the following domains using validated measures: self-rated health, cognitive function, nutritional status, comorbidity, ECOG performance status, and functional status.

Abbreviated CGA (aCGA),[165,166] Barber questionnaire,[167] Fried Frailty Criteria,[147,168] Geriatric 8 (G-8),[169-171] Groningen Frailty Index,[166] Triage Risk Screening Tool (TRST),[171] Vulnerable Elders Survey (VES-13),[170,172-175] and Lachs' screening test[176] 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 al assessed the sensitivity and specificity of frailty screening methods that could potentially be useful in the selection of patients for CGA.[177] G-8 and TRST had the highest sensitivity (87% and 92%, respectively) and aCGA had the highest specificity (97%) for predicting frailty on CGA. In the ONCODAGE prospective multicenter cohort study that evaluated the diagnostic accuracy of G-8 and VES-13 as a predictive screening tool to identify older patients who would require CGA, G-8 was more sensitive and VES-13 was more specific. Abnormal G-8 score, advanced stage, male sex, and poor performance status were independent prognostic factors of 1-year survival.[178]

While 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 (ADL and IADL) 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 CGA. Given the lack of data supporting the use of any one screening tool for predicting outcome of a CGA, screening tools should not replace CGA in the management of older patients with

cancer. However, screening tools could be used to identify those patients who would benefit from a CGA prior to initiation of therapy.[179,180]

Approach to Decision Making in Older Patients with Cancer

Older patients can be classified into three 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.[5] Chronologic age by itself is not reliable in estimating life expectancy, functional reserve, or the risk of treatment complications.[181] While it is not possible for a physician to predict the exact life expectancy of an individual patient, it is possible to provide an estimate of whether a patient is likely to live longer or shorter than an average person of similar age.[22-24,182-185]

Life expectancy at a given age can be estimated using life table data as suggested by Walter and Covinsky.[182] For example, about 25% of the healthiest 75-year-old women will live more than 17 years, 50% will live at least 12 years, and 25% will live less than 7 years. Lee and colleagues developed and validated a potentially useful tool for clinicians to estimate the 4-year mortality risk.[184] Patients can be stratified into three groups of varying risk of mortality (high, intermediate, or low) based on the prognostic index, which incorporates demographic variables (age and sex), self-reported comorbid conditions, and functional measures.[184] Carey and colleagues also developed a similar functional morbidity index based on self-reported functional status, age, and gender to stratify elders into varying risk groups for 2-year mortality.[183]

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. More generally, a useful collection of tools to estimate the general mortality risk in the older adult can be found online at http://eprognosis.ucsf.edu/. Life expectancy calculators available at this website could be utilized 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 anticipated life expectancy. These calculators should be used in conjunction with clinical judgment.

Following 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. 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.[186,187]

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. It is essential that key concepts and information regarding the diagnosis of cancer and treatment should be communicated to older patients in a way that they will be able to understand. See *Optimizing Communication with Older Adults* in the algorithm. Sessums et al 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.[187] Irrespective of age, a person who is functionally 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, advance 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. 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.[5]

The potential benefits of cancer treatment include prolonged survival, maintenance, and improvement of QOL and function, as well as 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 is recommended for all patients.

Surgery

In general, age is not the primary consideration for surgical risk, although the physiologic status of the patient needs to be assessed.[188] Performance status and comorbidities of the patient are more important factors than patient's age when considering surgical treatment options for older adults.[189] 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.[126]

The Surgical Task Force report from SIOG (International Society of Geriatric Oncology) reported that in many malignancies (breast, gastric, and liver) the surgical outcomes in older patients with cancer were not significantly different from their younger counterparts.[190] Preoperative Assessment of Cancer in the Elderly (PACE) was developed to determine the suitability of older patients for surgical intervention.[191] 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 prior to surgery.[192,193] 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. Following surgery, physical and/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.[194,195] Older age is also a risk factor for postoperative delirium. The HELP[122,123] and National Institute for Health and Clinical Excellence (NICE)

guidelines[196] provide recommendations for the management of delirium in hospitalized patients ≥70 years.

Radiation Therapy

RT (external beam RT or brachytherapy) can be offered either in the curative or palliative setting.[197,198] Available data from the literature indicate that RT can be highly effective and well tolerated, so that age alone need not be a limiting factor in older patients with cancer.[199,200] Radiation oncologists, like all other clinicians caring for older patients with cancer, must be careful of the potential to overtreat older adults with substantial competing risks of non-cancer death, as well as the potential to undertreat older adults because of an underestimation of life expectancy in patients with advanced age but few significant comorbid conditions.

It is important to consider several general principles when developing an individualized treatment plan with RT in older patients. The decision to offer RT to older patients with cancer should be based on the following factors: 1) evaluation of the benefits and risks associated with RT; 2) careful consideration of the patient's underlying functional reserve; and 3) an understanding of the differences in the biology of cancers and their responsive to therapy in this patient population. Nutritional support and pain control for treatment-induced mucositis are recommended for patients receiving RT. Concurrent chemoradiation, however, should be used with caution; dose modification of chemotherapy may be necessary to reduce toxic side effects.

Incomplete and interrupted courses of RT can compromise the efficacy of treatment as well as the ability to deliver higher doses of RT in the future. Therefore, it is important to consider alternative approaches in patients with extreme functional limitations and ensure maximal supportive care. Advanced RT techniques (eg, intensity-modulated radiation therapy [IMRT], image-guided radiation therapy [IGRT] and stereotactic body radiation therapy [SBRT] or stereotactic ablative radiotherapy [SABR]) facilitate the delivery of large doses of radiation to small target volumes while limiting the risk of radiation-induced damage to normal surrounding tissues and organs at risk (OARs).[200] Judicious application of these techniques may also help to assuage concerns about the risks of RT in older adults. Hypofractionated RT may also help to improve treatment tolerability by limiting overall treatment time without compromising clinical outcomes in some patients.[201] Since the biologic characteristics of certain cancers are different in older patients compared to their younger counterparts and partly because of the decreased tolerance of treatment by older patients, treatment should be individualized based on the nature of the disease and the performance status of the patient.

Chemotherapy

Several retrospective studies have reported that the toxicity of chemotherapy is not more severe or prolonged in persons older than 70 years of age.[202-205] However, the results of these studies cannot be generalized for the following reasons:

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

Nevertheless, these studies are important, because they demonstrate that age, by itself, is not a contraindication to cancer chemotherapy. Therefore, patient selection is extremely important to maximize the benefits of adjuvant chemotherapy in older patients with cancer.

Increased age has been associated with changes in the pharmacokinetics and pharmacodynamics of cancer therapy and increased susceptibility of normal tissues to toxic complications.[206] Pharmacodynamic changes of interest include reduced repair of DNA damage and increased risk of toxicity. Pharmacokinetic changes of major concern include decrease in the glomerular filtration rate (GFR) and volume of distribution of hydrosoluble drugs. Although the hepatic uptake of drugs and the activity of cytochrome P450 enzymes also decrease with age, the influence of these changes on cancer chemotherapy is not clear. Intestinal absorption may decrease with age, but it does not appear to affect the bioavailability of anticancer agents. The pharmacokinetics of antineoplastic drugs is unpredictable to some extent; thus, drug doses should be adjusted according to the degree of toxicity that develops. However, adequate dosing is necessary to ensure the effectiveness of therapy.

Extermann and colleagues have devised the MAX2 index for estimating the average per-patient risk for toxicity from chemotherapy.[207] In a retrospective analysis, Shayne et al identified advanced age (≥65 years), greater body surface area, comorbidities, anthracycline-based regimens, a 28-day schedule, and febrile neutropenia as independent predictors of reduced dose intensity among patients with early-stage breast cancer receiving adjuvant chemotherapy.[208] In another retrospective analysis of older patients (≥65 years) with invasive breast cancer, the type of adjuvant chemotherapy regimen was a better predictor of toxicity than increased age or comorbidity score.[209] Anthracycline-based regimen resulted in greater grade 3 or 4 toxicity, hospitalization, and/or febrile neutropenia, whereas treatment delays due to myelosuppression were more frequent with the cyclophosphamide-containing regimen. Among older patients with ovarian cancer, those receiving standard-dose chemotherapy were more likely to experience cumulative toxicity and delays in therapy.[210]

Other investigators have developed tools incorporating components of CGA to assess the individual risk of severe toxicity from chemotherapy in older patients.[211-213] Hurria and colleagues have developed CSGA for predicting treatment-related toxicity in older patients with cancer which has also been validated in an independent cohort study of 250 older adults (≥65 years) with a solid tumor.[211,212] The following factors were predictive of grade 3 to 5 toxicity: age ≥72 years; type of cancer (gastrointestinal or genitourinary); standard dose chemotherapy; polychemotherapy; hemoglobin (male: <11g/dL; female: <10 g/dL); creatinine clearance <34 mL/min; hearing impairment described as fair or worse; one or more falls in the last 6 months; limited in walking one block; the need for assistance with taking medications; and decreased social activities due to physical or emotional health. Extermann et al have developed the chemotherapy risk assessment scale for high-age patients (CRASH) score, which could be useful in predicting significant differences in the risk of severe toxicity in older cancer patients starting a new chemotherapy.[213] In this model, diastolic blood pressure, IADL, lactate dehydrogenase, and the type of treatment were the best predictors of hematologic toxicity. Performance status, cognitive function, nutritional status, and the type of therapy were the best predictors of non-hematologic toxicity.

Side Effects of Chemotherapy

In older patients undergoing chemotherapy, the most common complications include myelosuppression resulting in neutropenia, anemia, or thrombocytopenia; mucositis; renal toxicity; cardiac toxicity; and neurotoxicity. Older patients appear to be at special risk for severe and prolonged myelosuppression and mucositis, increased risk for cardiomyopathy, and increased risk for central and peripheral neuropathy. In addition, they are also at risk for infection (with or without neutropenia), dehydration, electrolyte disorders, and malnutrition either as a side effect of the chemotherapy or directly from the tumor. Chemotherapy can also affect cognition, function, balance, vision, hearing, continence, and mood.[214] The combination of these complications enhances the risk of delirium and functional dependence. It is essential to detect and correct these complications (that may interfere with treatment) in order to achieve maximum benefit from chemotherapy. Prevention and/or amelioration of some of the common chemotherapy-related complications are discussed below.

Cardiovascular Toxicity

Anthracyclines are associated with increased cardiac toxicity resulting in left ventricular dysfunction (LVD) and CHF.[215,216] Other antineoplastic drugs associated with significant cardiovascular complications include alkylating agents, antimetabolites, and microtubule-stabilizing agents. These drugs may have an additional effect on anthracycline-induced cardiovascular toxicity. Risk factors for anthracycline-induced cardiovascular toxicity include an existing or history of heart failure or cardiac dysfunction, hypertension, diabetes and coronary artery disease, older age (independent of comorbidities and performance status), prior treatment with anthracyclines, higher cumulative doses, and short infusion duration.[217] Age is also a significant risk factor for CHF in patients receiving anthracycline-based regimens.[216] HER2 status, hypertension, and coronary artery disease have also been identified as significant predictors for heart failure in patients with breast cancer treated with anthracycline.[218] Dexrazoxane, an iron chelator, has been shown to reduce anthracycline-induced cardiac toxicity in randomized clinical trials involving patients with advanced or metastatic breast cancer.[219-221]

Cardiac toxicity has also been a concern in patients receiving trastuzumab.[222-225] In a single-center, retrospective analysis of older patients (≥70 years; n = 45) with breast cancer, Serrano et al reported an increased incidence of cardiotoxicity among patients with a history of cardiac disease and/or diabetes treated with trastuzumab.[225] Asymptomatic cardiotoxicity was observed in 12.5% of patients with early-stage breast cancer; 24% of those with advanced breast cancer and 8.9% of all patients with advanced breast cancer developed symptomatic CHF. Trastuzumab has been associated with cardiac dysfunction and CHF in patients with HER-2-positive metastatic breast cancer, especially when used in combination with anthracyclines.[222,226,227] However, in the long-term follow-up of the HERA trial the incidence of severe CHF, LVD, and discontinuation of trastuzumab as a result of cardiac disorders remained low (0.8%, 9.8%, and 5.1%, respectively) in patients who received trastuzumab.[228] A combined review of cardiac data from the NSABP-31 and NCCTG N9831 clinical trials also showed that the incidence of symptomatic heart failure events was 2.0% in patients treated with adjuvant trastuzumab and the majority of these patients recovered with appropriate treatment.[229] In a large, population-based, retrospective study of older patients with stage I-III breast cancer (≥66 years; 9,535 patients; 2,203 patients received trastuzumab), the use of trastuzumab resulted in a CHF rate of 30%, which is substantially higher than that reported in clinical trials. Among patients treated with trastuzumab,

older age (≥80 years), hypertension, coronary artery disease, cardiac comorbidities, and weekly administration of trastuzumab were associated with increased risk of CHF.[230]

Emerging data from clinical studies suggest that trastuzumab, when used in combination with non-anthracycline–based chemotherapy, has similar efficacy with lower rates of cardiac events in patients with early-stage as well as metastatic HER-2-positive breast cancer.[231-233] The subgroup analysis of the randomized trial that evaluated trastuzumab in combination with docetaxel and pertuzumab in patients with HER2-positive metastatic breast cancer (808 patients; 127 patients were ≥65 years) did not show any increase in the risk of cardiac dysfunction associated with trastuzumab, and there was also no evidence of late or cumulative cardiac toxicity.[233] In addition, the results also showed no significant correlation between age and the development of left ventricular systolic dysfunction in older patients. Additional data are needed regarding the tolerability of these regimens in older patients.

Renal Toxicity

The GFR decreases with age, which in turn delays elimination of many drugs. Delayed renal excretion may enhance the toxicity of drugs whose parent compounds are excreted by the kidneys (ie, carboplatin, oxaliplatin, methotrexate, bleomycin) and drugs that are converted to active (ie, idarubicin, daunorubicin) or toxic metabolites (ie, high-dose cytarabine).[5] Dose adjustment to the measured GFR should be considered for these drugs to decrease systemic toxicity.

Renal insufficiency is common in older patients with cancer, particularly in patients receiving nephrotoxic drugs, patients with genitourinary cancers, or patients with multiple myeloma. In patients with preexisting renal problems who are at a greater risk of renal impairment, the use of nephrotoxic drugs should be limited or avoided. Serum creatinine is not a good indicator of renal function in older adults. Calculation of creatinine clearance is recommended to assess renal function and adjust dose to reduce systemic toxicity.

Neurotoxicity

Neurotoxicity is also a dose-limiting toxicity associated with chemotherapy.[234] Vinca alkaloids, cisplatin, and taxanes induce peripheral neurotoxicity. Methotrexate, cytarabine, and ifosfamide are associated with central neurotoxic side effect. Purine analogs (eg, fludarabine, cladribine, pentostatin) are associated with life-threatening neurotoxicity at significantly higher doses than the recommended clinical dose.[235] High-dose cytarabine can cause an acute cerebellar syndrome. Patient's age (greater than 60 years), drug dose and schedule, and renal and hepatic dysfunction are the most important risk factors for cytarabine-induced cerebellar toxicity.[236,237]

Management of neurotoxicity mainly consists of dose reductions or lower dose intensities. Older patients are particularly susceptible to the toxicity of cytarabine-based regimens due to decreased renal excretion of the toxic metabolite ara-uridine, and increased vulnerability of the cerebellum. Particular attention should be paid to the use of cytarabine in high doses, especially in patients with renal insufficiency. Dose reductions are necessary in patients with reduced GFR. The guidelines recommend monitoring for cerebellum function, hearing loss, and peripheral neuropathy.

Myelosuppression

Available data from various studies have shown that the risk of myelosuppression increases substantially by age 65 years.[238-242] The risk of myelosuppression is decreased by 50% when using growth factors.[243-245] Dose reductions may compromise the effectiveness of

treatment. The use of growth factors in these circumstances does not appear to be associated with increased cost and may even be cost saving if it prevents lengthy hospitalizations from neutropenic infections in older persons.

Neutropenia

Neutropenia is the major dose-limiting toxicity associated with chemotherapy, especially in older patients. Among older patients with aggressive non-Hodgkin's lymphoma treated with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy, the incidences of fever and neutropenia were significantly higher for patients aged ≥70 years (42% vs. 8% for patients aged 61–69 years; $P < .0001$).[246] In patients ≥60 years receiving induction or consolidation chemotherapy for AML, the prophylactic use of hematopoietic growth factors results in faster recovery of neutrophil and shorter hospitalization, but it does not impact OS.[247,248]

Meta-analysis of controlled clinical trials on the prophylactic use of recombinant granulocyte colony-stimulating factors (G-CSF) has confirmed their effectiveness in reducing the risk of febrile neutropenia.[249] Some concerns have been expressed that the combination of growth factors and topoisomerase II inhibitors may be associated with increased risk of acute leukemia; however, these data are controversial.[250,251] Despite these caveats, the use of growth factors appears to be the best established strategy to improve treatment in this group of patients.[252] The EORTC has issued similar recommendations for the prophylactic use of G-CSF in older patients with cancer.[253] The NCCN Guidelines for Myeloid Growth Factors address the use of G-CSFs in patients with solid tumors and non-myeloid malignancies.

Anemia

Anemia has been shown to be a risk factor for chemotherapy-related toxicity and is one of the factors responsible for the reduction in volume of distribution, which may result in increased peak concentration and increased toxicity of drugs.[254] Anemia is also associated with cardiovascular disease, CHF, coronary death, and dementia.[255-258] Anemia is also significantly associated with multidimensional loss of function (mobility limitations, impaired cognition, and dysphagia) in individuals ≥70 years and higher rates of functional disability in individuals ≥65 years with cancer.[259,260]

In patients with severe anemia, blood transfusions are necessary to prevent serious clinical consequences. There is increasing controversy regarding the use of erythropoiesis-stimulating agents (ESAs). ESAs have been demonstrated to decrease the need for transfusion in patients receiving chemotherapy.[261] It also appears to be beneficial to complement the administration of erythropoietin with oral or parenteral iron, although this is not specific for older patients. However, recent randomized studies have reported decreased survival and poorer tumor control among cancer patients receiving erythropoietic drugs for correction of anemia and target hemoglobin levels 12 g/dL.[262] The use of ESAs in patients with cancer is also associated with increased risks of venous thromboembolism and mortality.[263,264] The risks of shortened survival and the disease progression have not been excluded when ESAs are dosed to a target of hemoglobin levels of less than 12 g/dL.

In July 2008 based on the results of these trials, the FDA strengthened its warnings to alert physicians of increased risk of tumor progression and shortened survival in patients with advanced breast, cervical and head and neck cancers, lymphoid neoplasms and NSCLC. Physicians were advised to use the lowest dose necessary to avoid transfusion. In addition, the use of ESAs is restricted to the treatment of anemia

specifically related to myelosuppressive chemotherapy without curative intent. ESAs should be discontinued once the course of chemotherapy has been completed and the anemia has resolved. The panel recommends that anemia in older patients with cancer should be managed as outlined in the NCCN Guidelines for Cancer- and Chemotherapy-Induced Anemia.

Thrombocytopenia

Chemotherapy-induced thrombocytopenia (CIT) is a common hematologic toxicity associated with cytotoxic and myeloablative chemotherapy. Dose reductions and/or interruptions of chemotherapy regimens are necessary in patients with severe thrombocytopenia. While chemotherapy-induced anemia and neutropenia can be managed with hematopoietic growth factors, safe and effective treatment of CIT is still a significant problem. Recombinant interleukin-11 is the only currently approved treatment of CIT in patients with nonmyeloid malignancies.[265] However, it is toxic and of minimal clinical benefit. Ongoing clinical trials are also evaluating the efficacy of thrombopoietin-like agents such as romiplostim and eltrombopag for the treatment of CIT.[266]

Nausea and Vomiting

Chemotherapy-induced nausea and vomiting (CINV) is a debilitating side effect that can significantly affect a patient's QOL and compliance with treatment. Serotonin (5-HT3)-receptor antagonists, neurokinin-1-receptor antagonists, and corticosteroids are the most effective antiemetic drugs used for the management of CINV.[267] Older patients may have an increased risk of toxicity from antiemetic drugs due to age-related physiologic changes in drug absorption, distribution and excretion, drug interactions, and polypharmacy used to treat comorbidities.[268,269] Therefore, the selection of appropriate antiemetic therapy in older patients should be based on individual patient characteristics, prior history of CINV, the emetogenic potential of the specific chemotherapeutic agent, and most importantly the side effect profile of the antiemetic agent. For example, QTc prolongation has been reported as a class effect of 5-HT3–receptor antagonists, especially dolasetron, tropisetron, and palonosetron, and these should be used with caution in older patients with cardiovascular complications.[268] CINV should be managed as described in the NCCN Guidelines for Antiemesis and the NCCN Guidelines for Palliative Care.

Diarrhea

Diarrhea is a well-recognized side effect associated with a number of chemotherapeutic agents, particularly fluorouracil and irinotecan. Loss of fluids and electrolytes associated with persistent and severe diarrhea can lead to dehydration, renal insufficiency, and electrolyte imbalance.[270] Furthermore, chemotherapy-induced diarrhea can lead to dose reductions, delay in therapy, or discontinuation of chemotherapy, which ultimately affect clinical outcomes.[271] Based on the results from various clinical trials, the ASCO guidelines for the comprehensive evaluation and management of cancer treatment-induced diarrhea recommend loperamide as the standard therapy for mild-to-moderate diarrhea.[270] Octreotide (subcutaneous or intravenous if the patient is severely dehydrated) may be beneficial for patients with severe diarrhea or diarrhea that is refractory to loperamide therapy.

The NCCN Guidelines recommend early aggressive rehydration and management with octreotide (if oral treatments are ineffective) for older patients with chemotherapy-induced diarrhea.

Mucositis

Oral and gastrointestinal mucositis are significant complications of radiotherapy and chemotherapy. The risk of mucositis increases with age. In a phase III randomized study of 212 patients with hematologic

cancers undergoing high-dose chemotherapy and total body irradiation followed by autologous hematopoietic stem-cell transplant, palifermin (human keratinocyte growth factor) was associated with a significant reduction of oral mucositis compared to placebo (20% vs. 62%).[272] Palifermin is approved for the treatment of oral mucositis in patients with hematologic malignancies receiving myeloablative therapy requiring hematopoietic stem cell support. Recent studies have reported that palifermin is also well tolerated and effective in the prevention of oral mucositis in patients with metastatic colorectal cancer treated with fluorouracil-based chemotherapy and in patients with head and neck cancer treated with postoperative or definitive chemoradiation therapy.[273-275] A new time-released preparation of glutamine has shown promising results in the management of oral mucositis in patients with breast cancer receiving anthracycline-based chemotherapy.[276] However, the safety and efficacy of pharmacologic management of chemotherapy-induced oral mucositis in patients with non-hematologic malignancies is yet to be firmly established. Once mucositis has occurred, patients should be kept well hydrated with intravenous fluids. Early hospitalization may be necessary for patients who develop dysphagia or diarrhea.

Insomnia

Insomnia is characterized by difficulty falling or staying asleep, waking up too early, or experiencing poor-quality nonrestorative sleep associated with daytime impairment (fatigue, poor concentration, daytime sleepiness, or concerns about sleep).[277] The incidence of insomnia in patients with cancer has been reported to be three times higher than that reported in the general population and ranges from 25% to 69%, depending on the type of cancer.[278,279] In a longitudinal study that assessed the prevalence and natural course of insomnia in patients with cancer during an 18-month period, Savard et al reported higher rates of insomnia in patients with breast (42%–69%) and gynecologic (33%–68%) cancer and lower rates among men with prostate cancer (25%–39%).[279]

Insomnia is more prevalent in older adults, and older patients with cancer should be screened for sleep disturbances prior to the initiation of treatment and at regular intervals during the course of treatment. The AGS has provided recommendations for the diagnosis, evaluation, and management of insomnia in older adults.[277] The recently published Pan-Canadian practice guidelines also provide recommendations for the prevention, screening, assessment, and treatment of sleep disturbances in older patients with cancer.[280]

Cognitive behavioral therapy (CBT) and lifestyle modifications are the preferred first-line treatment options for the management of insomnia in older patients.[277,280] The effectiveness of CBT with multicomponent interventions (stimulus control, sleep restriction, cognitive therapy, sleep hygiene, and fatigue management) for the management of insomnia in patients with cancer has been demonstrated in randomized clinical trials.[281-284] Adherence to CBT has been shown to yield greater sleep improvements among women following primary treatment for breast cancer.[285]

Pharmacologic therapy may be necessary for some patients until CBT takes effect.[277,280] Benzodiazepines, non-benzodiazepines, and melatonin-receptor agonists are the FDA-approved classes of drugs for the treatment of insomnia.[286,287] However, due to some of the severe adverse effects associated with these benzodiazepines and non-benzodiazepines (eg, impaired postural stability, fractures, cognitive impairment),[286] these drugs are not recommended as first-line therapy for the treatment of insomnia in older adults.[277,280] If pharmacologic therapy is to be utilized, it is recommended only for

short-term use, with the lowest dose that is safe and effective to address the particular type of sleep disturbance in an individual patient.

Targeted Therapy

The emergence of targeted therapies (monoclonal antibodies and small molecules targeted against specific molecular pathways required for the development of a particular malignancy) has significantly improved outcomes in a variety of malignancies. The use of targeted therapies in older patients appears to be promising in view of their better efficacy and toxicity than conventional chemotherapeutic agents.[288,289] However, these drugs are also associated with some unique and severe toxicities.[290] For example, cardiovascular complications such as LVD are associated with HER2 inhibitors (trastuzumab) and hypertension and arterial thromboembolic events (ATEs) are associated with vascular endothelial growth factor receptor (VEGFR) inhibitors (bevacizumab),[291-293] whereas dermatologic toxicities (acneiform rash and hand-foot skin reaction) are the major adverse effects of epidermal growth factor receptor (EGFR) inhibitors (ie, erlotinib, sunitinib, sorafenib, cetuximab).[294]

There are limited but growing data available on the safety and efficacy of targeted therapies in older patients with cancer. Prospective clinical trials that include a sufficiently large number of older patients are needed to accurately determine the efficacy and tolerability of targeted therapies in this cohort of patients. In patients who are not able to tolerate cytotoxic chemotherapy, the risk-benefit ratio should be considered prior to initiation of targeted therapy and the use of targeted therapies should be individualized.

See *Disease-Specific Issues* for the efficacy and tolerability of specific targeted therapies in older patients with cancer.

Adherence to Therapy

Adherence to the prescribed regimen, especially oral therapy, is essential to derive maximal clinical benefit. While older age per se is not a consistent risk factor for non-adherence, older adults are at an increased risk for non-adherence 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.[295]

Discontinuation and nonadherence to adjuvant hormonal therapy is well documented in women with early-stage breast cancer.[296] 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%.[297-300] 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, those with an increase in the 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.[300] 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.[297-299]

Adherence to adjuvant chemotherapy has also been evaluated in older patients with early-stage breast cancer.[301-303] In the randomized study

(CALGB 49907) that evaluated adjuvant chemotherapy with oral capecitabine vs. standard chemotherapy in 161 women (≥65 years) with early-stage breast cancer, 25% of the patients took fewer than 80% of the planned doses.[302] Non-adherence was more likely among women with node-negative disease and mastectomy. Adherence was not related to age, tumor stage, or hormone receptor status. However, in other studies, poor adherence to adjuvant chemotherapy was more frequent in older patients (≥65–75 years).[301,303]

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 non-adherence to cancer therapy.[304-307] Among 8,769 women treated with adjuvant hormone therapy for stage I-III breast cancer, Hershman et al identified early discontinuation and non-adherence to adjuvant hormonal therapy as independent predictors of increased mortality.[304] 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 non-adherence (81.7% and 77.8%, respectively; $P < .001$). In the ADAGIO study, non-adherence was associated with poorer response to imatinib in patients with chronic myeloid leukemia (CML); non-adherence rates were significantly higher for patients with suboptimal response compared to those with optimal response to imatinib (23% and 7%, respectively).[305] Marin and colleagues also identified adherence as the only independent predictor for achieving complete molecular response on standard-dose imatinib in patients with CML.[306] Poor adherence to imatinib therapy has also been identified as the most important factor contributing to cytogenetic relapse and imatinib failure.[307]

Treatment-related adverse events, complexity of regimens, poor understanding of the need for treatment, and the consequences of non-adherence are some of the common barriers to adherence. In a multicenter, prospective, open-label, randomized trial of exemestane vs. letrozole (n = 503), 32.4% discontinued initial therapy within 2 years due to adverse effects and the median time to treatment discontinuation was 6 months.[308] 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 most important factors for increasing compliance.[309]

In older patients with cancer, assessment of risk factors for non-adherence is recommended when considering a treatment regimen that will include an oral agent. Close monitoring of patient's 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 non-adherence to therapy.

Disease-Specific Issues

Since the biologic characteristics of certain cancers are different in older patients compared to their younger counterparts and partly because of the decreased tolerance of treatment by older patients, treatment should be individualized based on the nature of the disease and the performance status of the patient. Disease-specific issues related to age in some cancer types are discussed below.

Breast Cancer

Breast cancer in older women is associated with a more favorable tumor biology due to the high prevalence of hormone receptor-positive, HER2-negative, slowly proliferating tumors.[310,311] Nevertheless, women older than 75 years are usually managed with less aggressive treatment and have higher mortality rates from early-stage breast cancer than younger women.[312-314]

Axillary lymph node dissection (ALND) in patients with early breast cancer improves locoregional control and provides staging information but is also associated with undesirable morbidity. Data from a randomized clinical trial suggest that ALND did not result in improvement in DFS or OS compared to sentinel lymph node dissection alone in patients with invasive breast cancer (T1/T2) with limited sentinel lymph node involvement who were treated with breast conservation and systemic therapy.[315] Older patients with early-stage and clinically node-negative breast cancer also did not benefit from ALND in terms of breast cancer mortality or survival.[316-318] In the absence of definitive evidence demonstrating superior survival associated with ALND, this procedure can be considered optional for the following patients (if there are no palpable axillary nodes): older patients with particularly favorable tumors, those with serious comorbid conditions, and patients for whom the selection of adjuvant systemic therapy is unlikely to be affected.

RT as a component of breast-conserving therapy after lumpectomy is not always necessary in selected women 70 years of age or older with stage I breast cancer. In a study that randomized 636 women (≥70 years) treated with lumpectomy for clinical stage I, estrogen receptor-positive breast cancer to tamoxifen with whole breast RT or tamoxifen alone, locoregional recurrence was slightly higher among women who did not receive RT.[319,320] At the median follow-up of 12.6 years, the 10-year local recurrence rate was 2% and 9%, respectively, for those who received tamoxifen with RT and tamoxifen alone. However, there were no significant differences in time to mastectomy, time to distant metastasis, breast cancer-specific survival, or OS between the two groups.[320] The 10-year OS rates were 67% and 66%, respectively, for the two groups and the estimated 10-year breast cancer–specific survival rates were 97% and 98%, respectively. In this study, all patients received adjuvant tamoxifen for 5 years. Results of the recently published PRIME II study led the authors to conclude that since the rate of ipsilateral recurrence is low, omission of whole breast RT following breast-conserving surgery could be considered for some women 65 years of age or older with early-stage low-risk breast cancer (hormone receptor-positive, axillary node-negative, T1-T2 up to 3 cm at the longest dimension, and clear margins; grade 3 tumors or lymphovascular invasion).[321] In this study, 1326 women aged ≥65 years who had undergone breast-conserving surgery for early-stage breast cancer and receiving adjuvant endocrine treatment were randomized to whole-breast RT and no further treatment. After a median follow-up of 5 years, the ipsilateral recurrence rate was 1.3% in women assigned to whole-breast RT and 4.1% for those assigned no RT (P = .0002), with no difference in OS between the two groups. The 5-year OS rate was 93.4% in both groups.

The panel concluded that omission of RT can be considered in women ≥70 years with stage I estrogen receptor-positive breast cancer who undergo a lumpectomy with negative margins and who are likely to complete 5 years of endocrine therapy. Given that the PRIME study results are based on the 5-year follow-up, the panel concluded that at the present time there is not enough evidence to extrapolate these

results to any patient ≥65 years with a life expectancy of greater than 5 years.

Primary endocrine therapy with aromatase inhibitors or tamoxifen has also been evaluated in older women with operable hormone receptor-positive breast cancer.[322,323] In the Cochrane Database Systematic Review of randomized trials that evaluated primary endocrine therapy versus surgery (with or without adjuvant endocrine therapy) in women 70 years of age or older with early-stage breast cancer, the OS was not significantly different in women treated with surgery or primary endocrine therapy.[322] However, there was a statistically significant difference in progression-free survival (PFS) that favored surgery with or without endocrine therapy. The findings from another recent systematic review also demonstrated an advantage for surgery over primary endocrine therapy in terms of disease control and survival benefit in patients with an estimated life expectancy of 5 or more years. However, there are no well-defined guidelines to aid in the selection of patients for primary endocrine therapy. At the present time, primary endocrine therapy should be reserved for select patients with limited life expectancy and who are not candidates for surgery.

Older women with stage I-III breast cancer derive similar clinical benefits from adjuvant hormonal therapy[324-326] compared to younger women. Adjuvant hormonal therapy is widely used in older women with breast cancer because of the increase in the proportion of hormone-receptor-positive tumors with age.

The age-associated benefit of adjuvant chemotherapy has been more controversial, with some studies suggesting a decreased benefit from adjuvant chemotherapy with increasing age[327] and others suggesting a preserved benefit in patients across all age groups. Overall, age-specific data in this population are limited. However, in the CALGB 49907 study, adjuvant chemotherapy with CMF (cyclophosphamide, methotrexate, and fluorouracil) or doxorubicin plus cyclophosphamide was superior to capecitabine alone in women ≥65 years with invasive breast cancer.[328] The 3-year RFS rates were 68% and 85%, respectively, for the capecitabine group and the chemotherapy group ($P < .001$). The corresponding OS rates were 86% and 91%, respectively ($P = .02$).[328] An unplanned subset analysis of this trial showed that the benefit was pronounced in women with hormone receptor-negative tumors ($P < .001$). The results of the randomized phase III trial (ELDA) showed that weekly docetaxel did not improve DFS compared to CMF as adjuvant treatment for older women (65–79 years) with early-stage breast cancer.[329] Docetaxel was associated with severe nonhematologic toxicity and worse QOL.

Older women with advanced or metastatic breast cancer (HER2-positive or HER2-negative and hormone receptor-positive) also derive similar benefits from first-line therapy compared to their younger counterparts.[233,330] In a phase III randomized study, the combination of pertuzumab with trastuzumab and docetaxel resulted in superior PFS compared to treatment with trastuzumab, docetaxel, and placebo in older patients (≥65 years) with HER2-positive metastatic breast cancer.[233] The median PFS was 21.6 months in the pertuzumab arm compared to 10.4 months in the placebo arm. However, non-hematologic toxicities (diarrhea, decreased appetite, vomiting, and fatigue) resulting in dose-reductions were more frequent in older patients. The results of another phase III randomized study confirmed that the combination of everolimus with exemestane resulted in an improvement in PFS in patients with HER2-negative, hormone receptor-positive breast cancer, regardless of patient age.[330] This combination was associated with an increased risk of stomatitis, pneumonitis, infection, rash, and hyperglycemia. Adverse event profiles

were similar in older and younger patients. Careful monitoring and appropriate dose reductions or interruptions for the management of adverse events are recommended.

Regular mammograms may be helpful for early detection of recurrence or new primaries; however, the benefits are likely quite small for women with a life expectancy of less than 5 years.[331] Decisions about mammograms for older breast cancer survivors should include discussions with patients about their risk of developing recurrent breast cancer, the potential benefits of mammograms in improving outcomes, the potential harms of mammograms (including false positives and overdiagnosis or overtreatment), and patients' values and preferences.

Central Nervous System Cancers

Glioblastoma Multiforme/Anaplastic Astrocytoma

Surgery is the primary treatment option for newly diagnosed patients with glioblastoma multiforme (GBM) or anaplastic astrocytoma. Available evidence suggests that gross total resection is associated with greater OS in patients ≥70 years.[332,333] In a small, randomized study involving patients ≥65 years (n = 30), the estimated median survival time was longer after open craniotomy and resection of the tumor (171 days compared to 85 days after the stereotactic biopsy; *P* = .035).[332] For patients ≥65 years, gross total resection was associated with a longer survival compared to biopsy and subtotal resection in a retrospective analysis.[333] It is difficult to be certain, given the small size of the randomized trials studies and the retrospective nature of other studies, whether the improved survival is a direct effect of the degree of surgery or related to selection bias. Furthermore, the median survival after resection alone is less than 12 months, indicating that additional treatment options are needed. In a retrospective review, aggressive treatment with all three components (RT, chemotherapy, and surgery) was associated with best OS.[334] The extent of surgical resection is important in older patients as well and age alone should not preclude a more complete resection, if technically feasible, in older patients with high-grade glioma.[335]

Surgery followed by RT in combination with concurrent and adjuvant temozolomide is the standard treatment for newly diagnosed GBM in patients younger than 70 years of age.[336] In the phase III randomized trial, concurrent chemoradiation therapy with adjuvant temozolomide and RT followed by 6 months of adjuvant temozolomide improved survival rates in patients with newly diagnosed GBM, and the survival benefit was seen in all patients between 60 and 70 years of age.[336] At 5-year follow-up, OS rates were 27%, 16%, 12%, and 9.8% at 2, 3, 4, and 5 years, respectively, for those who received RT with concurrent temozolomide. The corresponding survival rates were 11%, 4%, 3%, and 2% for those treated with RT alone. Recent reports from a global randomized phase III clinical trial (562 patients; ≥65 years) confirmed that the addition of concurrent and adjuvant temozolomide to hypofractionated RT (40 Gy in 15 fractions over 3 weeks) is well tolerated and significantly improves OS and PFS in older patients with newly diagnosed GBM and good performance status.[337] The median OS and PFS for patients who received RT with concurrent and adjuvant temozolomide were 9.3 months and 5.3 months, respectively, compared to 7.6 months and 3.9 months for those who were treated with RT alone (*P* < .0001). Patients with MGMT methylated tumors benefited the most from the addition of temozolomide to RT. Earlier reports from other investigators also suggest that the addition of temozolomide to standard RT (60 Gy) or short-course RT (40 Gy in 15 fractions over 3 weeks) can prolong survival with acceptable toxicity in older patients with GBM.[338-341] In a phase II trial of 71 patients (≥70 years of age) with newly diagnosed GBM, treated with short-course RT (40 Gy in 15 fractions over 3 weeks)

in combination with temozolomide, the median OS and PFS were 12.4 months and 6 months, and the 1-year OS and PFS rates were 58% and 20%, respectively.[338] In a retrospective matched-pair analysis of older patients with newly diagnosed glioblastoma treated with RT alone (n = 103) or in combination with concurrent and adjuvant temozolomide (n = 190), the combined modality treatment prolonged survival in patients over the age of 70 and 75 years.[339] In patients older than 70 years, the median survival was 7.5 and 3.2 months, respectively, for patients treated with RT and combined modality treatment ($P < .0001$). In patients older than 75 years, the corresponding median survival was 9.2 months and 3.2 months ($P < .0001$), respectively. In a propensity matched analysis of 127 patients (≥65 years) treated with temozolomide in combination with standard RT or short-course RT, the median OS (12 months vs.12.5 months) and PFS (5.6 months and 6.7 months) were similar for both treatment groups.[340] However, standard RT was associated with a significant increase in grade 2 and 3 neurologic toxicity and higher posttreatment dosing of corticosteroid. Results from another recent retrospective analysis also showed that the addition of temozolomide to standard or short-course RT resulted in similar OS in patients ≥65 years with newly diagnosed GBM.[341]

Postoperative RT alone has also been shown to effectively improve clinical outcomes in older patients with GBM.[342,343] In a randomized trial, older patients with GBM treated with surgery (≥60 years, n = 100) were randomized to either standard course RT (60 Gy in 30 fractions over 6 weeks) or an abbreviated course of RT (40 Gy in 15 fractions over 3 weeks).[342] The median OS was similar for both treatment groups (5.1 months for standard RT and 5.6 months for abbreviated course RT). However, among those who completed RT as planned, more patients who received standard RT required a post-treatment increase in corticosteroid dosage (49% compared to only 23% of those who received shorter-course RT). In a small randomized study that assessed supportive care alone or in combination with RT (50 Gy in 25 daily fractions) in patients 70 years of older (n = 85), at a median follow-up of 21 weeks, the median survival was longer for those who received supportive care plus postoperative RT compared to supportive care alone (29 weeks and 17 weeks, respectively).[343] RT was not associated with severe adverse events and the results of quality-of-life and cognitive evaluations over time also did not differ significantly between the treatment groups. The results of a recent randomized study showed that short-course RT (25 Gy in 5 daily fractions over 1 week) was non-inferior to standard-dose RT (40 Gy in 15 daily fractions over 3 weeks) for patients with newly diagnosed glioblastoma.[344]

More recent randomized phase III studies have demonstrated the non-inferiority of temozolomide compared to RT in older patients with anaplastic astrocytomas and glioblastomas.[345,346] In the NOA-08 randomized phase III trial (373 patients; ≥65 years with anaplastic astrocytoma or glioblastoma), the median OS (8.6 months and 9.6 months, respectively; $P = .033$) and event-free survival (EFS; 3.3 months and 4.7 months, respectively; $P = .043$) were not significantly different between the temozolomide and RT groups.[345] The Nordic phase III trial, which randomized 291 patients (≥60 years) with glioblastoma across three treatment groups (temozolomide, hyperfractionated RT, and standard RT), also reported significantly longer median OS with temozolomide compared to standard RT (8.3 months vs. 6.0 months; $P = .01$), but the median OS was similar for patients treated with temozolomide and hyperfractionated RT (8.4 months vs. 7.4 months; $P = .12$).[346]

The panel recommends that postoperative, hypofractionated, accelerated course RT (with the goal of completing the treatment in 2–3 weeks) either alone or in combination with concurrent and adjuvant

temozolomide is a reasonable treatment option for patients ≥70 years. In the absence of a randomized trial comparing combined modality therapy (standard or short-course RT with concurrent and adjuvant temozolomide) vs. standard or short-course RT or temozolomide alone, the panel does not recommend withholding temozolomide for older patients with newly diagnosed GBM in the absence of a specific contraindication. The benefit of concurrent chemoradiation is likely to be helpful for selected "fit" patients older than 70 years of age. Methylguanine DNA methyltransferase (MGMT) gene promoter methylation status has been identified as a predictive marker for survival benefit in patients treated with temozolomide, and this could be useful for the selection of older patients suitable for treatment with temozolomide in combination with RT.[345-347] In the NOA-08 trial, among patients treated with temozolomide, EFS was longer in patients with MGMT promoter methylation who received temozolomide than in those who underwent RT (8.4 months vs. 4.6 months) [345] In patients with no MGMT promoter methylation, the EFS was 3.3 months and 4.6 months, respectively, for patients treated with temozolomide and RT. In the Nordic phase III trial, patients treated with temozolomide who had tumor MGMT promoter methylation had significantly longer survival than those without MGMT promoter methylation (9.7 months vs. 6.8 months; *P* = .02), but MGMT promoter methylation status had no impact on survival for patients treated with RT.[346]

In a single-institution retrospective analysis, bevacizumab, an anti-VEGFR antibody, resulted in a significant improvement in PFS and OS in patients ≥55 years with poor performance status.[348] VEGFR expression was also significantly higher in patients ≥55 years, implying that bevacizumab could be beneficial for this group of patients with recurrent GBM.[348]

Primary CNS Lymphoma

High-dose methotrexate-based chemotherapy with whole-brain RT (WBRT) has improved survival for older patients with primary CNS lymphoma (PCNSL). However, patients older than 60 years treated with WBRT are at an increased risk of developing neurotoxicity. In a cohort study of 57 patients (median age of 65 years and median Karnofsky performance score of 70) with newly diagnosed PCNSL, Gavrilovic et al reported a median OS of 29 months for patients older than 60 years regardless of whether they received WBRT.[349] There was a striking increase in neurotoxicity in patients older than 60 years compared to younger patients (75% and 26%, respectively). Other studies have reported favorable outcomes with a reduced risk of delayed neurotoxicity in older patients treated with methotrexate-based chemotherapy alone.[350-352] In a retrospective review of 31 patients ≥70 years, high-dose methotrexate induced an overall radiographic response rate of 97%; the PFS and OS rates were 7 months and 37 months, respectively.[351] In another retrospective analysis, Ney et al reported a median OS of 25 months in patients ≥65 years treated with methotrexate-based chemotherapy alone.[352] A more recent retrospective analysis showed that high-dose methotrexate-based chemotherapy was also well tolerated and effective in patients ≥80 years (24 patients) with a response rate of 62.5%.[353] Median OS and PFS were 7.9 months and 6.5 months, respectively. The 2- and 3-year survival rates were 33% and 17%, respectively. These results indicate that patients ≥60 years with PCNSL should be treated initially with chemotherapy, saving WBRT for those with recurrent or refractory disease.

Gastrointestinal Cancers

Colon Cancer

Age alone should not be a contraindication for curative surgery in older patients with early-stage and resectable colorectal cancer.[354-356] Results of a retrospective study that evaluated age-related surgical risk and outcome in patients with colorectal cancer showed that the long-term results after surgery were more dependent on the stage of disease and on the type of adjuvant or palliative treatment than on age.[354] In the metastatic setting, a study by Adam et al compared the outcome of liver resection for colorectal metastases in older patients with that of younger patients; the 3-year OS was 57% in older patients and 60% in younger patients ($P < .001$).[357] The OS was similar among patients aged 70 to 75 years, 75 to 80 years, or at least 80 years (58%, 55%, and 54%, respectively; $P = .160$). Careful preoperative planning and non-emergent surgery are more likely to result in optimal outcomes.[357]

In the adjuvant setting, older patients derive similar benefit from fluorouracil-based chemotherapy as younger patients.[9,358] However, older patients may be at an increased risk for hematologic toxicities. In a pooled analysis of adjuvant chemotherapy trials, the relative benefit of OS from adjuvant chemotherapy was similar across all age groups, with no increased incidence of toxicities among patients ≥70 years, with the exception of leukopenia in one study.[9] The 5-year OS rate was 71% for those who received adjuvant chemotherapy compared to 64% for those who were untreated. However, after 5 years, the absolute benefit of chemotherapy was smaller in patients ≥70 years due to competing causes of death. Pooled analyses of data from adjuvant trials using newer regimens containing oxaliplatin did not show significant benefit in DFS or OS compared to fluorouracil and leucovorin in patients older than 70 years.[359] For patients ≥75 years with stage III colon cancer, a recent retrospective analysis suggests that oxaliplatin-containing regimens may offer a small incremental survival benefit over non-oxaliplatin regimens.[360] Due to the lack of data from prospective randomized studies, adjuvant chemotherapy with newer regimens should be considered on an individual basis for patients ≥70 years.

Fluorouracil-based palliative chemotherapy resulted in equal OS (10.8 months and 11.3 months, respectively; $P = .31$) and PFS (5.5 months and 5.3 months, respectively; $P = .01$) in older (≥70 years) and younger patients with metastatic colorectal cancer.[361] Infusional fluorouracil was more effective than bolus fluorouracil in both age groups. In a recent randomized trial (MRC FOCUS2) of older and frail patients with metastatic colorectal cancer, the addition of reduced-dose oxaliplatin to fluorouracil or capecitabine was not associated with a significant improvement in median PFS (5.8 months vs. 4.5 months; $P = .07$).[362] The same study also showed that the replacement of fluorouracil with capecitabine resulted in a higher rate of grade 3 or higher toxicity with no improvement in QOL. In the OPTIMOX1 study, oxaliplatin-based chemotherapy stop-and-go (FOLFOX7 for 6 cycles, maintenance without oxaliplatin for 12 cycles, and reintroduction of FOLFOX7) had similar efficacy and tolerability compared to the standard oxaliplatin-based regimen (FOLFOX4) in patients aged between 76 and 80 years with metastatic colorectal cancer,[363] implying that stop-and-go strategies or maintenance fluorouracil-based chemotherapy may be desirable for older patients with metastatic disease to minimize toxicities. Pooled analyses of large clinical trials have demonstrated the feasibility of treating metastatic colon cancer in older adults with FOLFOX or FOLFIRI with similar toxicity and efficacy to that seen in younger patients.[364,365] Bevacizumab[366,367] and anti-EGFR antibodies, cetuximab[368-370] and panitumumab,[371,372] have also been evaluated for the treatment of older patients with metastatic colorectal cancer.

Older patients (≥65 years) with metastatic colorectal cancer derive similar clinical benefit as younger patients with the use of bevacizumab in combination with chemotherapy.[366,367,373] In the BRiTE study, the median PFS was similar across all age cohorts. However, median OS and survival beyond progression declined with age.[367] In a retrospective analysis, the addition of bevacizumab to chemotherapy significantly improved PFS and OS in patients ≥65 years with metastatic colorectal cancer.[366] The results of another randomized phase III trial (AVEX study) also showed that the combination of bevacizumab and capecitabine was effective and well-tolerated in older patients (280 patients; ≥70 years) with previously untreated, unresectable, or metastatic colorectal cancer, not considered candidates for oxaliplatin-based or irinotecan-based chemotherapy.[373] The median PFS was significantly longer with bevacizumab and capecitabine than with capecitabine alone (9.1 months vs. 5.1 months). However, the use of bevacizumab is associated with a higher rate of ATEs, bleeding, and hypertension in older patients.

Data from retrospective studies have shown that cetuximab as a single agent or in combination with irinotecan has a favorable safety profile in heavily pretreated older patients (≥70 years) with metastatic colorectal cancer and the efficacy was similar to that observed in younger patients with acceptable tolerability.[368,369] In a phase II clinical trial, cetuximab was safe and moderately active when used as a first-line single agent in fit older patients with metastatic colorectal cancer.[370]

In the phase III trial that evaluated the activity of panitumumab plus best supportive care versus best supportive care alone in patients with metastatic colorectal cancer, panitumumab had a favorable effect on PFS regardless of age (HR = 0.51 and 0.60, respectively, for patients <65 years and >65 years).[371] The PFS, OS, and overall response rates were similar in older and younger patients.

Among patients with metastatic colorectal cancer treated with cetuximab and panitumumab, available evidence indicates that the presence of wild-type *KRAS* mutations is associated with higher response rates and PFS.[369,372] *KRAS* mutation testing could be helpful for the appropriate selection of patients who could benefit from treatment with cetuximab and panitumumab.

Rectal Cancer

Combined modality therapy with surgery, RT, and chemotherapy is the standard of care for the majority of younger patients with locally advanced disease. This approach is not widely used in older patients mainly because of treatment-related complications that could outweigh the benefits of rectal cancer treatment for this group of patients.[374-376]

Available evidence from some retrospective analyses suggests that selected older patients may have survival benefit with rectal cancer surgery similar to their younger counterparts.[377-381] However, postoperative complications are more severe in older patients.[382,383] In the Dutch trial that established the safety and efficacy of total mesorectal excision, postoperative complications occurred more frequently in older patients and were associated with a significantly higher risk of 6-month mortality in patients ≥75 years compared to those 75 or younger.[382] The overall 6-month mortality was 4 times higher in older patients than in younger patients (14% and 3.3%, respectively; $P < .001$).

A pooled analysis from 22 clinical trials with more than 8,000 rectal cancer patients demonstrated a reduction in the risk of local recurrence and death from rectal cancer with perioperative radiotherapy regardless of patient age.[384] However, the risk of death from non-cancer–related causes was increased in the older patient population. The Stockholm II trial, a population-based prospective randomized trial, also reported

similar findings on preoperative radiotherapy.[385] Although preoperative short-term radiotherapy reduced the risk of pelvic recurrence and improved survival after curative surgery, mortality from noncancer causes was higher especially in older patients treated with RT during the first 6 months after surgery. Cardiovascular disease was the main cause of postoperative mortality and intercurrent death following RT.

Retrospective studies have also reported that preoperative chemoradiation increases the feasibility of sphincter-preserving surgery with good tumor downstaging in patients ≥70 years with locally advanced cancer.[386-388] However, there are conflicting reports regarding the tolerance of this approach.[389,390] In one study, neoadjuvant chemoradiation was associated with comparable tolerability and response rates in vulnerable and fit older patients (≥70 years).[389] In another series, the majority of patients ≥75 years treated with combined modality treatment required early termination of treatment, treatment interruptions, and dose reductions.[390] Postoperative chemoradiation has also been associated with improved survival in older patients with node-positive stage III rectal cancer but not for those with stage II cancer.[386,391]

In the absence of data available from randomized studies, individualized treatment options are recommended for older patients with rectal cancer. Older patients should not be excluded (based only on chronologic age) from the curative treatment options that are available for younger patients.[189,392] Multidisciplinary evaluation and optimization of comorbidities are important for optimal patient outcomes in rectal cancer management. Medically fit older patients should be considered for a combined modality treatment approach or for participation in clinical trials designed for older patients with this disease.

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) in older patients is characterized by lower male/female ratio, lower rates of HCV infection, less advanced liver cirrhosis, and worse performance status.[393] Older patients with HCC may benefit from liver resection or transplantation.[394-396] Available evidence (primarily from retrospective studies) has shown no major difference in outcomes between carefully selected older patients and younger patients with HCC.[393,397-400] In general, older patients are less likely to receive liver transplantation than younger patients. A few centers have successfully transplanted highly selected patients older than 70 years, but the data are inadequate to make a recommendation regarding liver transplantation in the older patients with HCC.

Available evidence (primarily from non-randomized clinical trials and retrospective analyses) supports the use of SBRT in the management of patients with unresectable or locally advanced HCC. In a large prospective series of 102 patients with locally advanced HCC and Child-Pugh A liver function treated in sequential phase I and phase II trials, SBRT resulted in a 1-year local control rate of 87% and median survival of 17 months.[401] The majority of these patients were at high risk with relatively advanced-stage tumors. Limited safety data are available in patients with Child-Pugh B or poorer liver function.[402-405] The safety of SBRT for patients with Child-Pugh C cirrhosis has not been established. In a retrospective analysis of 185 patients treated with SBRT at two different dose levels (40 Gy in 5 fractions for patients with Child-Pugh A liver function and 35 Gy in 5 fractions for those with Child-Pugh B liver function), the 3-year local control and OS rates were 91% and 70%, respectively, with no significant differences in outcomes between dose levels.[405]

The panel decided to include a section highlighting the benefit of SBRT for older patients with HCC who may not be able to tolerate liver

resection or transplantation and locoregional therapies. The panel recommends that SBRT should be considered for those who may not be suitable for liver resection or transplantation due to the presence of comorbidities or compromised performance status. Patients with good liver function (Child Pugh Class A) and limited volume of disease are ideal candidates for SBRT, although those with Child-Pugh B cirrhosis can be safely treated with dose modifications and strict dose constraint adherence. Toxicity to treatment can be minimized by careful patient selection, appropriate radiation dose, and optimized dosimetry to meet normal tissue constraints.

Sorafenib is the standard systemic therapy for patients with advanced HCC. In a retrospective analysis of patients with advanced HCC treated with sorafenib, survival benefits were comparable in older (≥70 years) and younger patients (≤70 years); however, grade 3-4 adverse events occurred more frequently in older patients.[406] The median PFS was 2.99 months for older patients and 3.09 months for younger patients. The median OS was 5.32 months and 5.16 months, respectively. The incidence of grade 3 or 4 neutropenia (11.4% vs. 0.7%), malaise (11.4% vs. 2.2%), and mucositis (5.7% vs. 0.0%) were more frequent in patients ≥70 years. Therefore, more vigilant monitoring is warranted for older patients with advanced HCC treated with sorafenib.

Genitourinary Cancers

Bladder Cancer

Age alone should not be a criterion for making decisions regarding cystectomy, RT, and chemotherapy in older patients. Radical cystectomy with pelvic lymph node dissection (PLND) is the standard treatment for patients with muscle-invasive bladder cancer. In a SEER database analysis of 10,807 patients diagnosed with muscle-invasive bladder cancer, radical cystectomy resulted in a longer OS than treatment with RT in all age groups.[407] While the OS benefit was significantly higher in the radical cystectomy arm for patients 70 to 79 years (33 months vs. 19 months), the survival benefit was smaller in patients ≥80 years (18 months vs.15 months). In patients ≥80 years, there was a small OS benefit for radical cystectomy with PLND compared to bladder preservation with RT (21 months vs.15 months, respectively).[407]

In a randomized study that compared neoadjuvant chemotherapy plus cystectomy with cystectomy alone, the addition of neoadjuvant chemotherapy resulted in improved survival among patients with locally advanced cancer.[408] Median survival was 46 months and 77 months, respectively (P = .06), for patients assigned to cystectomy and cystectomy plus neoadjuvant chemotherapy, and the survival benefit was preserved with age.[408]

Intravesical immunotherapy with Bacillus Calmette-Guérin (BCG) has decreased efficacy, particularly in patients older than 80 years.[409,410] In one study, at a median follow-up of 24 months, the cancer-free survival rates were 39% and 61%, respectively, for patients older than 80 years and patients 61 to 70 years treated with BCG (P = .0002).[409] Age was an independent risk factor for decreased response after taking into account the stage, grade, sex, and prior treatment.[409] In the second study, the percent of patients free from disease at 5 years after BCG therapy was 27% and 37%, respectively (P = .005), for patients ≥70 years and patients <70 years.[410]

Older age does not appear to be associated with worse late pelvic toxicity after curative intent selective bladder preservation, and older patients appear to have similar response rates and disease-specific survival compared to younger patients following curative intent selective bladder preservation.[411,412]

Kidney Cancer

Surgical resection remains an effective treatment for patients with localized renal cell carcinoma (RCC). However, in a recent study, Lane et al reported that surgical management of clinically localized renal cortical tumors was not associated with increased survival in patients ≥75 years.[413] Radical nephrectomy resulted in renal dysfunction in 86% of patients and was a significant predictor of cardiovascular mortality. The authors concluded that the surgical management of older patients with localized RCC should be individualized based on predicted life expectancy.

Recently, several targeted therapies including bevacizumab,[414] sorafenib,[415,416] sunitinib,[417,418] and mammalian target of rapamycin inhibitors (everolimus and temsirolimus)[419,420] have been evaluated in older patients with metastatic RCC. Sorafenib, sunitinib, and everolimus have similar efficacy in younger and older patients with advanced RCC.

In the retrospective analysis of the Advanced Renal Cell Carcinoma Sorafenib (ARCCS) program in North America, the median OS (46 weeks vs. 50 weeks; *P* = .4) and PFS (42 weeks vs. 35 weeks; *P* = .8) were similar for patients ≥70 years and patients <70 years with advanced RCC.[416] The incidences of most common adverse events (grade 3 or higher; rash or desquamation [5% in both groups], hand-foot skin reaction [8% and 10%, respectively], hypertension [5% vs. 4%, respectively], and fatigue [7% vs. 4%, respectively]) were also similar in both age groups.[416] In a pooled analysis of data from 6 prospective clinical trials that evaluated the efficacy and safety of sunitinib in patients with metastatic RCC (n = 1059), the median PFS (9.9 months and 11 months, respectively; *P* = .083) and OS (23.6 months and 25.6 months, respectively; *P* = .544) were similar for patients <70 years and for those ≥70 years.[418] The incidences of adverse events were also similar, although some (fatigue, decreased appetite/weight, cough, peripheral edema, anemia, and thrombocytopenia) were more common in older patients.

Temsirolimus was associated with an improved OS (*P* = .008) and PFS (*P* < .001) compared to interferon among patients with metastatic RCC and poor prognosis.[419] In a multicenter, randomized phase III trial, the median OS was 10.9 months for the temsirolimus group compared to 7.3 months and 8.4 months, respectively, in the groups treated with interferon alfa alone or in combination with temsirolimus. Temsirolimus alone was associated with fewer incidences of grade 3 or 4 adverse events than interferon. Interferon is not recommended for older patients because of its increased toxicity. In a subgroup analysis of a phase III trial that evaluated the safety and efficacy of everolimus in patients with metastatic RCC, median PFS was 5.36 months and 5.13 months, respectively (*P* < .001), for patients ≥65 years and ≥70 years.[420] Older patients were at increased risk of adverse events including stomatitis, anemia, and infection.

Prostate Cancer

Management of older patients with prostate cancer is similar to that of younger patients.[421] Treatment options are based on the anticipated life expectancy of individual patients and whether they are symptomatic.

The use of long-term androgen deprivation therapy (ADT) in combination with RT is an effective treatment option (associated with improved cancer-specific survival and OS) for all patients with high-risk prostate cancer. However, the significant side effects of long-term ADT (increased risk of fracture due to osteoporosis, glucose intolerance, and thromboembolic events) are of particular concern in older men who often present with multiple comorbidities.[422-424] ADT significantly decreases muscle mass, and treatment-related sarcopenia appears to

contribute to frailty and increased risk of falls in older men.[425,426] Attention to bone health is warranted in older patients.

The efficacy of short-course ADT (4–6 months) in combination with RT for locally advanced prostate cancer has also been demonstrated in randomized clinical trials.[427-430] In one randomized trial (that also assessed the interaction between the level of comorbidity and treatment), the survival benefit associated with the addition of 6 months of ADT to RT was restricted only to men without moderate or severe comorbidity.[427] Results from another study also suggest that 6-month ADT produces long-term testosterone suppression, which may provide the cancer-specific survival benefit observed with long-term hormonal therapy in men of advanced age.

Based on these findings, the panel concluded that in men of advanced age with high-risk prostate cancer and moderate-to-severe comorbidity, shorter course (4–6 months) of ADT with RT can be considered over longer course (28–36 months) ADT.

Docetaxel-based chemotherapy has been effective in older patients with metastatic castration-recurrent prostate cancer (mCRPC).[431-433] The results of the subgroup analysis of the TAX 327 trial showed a survival benefit for 3-weekly docetaxel and prednisone compared with the weekly schedule of the same regimen and mitoxantrone and prednisone across all age groups for patients with mCRPC. The median OS was 18.9 months, 16.1 months, and 12.5 months, respectively. Among patients treated with 3-weekly docetaxel and prednisone, the median OS was 18.9 months, 18.6 months, and 20.4 months, respectively, for patients ≥75 years, 65 to 74 years, and < 65 years, respectively. The corresponding 1-year OS rates were 68%, 74%, and 76%, respectively. The tolerability was similar for both the 3-weekly and weekly docetaxel and prednisone. However, there was a trend toward increasing frequency of grade 3-4 toxicities with increasing age. Every-3-week dosing of docetaxel and prednisone is the preferred regimen (with close monitoring for toxicity) for fit older patients with mCRPC.

Recently, cabazitaxel has demonstrated activity in patients with mCRPC that has progressed on docetaxel-based chemotherapy.[434] In a randomized phase III trial, cabazitaxel with prednisone improved OS compared to mitoxantrone plus prednisone. The survival benefit was seen across all age groups.[435] The HRs for OS were 0.62 and 0.81, respectively, for older (≥65 years) and younger patients. Growth factor support is strongly recommended for patients ≥65 years receiving cabazitaxel due to the increased risk of neutropenia in these patients.

Gynecologic Cancers

Ovarian Cancer

Population-based studies suggest that older women are often managed with less aggressive treatment, which may have an impact on the clinical outcome.[436-440] In an analysis from the Geneva Cancer Registry that included younger and older women diagnosed with primary ovarian cancer, the 5-year disease-specific survival was 18% for women ≥70 years compared to 53% for young women.[438] Older women also had a 2-fold increased risk of death from ovarian cancer compared to younger women. Among older women, the use of surgery and chemotherapy decreases with increasing age and the presence of comorbidities. In a SEER database analysis of 4,617 women (≥65 years) with untreated ovarian cancer, 53% of women ≥80 years did not receive any chemotherapy compared with 14% of women who were 65 to 69 years of age.[440]

In the United States, the proportion of older women treated with ovarian cancer-directed surgery and chemotherapy varies widely (53%–83% for

surgery and 48%–93% for chemotherapy) depending on the geographic location.[439] In a population-based analysis designed to predict treatment outcomes and risk factors for early death among older patients with advanced ovarian cancer, oncology treatment facility was also identified as an independent predictor of OS at 12 months from diagnosis, in addition to patient's age, stage at presentation, and the presence of comorbidities.[441] Therefore, improving access to high-quality cancer care may have the greatest impact on improving outcomes in older patients.

Primary treatment for ovarian cancer consists of appropriate surgical staging and cytoreductive surgery, followed by systemic chemotherapy. Older patients with advanced cancer are less likely to enroll in prospective Gynecologic Oncology Group clinical trials, despite the fact that the incidence of stage III-IV ovarian cancer is higher in older women compared to their younger counterparts (82% in women ≥65 years vs. 67% in women <65 years).[442] As a result, there are very limited prospective data regarding the treatment of older patients with newly diagnosed ovarian cancer.

A retrospective exploratory analysis of the AGO OVAR-3 phase III trial, which included 103 patients (≥70 years; 13% of the study population), demonstrated that doublet chemotherapy (paclitaxel with cisplatin or carboplatin) is feasible and tolerable in older patients with advanced ovarian cancer, although early discontinuation was more frequent among older patients.[443] Available evidence from retrospective analyses suggests that intraperitoneal (IP) chemotherapy can be administered safely in selected older patients with adequate support and dose modifications.[444,445] Although older patients were less likely to complete the planned number of IP chemotherapy cycles, there was no significant association between age and complication rate or PFS.[444] Retrospective analysis of the SOCRATES trial showed that older patients with platinum-resistant ovarian cancer have a poor outcome.[446] The proportion of patients ≥70 years treated with secondary cytoreductive surgery was significantly lower than the younger patients (8.9% vs. 23.9%; *P* = .0018), and response rates to second-line chemotherapy were also significantly lower for older patients (46.5% vs. 67.2%; *P* = .0004).

Age is an important factor that influences the selection of treatment for patients with advanced-stage ovarian cancer. In a retrospective analysis of 1,895 patients with stage III epithelial ovarian cancer treated with primary surgery and chemotherapy, increasing age, poor performance status, mucinous or clear-cell histology, and macroscopic disease at surgery were identified as poor prognostic factors.[447] Older age (≥70 years) and the presence of two or more comorbidities have been associated with failure to complete the planned course of chemotherapy.[448,440] CGA could be useful to assess the individual risk of severe toxicity associated with chemotherapy in older women with ovarian cancer.[17]

Head and Neck Cancers

Surgery is associated with good clinical outcomes with acceptable complication rates in older patients; however, complication rates increase with comorbidities.[449,450] In a retrospective analysis of older patients (≥70 years), the overall complication rate was 63% and 54% of patients experienced clinically important surgical and/or medical complications.[449] Bilateral neck dissection, male sex, presence of two or more comorbidities, and advanced stage of disease were associated with postoperative complications.[450]

Older patients (≥70 years) with squamous cell carcinoma of the head and neck (SCCHN) who are treated with RT experience similar OS in comparison to younger patients.[451] Although there were no significant

differences in late toxicities in older patients compared to those younger than 70 years (median of 3 years of follow-up), severe grade 3 and 4 functional acute toxicity was significantly more frequent in older patients (67% for patients ≥65 years compared to 49% for younger patients).[451]

Few patients older than 70 years have been included in trials evaluating induction chemotherapy, and there are limited data on the efficacy and toxicity of such an approach in this subset of patients.[452,453] Randomized trials and meta-analyses have reported that concurrent chemoradiation offers greater benefit than RT or induction chemotherapy alone, but older patients are also at higher risk for acute toxicities.[454-456]

In a prospective randomized study that included 255 patients ≥60 years, concurrent chemoradiation was superior to RT alone or induction chemotherapy followed by RT for laryngeal preservation and locoregional control in patients (both older and younger than 60 years) with localized laryngeal cancer.[454] In the meta-analysis of chemotherapy in head and neck cancer, concurrent chemoradiation offered a significant OS benefit of 4.5% at 5 years compared to RT alone in patients with non-metastatic SCCHN.[456] However, this survival benefit decreased with increased age (≥71 years). In another retrospective analysis, older age was identified as the most significant factor associated with severe late toxicities (feeding tube dependence 2 years after RT, pharyngeal dysfunction, and laryngeal dysfunction) after concurrent chemoradiation.[455] There are not enough data in patients older than 70 years to draw firm conclusions regarding a survival advantage of adding concurrent chemotherapy to RT. Similarly, too few patients older than 70 years with resected SCCHN have been evaluated in the adjuvant therapy trials and there are limited data regarding the benefit of adding cisplatin to RT.[456]

Cisplatin-based chemotherapy is associated with increased toxicity in older patients with recurrent head and neck cancer.[457] In a review of two phase III randomized trials conducted by the ECOG that evaluated cisplatin with paclitaxel or fluorouracil, objective response rates (28% vs. 33%; $P = .58$) and median time to progression (5.25 months vs. 4.8 months; $P = .69$) were similar for older and younger patients, respectively.[457] However, the incidence of severe nephrotoxicity, diarrhea, and thrombocytopenia were higher among older patients.

Cetuximab has been evaluated only in few patients with head and neck cancer. For patients with locally advanced SCCHN, there is limited evidence regarding the benefit of adding cetuximab to RT in patients older than 64 years.[458] Available evidence does not allow one to draw firm conclusions regarding a survival advantage of concurrent cetuximab plus RT. There is also limited evidence regarding the benefit of adding cetuximab to chemotherapy in the treatment of patients older than 64 years with recurrent or metastatic SCCHN.[459]

Lung Cancers

NSCLC

Surgical resection and mediastinal lymph node dissection is the standard treatment for patients with early-stage NSCLC. Retrospective studies have demonstrated that age alone is not a contraindication for surgery and surgery is well tolerated in carefully selected patients.[460-464] Long-term follow-up of older patients (≥70 years) showed that the mortality and prognosis were similar to those in younger patients.[460] The postoperative mortality and the 5-year survival rates were 3% and 48%, respectively, for older patients. However, pneumonectomy was associated with a higher mortality rate in patients ≥70 years than younger patients (22% and 3.2%, respectively; $P < .005$).[465] Therefore, pneumonectomy should be performed with caution in older patients. SBRT has recently emerged

as an effective treatment option for patients with medically inoperable, early-stage NSCLC, resulting in high rates of local control and OS. The panel reviewed data from retrospective studies and population-based analysis that have evaluated the efficacy of SBRT in older patients with early-stage NSCLC.[466-469] A SEER database analysis of 9,093 patients (median age 75 years) compared the outcomes of lobectomy, sublobar resection, or stereotactic ablative radiation as a definitive treatment for early-stage, node-negative NSCLC.[466] In the propensity score matching analysis, lobectomy and SBRT were associated with similar OS and lung cancer-specific survival (LCSS) suggesting that SABR may be a good option among patients with very advanced age and multiple comorbidities. In a multi-institutional retrospective analysis of older patients (≥75 years) treated with SBRT for stage I NSCLC, high tumor control and low toxicity were similar to those reported in younger patients.[467] The results of a pooled analysis of two randomized trials (designed to assess the efficacy of SBRT compared with lobectomy for early-stage NSCLC in operable patients, but closed due to poor accrual) suggest that and SBRT could be an alternative option for early-stage NSCLC in patients who are not surgical candidates.[468] In the intent-to treat analysis of 58 patients randomly assigned to SABR and surgery, the estimated 3-year OS rate was 95% in the SBRT group compared to 79% in the surgery group (P = .037). The 3-year recurrence-free survival rates were 86% and 80%, respectively (P = .54).[468] Results of a recent retrospective analysis from the National Cancer Data Base also showed that SBRT is associated with improved survival in older patients with concurrent comorbid conditions and medically inoperable early-stage NSCLC.[469] The panel recommends SBRT for patients who are medically inoperable or who decline surgery after thoracic surgery evaluation.

Older patients with completely resected NSCLC derive similar survival benefits with adjuvant chemotherapy as younger patients.[470-472] A pooled analysis of 4,584 patients from five trials of adjuvant cisplatin-based chemotherapy showed that older patients had a survival benefit that was similar to that of their younger counterparts, without significant toxicity.[472] Another retrospective analysis of the Intergroup study (JBR.10) also showed that adjuvant vinorelbine and cisplatin improved survival in patients older than 65 years with acceptable toxicity.[471]

In older patients with locally advanced NSCLC, combined modality therapy (concurrent chemotherapy with RT given once or twice daily) has resulted in disease control and survival rates similar to that observed in younger patients; however, toxicities (esophagitis, pneumonitis, and myelosuppression) were more pronounced in older patients, especially in patients with poor performance status.[473-475] Langer et al reported that concurrent chemotherapy with once-daily RT was beneficial to older patients with locally advanced NSCLC. Median survival time was 22.4 months with concurrent chemotherapy with daily RT compared to 16.4 months and 10.8 months, respectively, for concurrent chemotherapy with twice-daily RT and sequential chemotherapy and daily RT. Short-term toxicities were more pronounced in the older patients.[473] Schild et al also reported that older and younger patients had similar survival benefit from concurrent chemoradiation therapy.[474] The 2- and 5-year survival rates were 36% and 13%, respectively, in older patients with locally advanced disease compared to 39% and 18%, respectively, in patients younger than 70 years (P = .4). Pneumonitis and myelosuppression were more pronounced in the older patients. In some studies, combined modality treatment was associated with excess toxicity and no survival benefit for the older patients.[475-477] More recently, in a phase III randomized

trial, Atagi et al also reported significant survival benefit for chemoradiation in older patients (n = 200) with locally advanced cancer.[475] At a median follow-up of 19 months, the median OS was 22.4 months and 16.9 months, respectively, for the chemoradiation therapy and RT alone groups (*P* = .0179). Grade 3-4 hematologic toxicities and grade 3 infection rates were higher in the chemoradiation therapy group, whereas incidences of grade 3-4 pneumonitis and late lung toxicity were similar between the two groups. Combined modality therapy is therefore an effective treatment option for selected fit older patients with locally advanced disease; however, careful attention to the management of toxicities is needed.

Chemotherapy is associated with improved quality of care in comparison to best supportive care in older patients with advanced disease.[478,479] In the ELVIS study, vinorelbine plus best supportive care was superior to best supportive care alone, in terms of both survival and QOL.[478] Median survival and 1-year survival were significantly better in the vinorelbine arm. The results of the subgroup analyses of phase III trials evaluating chemotherapy for patients with advanced NSCLC have shown that older patients in good performance status derive similar clinical benefit with combination chemotherapy as the younger patients. However, the incidences of toxicities are higher among older patients.[240,480,481] The two trials that have compared the combination of vinorelbine and gemcitabine with single-agent vinorelbine or gemcitabine in older patients with advanced NSCLC have shown conflicting results.[482,483] The results of the Southern Italy Cooperative Oncology Group (SICOG) phase III trial showed that the combination of gemcitabine and vinorelbine was associated with a significantly better survival than vinorelbine alone in older NSCLC patients.[482] However, in the MILES study, the combination of gemcitabine and vinorelbine was more toxic and failed to show any survival advantage over single-agent therapy with vinorelbine or gemcitabine alone.[483] There are emerging data confirming the survival benefit of 2-drug regimens compared to single-agent therapy for patients with advanced disease. In the recent multicenter randomized phase III trial (IFCT-0501), the combination of paclitaxel and carboplatin was associated with a significantly longer survival in patients ≥70 years (performance status 0-2) with advanced NSCLC than single-agent therapy with vinorelbine or gemcitabine, despite an increased risk of side effects (including febrile neutropenia, asthenia, and toxic death rate) with combination therapy.[484] Median OS was 10.3 months and 6.2 months, respectively, and the 1-year survival rates were 44.5% and 25.4%, respectively.

Bevacizumab and erlotinib have been evaluated in older patients with advanced NSCLC. A retrospective subset analysis of the phase III study (ECOG 4599) and a recent SEER-Medicare analysis suggest that the addition of bevacizumab to paclitaxel and carboplatin may not be associated with any survival benefit in older patients.[485,486] In the subset analysis of the ECOG 4599 study, although there was a trend towards higher response rate (29% vs. 17%; *P* = .067) and PFS (5.9 months vs. 4.9 months; *P* = .063) with paclitaxel, carboplatin, and bevacizumab (PCB) compared with paclitaxel and carboplatin, older patients randomized to PCB experienced a higher degree of toxicity (87% vs. 61%; *P* < .001) with no improvement in OS (11.3 months vs. 12.1 months; *P* = .4).[485] Erlotinib, although active and relatively well tolerated in chemotherapy-naive older patients (≥70 years) with advanced NSCLC, is associated with higher incidences of interstitial lung disease and toxicity-related discontinuation (5% and 12%, respectively),[487] compared to only 1% and 5% observed in the erlotinib arm of the BR.21 trial where the median age was only 62 years. A recent subgroup analysis of the BR.21 trial also confirmed that older patients

experienced greater toxicity and prolonged dose interruptions compared to younger patients, even though survival and quality-of-life benefits were similar for both groups.[488]

SCLC

Combined modality therapy is the recommended treatment for patients with limited-stage disease, whereas chemotherapy alone is the standard treatment option for patients with extensive-stage disease. Available data suggest that older patients have a survival benefit with combination chemotherapy regimens containing platinum and etoposide, albeit with higher treatment-related toxicities.[489-492]

In a retrospective analysis of the INT 0096 trial that evaluated cisplatin, etoposide, and thoracic RT administered once or twice daily for patients with limited-stage SCLC, the reported response rate (88% vs. 80%; *P* = .11), 5-year EFS rate (19% vs. 16%; *P* = .18), time to local failure, and duration of response were similar for patients ≥70 years and those <70 years.[489] However, hematologic (grade 4–5: 61% vs. 84%; *P* < .01) and other fatal toxicities (1% vs. 10%; *P* = .01) were more severe among patients ≥70 years. In addition, the 5-year OS rate was also higher for patients younger than 70 years (22% vs. 16%; *P* = .05). Age-specific subset analysis of the NCCTG phase III trial (209 patients) that compared etoposide and cisplatin with either twice-daily or once-daily RT in patients with limited-stage SCLC also reported similar findings.[490] The 2-year and 5-year survival rates were not significantly different between the 2 age groups (48% and 22%, respectively, for patients >70 years compared to 33% and 17%, respectively, for patients ≥70 years; *P* = .14). However, the incidence of severe pneumonitis (6% vs. 0%; *P* = .008) and grade 5 toxicity (5.6% vs. 0.5%; *P* = .03) were significantly higher among patients ≥70 years.

Regimens containing carboplatin or cisplatin appear to be equally effective in terms of clinical outcomes, differing only in their toxicity profiles.[493,494] The COCIS meta-analysis of individual patient data from four randomized trials showed that carboplatin-containing chemotherapy was associated with a significantly higher incidence of severe neutropenia, anemia, and thrombocytopenia, whereas nausea/vomiting, renal toxicity, and neurotoxicity were higher with cisplatin-containing regimens.[494] In the PFS analysis by the subgroups, carboplatin-based regimens were more favorable for older patients than cisplatin-based regimens.

The use of attenuated doses of chemotherapy, although better tolerated, is associated with inferior outcomes in older patients.[491] In a phase II trial, chemotherapy with cisplatin and etoposide at two different dose levels (attenuated-dose and full-dose with lenograstim support) was well tolerated in patients ≥70 years (n = 95), although grade 3-4 myelotoxicity was higher with the full-dose regimen (12% compared to 0% for the attenuated dose regimen). The overall response rate and 1-year survival rates were 39% and 18%, respectively, for the attenuated-dose regimen, compared to 69% and 39% for the full-dose regimen.

Prophylactic cranial irradiation (PCI) is effective in decreasing the incidence of cerebral metastases in patients with SCLC (limited and extensive stage) responding to initial chemotherapy. A recent report from a pooled analysis of four prospective trials showed that PCI was also associated with significant improvement in survival among older patients (≥70 years of age) with SCLC and the survival advantage was more significant in patients with extensive-stage SCLC.[495] However, PCI is also associated with more adverse events and increased neurotoxicity in older patients compared to younger

patients, with older age being the most significant predictor of chronic neurotoxicity.[496,497]

The panel concluded that patients 70 years and older with extensive-stage SCLC and response to chemotherapy may benefit from PCI. However, given the strong relationship between declining cognitive function and age, the panel emphasizes that patients with poor performance status or impaired neurocognitive functioning should not be treated with PCI.

Malignant Pleural Mesothelioma

Mesothelioma is a rare type of cancer that occurs in older individuals (median age 72 years). Asbestos exposure is a risk factor for mesothelioma. Malignant pleural mesothelioma (MPM) is the most common subtype. Mesothelioma can also occur in the lining of other sites (eg, peritoneum and pericardium). Older age (≥75 years), non-epithelioid histology, advanced-stage disease, and presence of comorbidities are associated with shorter OS.[498] Treatment options for patients with mesothelioma include surgery, RT, and/or chemotherapy. There are limited data regarding the surgical management of MPM in older adults. In single-institution retrospective studies, older age had a significantly negative impact on survival among patients treated with radical surgery for MPM.[499,500] Pemetrexed-based chemotherapy has been safe and effective in selected older patients with MPM.[498,501] In a pooled analysis of data from two phase II studies (178 patients), there was no significant difference in outcomes between older (≥70 years) and younger patients (<70 years) treated with pemetrexed and carboplatin as first-line therapy; however, hematologic toxicity was slightly worse in patients ≥70 years.[501]

Melanoma

Melanoma in older patients is characterized by the presence of thicker and more ulcerated tumors compared to younger patients and is often diagnosed at a later stage.[502] As with other cancers, age alone should not be a limiting factor in the selection of treatment (surgery, RT, or systemic therapy) for older patients with melanoma. Surgical excision is the primary treatment for melanoma. Adjuvant RT may be considered to improve local control if optimal surgery cannot achieve a negative margin. Systemic therapy with novel agents (ipilimumab, vemurafenib, dabrafenib, and trametinib) is now considered the standard of care for advanced, unresectable, or metastatic melanoma. While there is no available evidence to suggest age-specific recommendations regarding the use of surgery or RT, data from clinical studies evaluating recently approved targeted therapies (as discussed below) suggest that older patients derive similar benefit compared to younger patients.

Ipilimumab is a monoclonal antibody directed against the immune checkpoint receptor, cytotoxic T lymphocyte antigen-4 (CTLA-4). In a randomized phase III study, ipilimumab, with or without a glycoprotein 100 peptide (gp100) vaccine improved OS compared to gp100 alone in patients with previously treated metastatic melanoma.[503] The prespecified subset analysis suggests that the survival benefit was also seen in patients ≥65 years (HR = 0.69 for ipilimumab plus gp100; HR = 0.61 for ipilimumab). The results of a more recent study suggest that treatment with ipilimumab and sargramostim resulted in longer OS and lower toxicity compared to ipilimumab alone in patients with unresectable stage III or IV melanoma.[504] The benefit was also observed in patients ≥65 years. These preliminary findings require confirmation in a larger cohort of patients and a longer follow-up.

Vemurafenib and dabrafenib are the two *BRAF* kinase inhibitors approved for the treatment of metastatic and unresectable melanoma. In phase III randomized trials, vemurafenib and dabrafenib significantly improved OS compared to dacarbazine in patients (≥18 years) with previously untreated *BRAF* (V600E)-mutated metastatic melanoma.[505,506] Vemurafenib was also associated with improved response rates and OS. In the prespecified subset analysis, the survival benefit was also observed in patients ≥65 years (HR for PFS = 0.26; HR for OS = 0.33).[505] No age-specific subset analysis was performed for dabrafenib. Trametinib, a selective small-molecule inhibitor of MEK1 and MEK2 (single agent or in combination with dabrafenib) has also resulted in improved PFS and OS in patients with *BRAF* (V600E)-mutated or *BRAF* (V600K)-mutated metastatic melanoma and the survival benefit (although not very significant) was also observed in patients ≥65 years as indicated by the prespecified subset analyses.[507-509]

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.[510,511] 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 following induction therapy.[512-514] 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.[513] 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 had a CR after completion of induction therapy with a median OS and DFS of only 14 months.[514] The inferior outcomes have been attributed to treatment-related mortality (7.5%) during induction and more resistant disease. The randomized phase II trial (GRAALL-SA1) showed that the addition of pegylated doxorubicin to vincristine and dexamethasone 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.[515] Dose-intensive induction therapy with hyperCVAD regimen induced CR rates of 84% in patients ≥60 years with an improved 5-year OS rate (20% compared with 9% on regimens that were used before hyperCVAD) and decreased incidence of disease resistance.[516] 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), resulting from the reciprocal translocation t(9;22) that fuses the *BCR* gene on chromosome 22 and the *ABL* gene located on chromosome 9, is the most frequent cytogenetic abnormality in older patients with ALL. BCR-ABL tyrosine kinase inhibitors (TKIs) (imatinib and dasatinib) in combination with steroids have been evaluated as induction therapy in older patients with Ph-positive ALL.[517,518] 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.[517] Median survival from diagnosis was 20 months. In another phase II study (n = 55; 12 patients were >60 years),

induction therapy with dasatinib and steroids and intrathecal chemotherapy induced complete remission rates in all patients.[518] 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 to induction chemotherapy.[519] Severe adverse events were significantly more frequent with induction chemotherapy (90% vs. 39%; *P* = .005). The OS was not significantly different between the two groups. The use of imatinib and steroids as consolidation therapy following induction chemotherapy has also resulted in improved outcomes (compared to historical controls) in older patients with Ph-positive ALL.[520]

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 hyperCVAD and rituximab, the 3-year complete remission duration was 67% for younger patients compared to 45% for patients ≥60 years.[521] The 3-year OS rates were 78% and 45%, respectively.

Acute Myeloid Leukemia

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.[522,523] In a retrospective analysis of 968 patients with AML, there was 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 to 57% in patients >75 years), and treatment-related mortality (especially in patients with poor performance status) within 30 days following induction therapy (82% among patients >75 years).[524]

In older patients ≥60 years, 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).[525] Despite these poor outcomes, standard intensive treatment has been shown to improve early death rates and long-term survival compared with palliative treatment in most patients with AML up to 75 to 80 years of age.[526,527]

Induction chemotherapy should be considered for older patients in good performance status with no comorbidities. The optimal chemotherapy regimen is unknown. In a randomized trial (1314 patients >56 years) that compared 3 different induction regimens, DAT (daunorubicin, cytarabine, and thioguanine), ADE (cytarabine, daunorubicin, and etoposide), or MAC (mitoxantrone and cytarabine), the remission rates in the DAT arm were significantly better than in the ADE (62% vs. 50%; *P* = .002) or MAC (62% vs. 55%; *P* = .04) arms, but there were no differences in the 5-year OS rates between the 3 regimens (2% vs. 8% vs. 10%, respectively).[528] The remission or survival rates were also not improved by the addition of G-CSF. In another study of 362 older patients with previously untreated AML (139 patients >70 years) randomized to daunorubicin, idarubicin, or mitoxantrone with a standard dose of cytarabine as induction therapy, there was no difference in efficacy among the 3 regimens in terms of CR rate, OS, and DFS.[529]

Induction therapy with intensified anthracycline doses and cytarabine has not been consistently associated with improved outcomes in older patients.[530-534] For example, the LRF AML14 trial did not show any difference in terms of CR rate or OS for patients treated with daunorubicin (50 mg/m^2 vs. 35 mg/m^2) and cytarabine (200 mg/m^2 vs.

400 mg/m^2) at 2 different dose levels.[531] In contrast to these findings, Lowenberg et al 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.[532] The CR rate was 64% and 54%, respectively (P = .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 of the UK NCRI AML17 trial showed that daunorubicin 90 mg/m^2 was not superior to daunorubicin 60 mg/m^2 either in terms of CR rate or OS in untreated patients with AML.[535] Idarubicin 12 mg/m^2 is a valid alternative to daunorubicin.[534] A combined analysis of two trials from Acute Leukemia French Association (ALFA) trials (ALFA-9801 and ALFA-9803) showed that induction therapy with idarubicin was associated with a significantly higher cure rate than daunorubicin (16.6% and 9.8%, respectively; P = .018) in patients ≥50 years.[534]

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.[536] The probability of obtaining a CR and the risk of treatment-related mortality can be calculated utilizing a web-based tool: http://www.aml-score.org/. 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 AML.

Chronic Myeloid Leukemia

TKI therapy is the standard of care for patients with newly diagnosed chronic phase CML. There are limited prospective data regarding the use of TKI therapy in older adults with CML. Available data suggest that the approach to treatment should be similar across the age spectrum.[537-544] Older adults, however, may be at greater risk of treatment-related toxicity and treatment discontinuation due to adverse events. Older age and cardiovascular risk factors were also associated with higher likelihood of arterial thrombotic events during treatment with ponatinib.[545] Underlying pulmonary disease may be associated with an increased risk of pleural effusion in older adults receiving dasatinib.[546] Similarly, underlying cardiovascular disease risk factors also appear to be associated with an increased risk of cardiovascular adverse events, including peripheral artery occlusion and myocardial infarction, during treatment with nilotinib.[545,547] Treatment with nilotinib is also associated with electrolyte abnormalities, including hyperglycemia and hyperlipidemia.[548] The clinician should monitor lipid profile and glucose levels prior to initiation of therapy and serial monitoring should be considered while on nilotinib.

Multiple Myeloma

High-dose therapy followed by autologous stem cell transplantation (HDT/ASCT) is the initial treatment option for younger patients. However, the role of this approach in older patients has not yet been established in randomized trials since the majority of these trials have included patients younger than 65 years. There is also a 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.[549-551] 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 age 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 prior to 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, PFS, time-to-treatment progression, and EFS in older patients with newly diagnosed multiple myeloma.[552-559] However, OS benefit was reported only in two of these studies. In the IFM 99-06 trial, which compared melphalan, prednisone, and thalidomide (MPT), MP, or reduced-intensity ASCT, median OS was 51.6 months, 33.2 months, and 38.3 months, respectively, for the three treatment groups; the MPT regimen was associated with a significantly better OS than the MP regimen (P = .0006) or reduced-intensity ASCT (P = .027).[554] In the IFM 01/01 trial, median OS was 44 months and 29 months, respectively (P = .028), for older patients (≥75 years) treated with MPT and MP.[555] MPT was associated with significant toxicity (constipation, fatigue, deep vein thrombosis [DVT], neuropathy, cytopenias, and infection).[559]

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 with newly diagnosed multiple myeloma ineligible for transplantation.[560] 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.[560] 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.

The results of an interim analysis of a recently published randomized phase III study (1,623 patients with previously untreated symptomatic multiple myeloma ineligible for stem cell transplantation), demonstrated that the continuous administration of lenalidomide and dexamethasone until disease progression significantly improved PFS in all subgroups of patients, including those ≥75 years.[561] The median PFS was 25.5 months for continuous lenalidomide and dexamethasone and 21.2 months with MPT. There was also a trend toward superior OS for lenalidomide and dexamethasone, although the difference was not statistically significant. The 4-year OS rate was 59% for continuous lenalidomide and dexamethasone and 51% for MPT.

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.[562,563] 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 to those ≥75 years (3-year OS rates were 74.1% and 55.5%, respectively; P = .011).[564] In the Spanish randomized trial (which 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), in the induction phase, VTP and VMP resulted in similar response rates (partial response rates were 81% and 80%, respectively) and OS, with different side effect profiles.[565] 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 to bortezomib and prednisone (39%).[565] In the updated report, after a longer follow-up (median 6 years), the median PFS was 32 months for VMP and 23 months for VTP arms (P = .09). VMP also significantly prolonged OS compared with VTP; the median OS was 63 and 43 months, respectively (P = .01).[566] The achievement of CR was associated with a significantly longer PFS (P < .001) and the benefit was more evident with VMP.

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 to VMP alone but did not result in an improvement in OS.[567] 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 54 months) showed that the VMPT-VT regimen significantly prolonged PFS compared to VMP, especially in patients younger than 75 years; the median PFS was 35.3 months with VMPT-VT compared to 24.8 months for VMP (P < .001).[568] The 5-year OS rates were 61% and 51%, respectively (P = .01).

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.[569]

Dexamethasone-Based Combination Therapy

Dexamethasone-based regimens are associated with increased mortality and severe hematologic toxicities compared to MP in older patients with newly diagnosed multiple myeloma not eligible for HDT/ASCT.[570,571] In a large randomized trial (IFM 95-01), which compared MP with dexamethasone-based regimens (dexamethasone, alone or in combination with melphalan or interferon), while there was no difference in OS between 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.[570]

The results of another 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.[571] 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 to low-molecular-weight heparin (LMWH) in patients with myeloma treated with a thalidomide-based regimen, whereas in older patients LMWH was more effective than warfarin.[572] 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 methyltransferase inhibitors such as azacitidine and decitabine have been shown to improve QOL by decreasing the risk of AML transformation as well as transfusion dependence compared to conventional regimens or best supportive care in patients with high-risk MDS.[573-577]

The subgroup analysis of the AZA-001 trial demonstrated that azacitidine significantly improved OS compared to conventional care, with no increased risk of toxicity in older patients (≥75 years) with intermediate- or high-risk MDS.[578] The 2-year OS rates were 55% vs. 15%, respectively ($P < .001$). In a study of 282 patients with high-risk MDS, previous treatment with low-dose cytosine arabinoside, bone marrow blasts greater than 15%, and abnormal or complex karyotype were identified as predictors of lower response rates. Performance status ≥2, intermediate- and poor-risk cytogenetics, presence of circulating blasts, and red blood cell transfusion dependency greater than or equal to 4 units/8 weeks were independent predictors of poorer OS.[579] For patients with higher-risk MDS, azacytidine 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, azacytidine schedule of 5 days on, 2 days off, and 2 days on did not seem to negatively impact the response rate or duration of response in patients ≥65 years.[580]

A recent report from the Spanish Registry of MDS also demonstrated the equal efficacy of 3 different schedules of azacytidine (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%.[581] 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.[582,583]

In the two large studies that included predominantly older patients with low- and high-risk MDS, decitabine (5-day schedule given as 15 mg/m^2 every 8 hours for 3 days at a dose of 135 mg/m^2 per course) resulted in durable responses, hematologic improvement, and improved time to AML transformation or death.[575,584] 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 there was no significant difference in OS (10.1 vs. 8.5 months; $P = .38$) and AML-free survival (8.8 vs. 6.1 months; $P = .24$) compared to best supportive care.[577] Longer duration of MDS and prior therapy were predictive factors for achieving CR, whereas

abnormalities of chromosomes 5 and/or 7, older age, and prior therapy were adverse prognostic factors for survival.[576]

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 of cytologic and cytogenetic abnormalities.[585,586] Lenalidomide has been shown to improve transfusion independence in patients with low-risk MDS without deletion of 5q.[587]

Allogeneic hematopoietic cell transplant (HCT) is considered to be a curative treatment option for younger patients with MDS. However, the majority of patients with MDS patients are older adults with a median age of 65 to 70 years at diagnosis. The role of allogeneic HCT is not well defined in this group of patients and there are very limited data in patients older than 75 years. Retrospective studies have shown that allogeneic HCT with non-myeloablative or reduced-intensity conditioning (RIC) regimens is safe and effective in carefully selected patients ≥70 years.[588-590] In the study that reported the long-term outcomes of patients (372 patients; 60–75 years) treated with non-myeloablative allogeneic HCT for hematologic malignancies in prospective clinical trials, the overall 5-year cumulative incidences of non-relapse mortality and relapse were 27% and 41%, respectively.[589] The 5-year OS and PFS rates were 35% and 32%, respectively, and the survival outcomes were not statistically significantly different when patients were stratified by age groups. In addition, increasing age was also not associated with increases in acute or chronic graft-vs-host disease or organ toxicities.[589] Another retrospective multicenter analysis of patients with MDS who received allogeneic HCT within the European Group for Blood and Marrow Transplantation registry (884 patients were 50–60 years and 449 patients were >60 years) also reported that there was no significant difference in non-relapse mortality and OS between the two age groups.[588] These findings suggest that age alone should not be a contraindication for allogeneic HCT in older patients with MDS. Treatment options for patients (60–75 years) with de novo MDS should be based on their International Prognostic Scoring System (IPSS) risk.[591] Allogeneic HCT with RIC was not associated with an improved life expectancy for patients with low/intermediate-1 IPSS MDS, while there was a potential improvement in life expectancy for those with intermediate-2 or high-risk IPSS MDS.[591] HCT comorbidity index (HCT-CI) could also be useful to guide the selection of patients for allogeneic HCT with RIC.[592]

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 to 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 QOL 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.

Chronologic 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 utilized 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.

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