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Senior Adult Oncology

Clinical Practice Guidelines in Oncology

Arti Hurria, MD; Ilene S. Browner, MD; Harvey Jay Cohen, MD; Crystal S. Denlinger, MD; Mollie deShazo, MD; Martine Extermann, MD, PhD; Apar Kishor P. Ganti, MD; Jimmie C. Holland, MD; Holly M. Holmes, MD; Mohana B. Karlekar, MD; Nancy L. Keating, MD, MPH; June McKoy, MD, JD, MBA; Bruno C. Medeiros, MD; Ewa Mrozek, MD; Tracey O'Connor, MD; Stephen H. Petersdorf, MD; Hope S. Rugo, MD; Rebecca A. Silliman, MD, PhD, MPH; William P. Tew, MD; Louise C. Walter, MD; Alva B. Weir, III, MD; and Tanya Wildes, MD

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 aged 65 years or older.[2] By 2030, an estimated 70% of all cancers will be diagnosed in adults aged 65 years or older.[3] Older individuals are more prone to develop cancer than younger individuals. Furthermore, the aging of the U.S. population and increased life expectancy of the elderly mean that cancer in older adults is becoming an increasingly common problem.

Unique issues must be considered when caring for older adults with cancer. The biology of certain neoplasms and responsiveness to therapy changes

NCCN Clinical Practice Guidelines in Oncology for Senior Adult Oncology

Key Words

NCCN Clinical Practice Guidelines, NCCN Guidelines, senior adult, elderly, advanced age, older patient, comprehensive geriatric assessment, cancer treatment *(JNCCN* 2012;10:162–209)

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.

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

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way.

Disclosures for the NCCN Guidelines Panel for Senior Adult Oncology

At the beginning of each NCCN Guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in *JNCCN* and online. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Guidelines for Senior Adult Oncology panel members can be found on page 209. (The most recent version of these guidelines and accompanying disclosures, including levels of compensation, are available on the NCCN Web site at www.NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit www.NCCN.org.

with patient age.[4] Furthermore, the patient's physiologic status, comorbidities, and preferences may influence the selection and tolerance to certain therapies. Together, these age-related issues form the basis for the development of guidelines that address special considerations in older adults with cancer.

Older adults with cancer are underrepresented in clinical trials for new cancer therapies.[5] Therefore fewer evidence-based data are available to guide the treatment of these patients. However, advanced age alone should not preclude the use of effective cancer treatment that could improve quality of life or extend meaningful survival.[6,7] Treatment that diminishes quality of life with no significant survival benefit should be avoided. The available data suggest that older patients with good performance status are able to tolerate commonly used chemotherapy regimens as well as younger patients, particularly when adequate supportive care is provided.[8–10] However, few studies have addressed patients at the extremes of age or those with poor performance status. The physiological 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.

These guidelines address specific issues related to the management of cancer in older individuals, including screening and comprehensive geriatric assessment, assessment of the risks and benefits of treatment, prevention of or decreasing complications from therapy, disease-specific issues, and management of patients unfit for standard treatment.

Text continues on p. 179

NCCN Senior Adult Oncology Panel Members

*Arti Hurria, MD/Chair†Þ℗
City of Hope Comprehensive Cancer Center
[g]Ilene S. Browner, MD†℗
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
[e]Harvey Jay Cohen, MD†℗
Duke Cancer Institute
[g]Crystal S. Denlinger, MD†
Fox Chase Cancer Center
*[b]Mollie deShazo, MD†
University of Alabama at Birmingham Comprehensive Cancer Center
[e]Martine Extermann, MD, PhD†
H. Lee Moffitt Cancer Center & Research Institute
*[c]Apar Kishor P. Ganti, MD†
UNMC Eppley Cancer Center at The Nebraska Medical Center
[h]Jimmie C. Holland, MDθ
Memorial Sloan-Kettering Cancer Center
[e]Holly M. Holmes, MDÞ℗Σ
The University of Texas MD Anderson Cancer Center
[h]Mohana B. Karlekar, MDÞ
Vanderbilt-Ingram Cancer Center
[e]Nancy L. Keating, MD, MPHÞ
Dana-Farber/Brigham and Women's Cancer Center
[e]June M. McKoy, MD, JD, MBAÞ℗£
Robert H. Lurie Comprehensive Cancer Center of Northwestern University
*[f]Bruno C. Medeiros, MD‡
Stanford Cancer Institute
*[a]Ewa Mrozek, MD†‡
The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute
[a]Tracey O'Connor, MD†
Roswell Park Cancer Institute
[f]Stephen H. Petersdorf, MD†‡ξ
University of Washington Medical Center/ Seattle Cancer Care Alliance
[a]Hope S. Rugo, MD†‡
UCSF Helen Diller Family Comprehensive Cancer Center
[e]Rebecca A. Silliman, MD, PhD, MPH℗
Consultant
*[a]William P. Tew, MD†Þ
Memorial Sloan-Kettering Cancer Center
[e]Louise C. Walter, MD℗
UCSF Helen Diller Family Comprehensive Cancer Center
*[d]Alva B. Weir, III, MD†‡
St. Jude Children's Research Hospital/ University of Tennessee Cancer Institute
*[f]Tanya Wildes, MD†
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University

NCCN gratefully acknowledges the review of the Senior Adult Oncology Guidelines by *Efrat Dotan, MD†

NCCN Staff: Mary Anne Bergman, and Hema Sundar, PhD

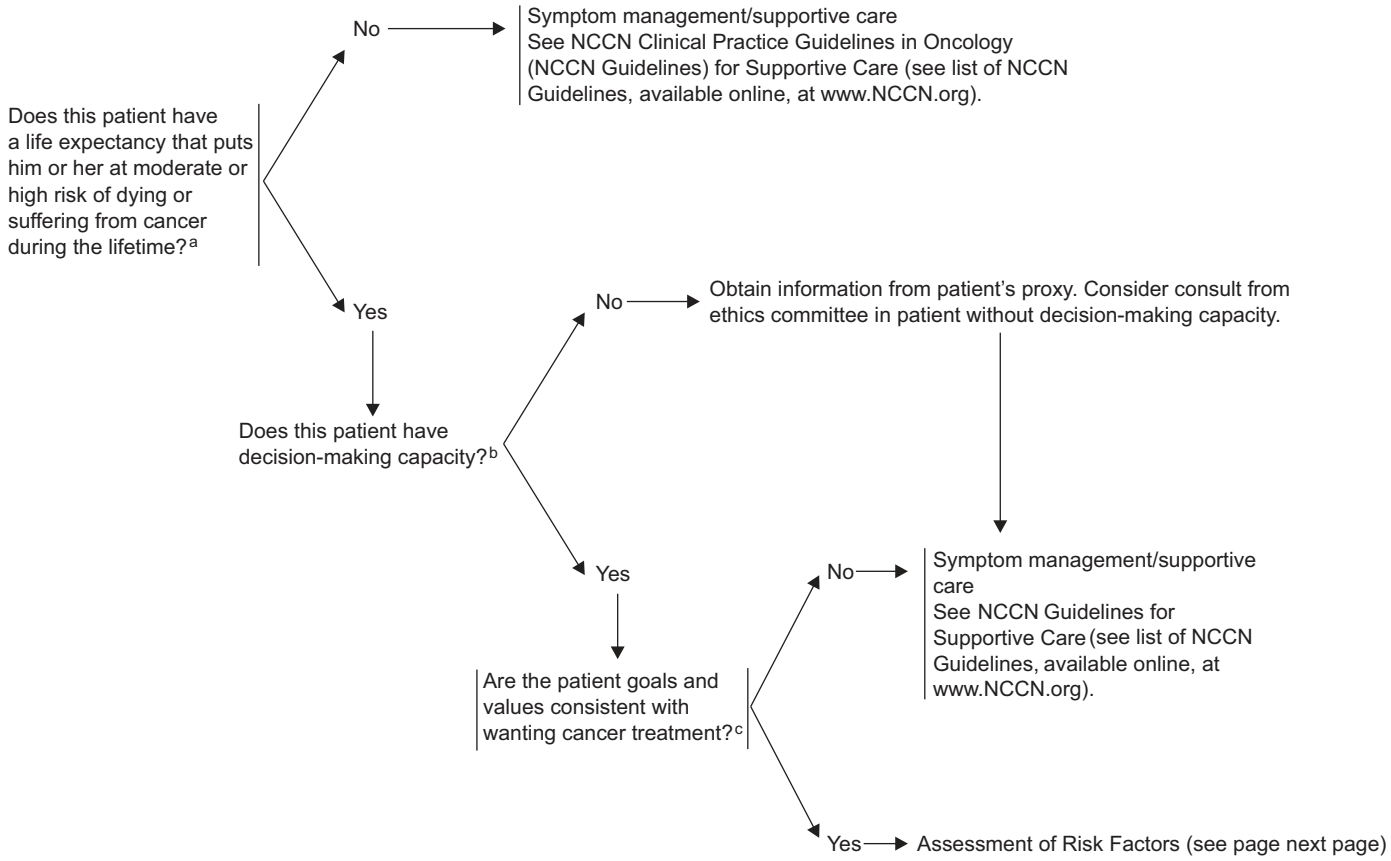
KEY:

*Writing Committee Member

Subcommittees: [a]Breast/Gynecological Cancers; [b]Bladder, Kidney, and Prostate Cancers; [c]Non–Small Cell Lung Cancers; [d]Head and Neck/Central Nervous System Cancers; [e]Geriatric Assessment; [f]Hematologic Malignancies; [g]Gastrointestinal Cancers; [h]Psychological/Palliative Care

Specialties: †Medical Oncology; ÞInternal Medicine, including Family Practice, Preventive Management; ℗Geriatric Medicine; θPsychiatry, Psychology, including Health Behavior; ΣPharmacology/Pharmacy; £Supportive Care including Palliative and Pain Management; ‡Hematology Oncology; ξBone Marrow Transplantation

APPROACH TO DECISION-MAKING IN THE OLDER ADULT



*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

[a] See histograms for age-specific life expectancy (page 167).
[b] Sessums LL, Zembrzuska H, Jackson JL. Does this patient have medical decision-making capacity? JAMA 2011;306:420-427.
[c] 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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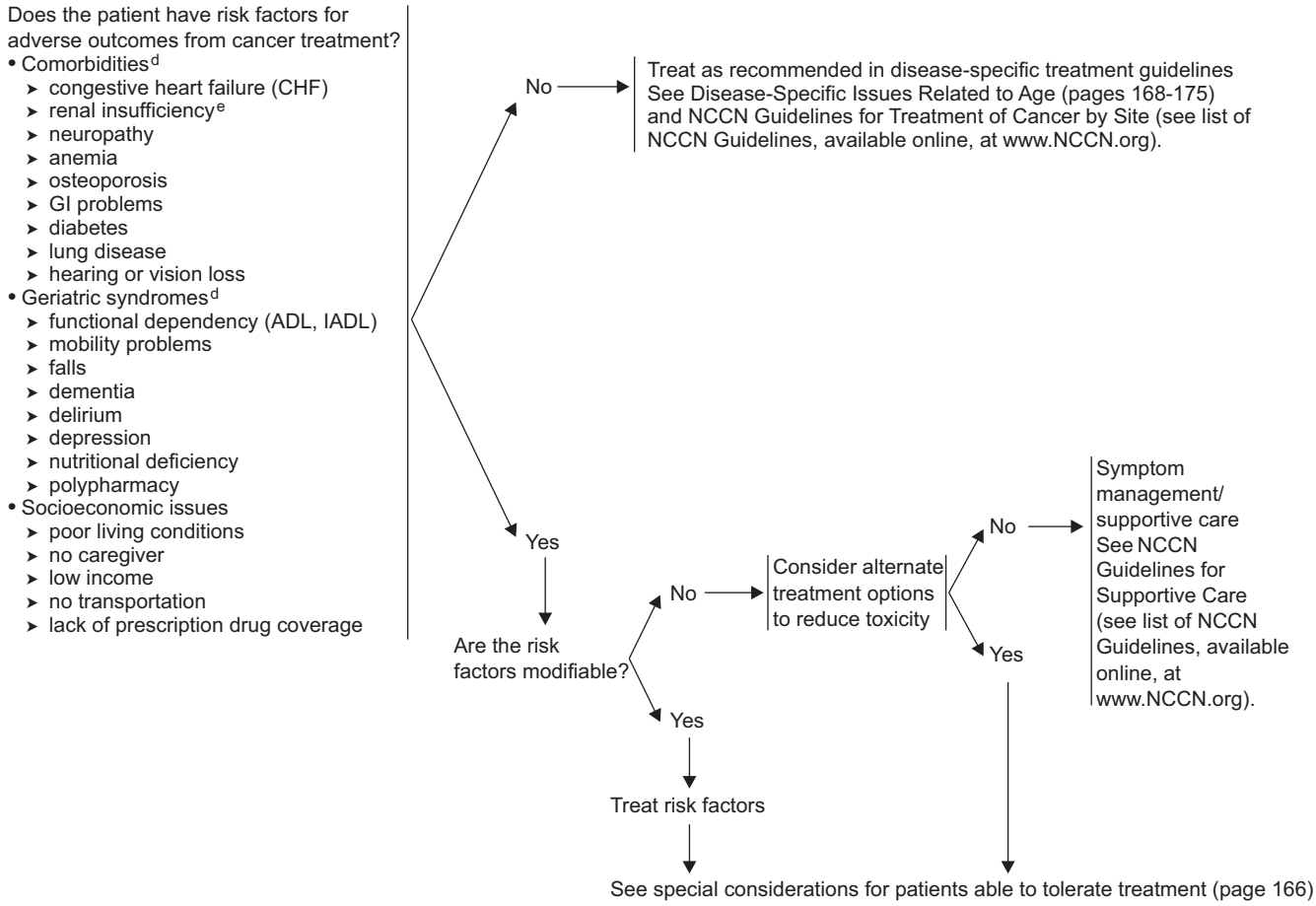
ASSESSMENT OF RISK FACTORS[d]



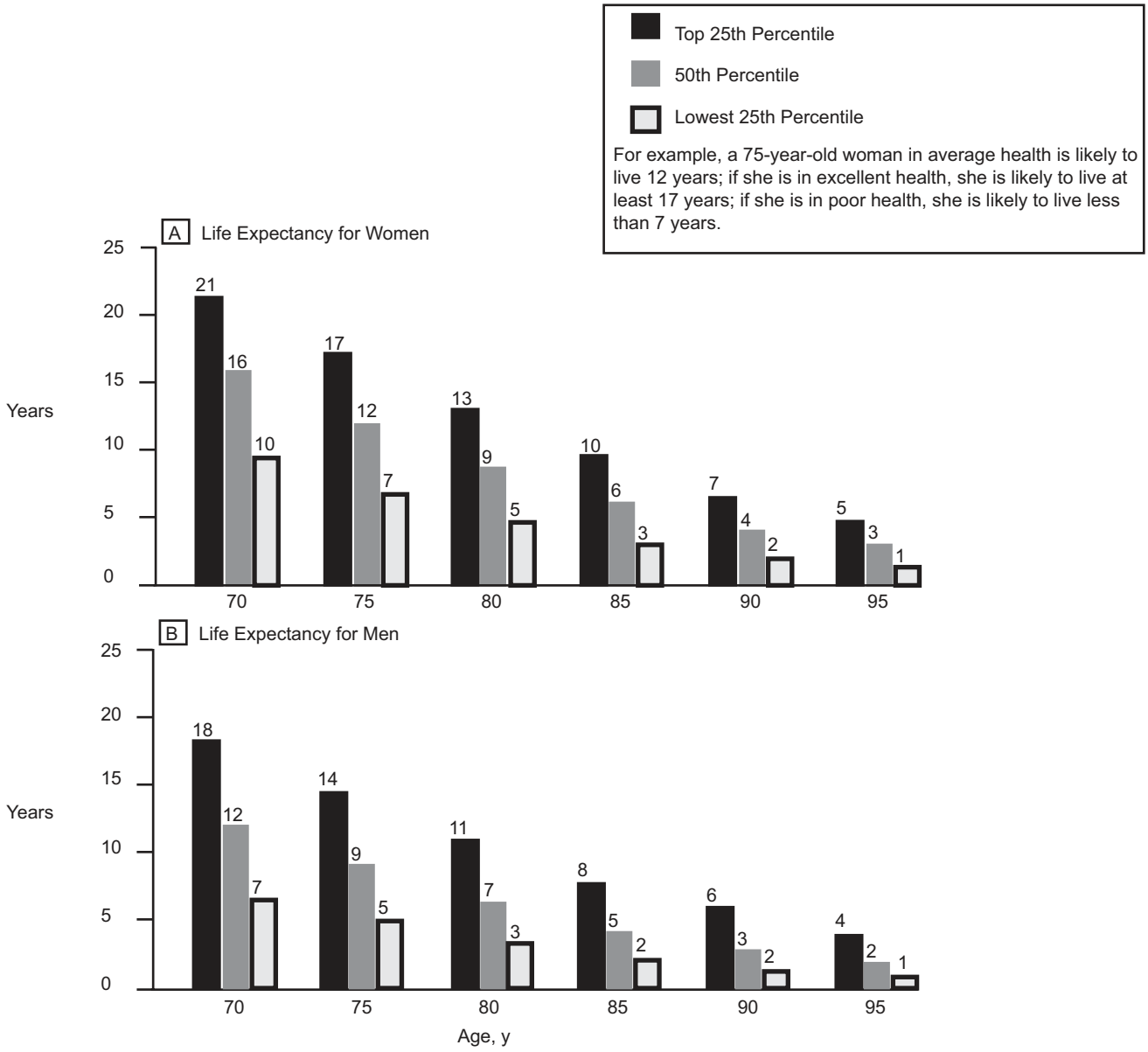
[d] See Comprehensive Geriatric Assessment (pages 176-177).
[e] The panel recommends calculation of creatinine clearance to assess renal function for all patients.

SPECIAL CONSIDERATIONS FOR PATIENTS ABLE TO TOLERATE TREATMENT[f]

Surgery	• In general, age is not a primary consideration for surgical risk • Emergency surgery carries increased risk of complications; special effort should be made to prevent/avoid emergency surgery • Assess physiologic status (using standard surgical evaluation tools)
Radiation therapy	• Use caution with concurrent RT/chemotherapy; dose modification of chemotherapy may be necessary • Nutritional support and pain control if RT-induced mucositis
Neurotoxicity	• Consider alternative regimens with nonneurotoxic drugs • Monitor hearing loss and avoid neurotoxic agents if significant hearing loss present • Monitor cerebellar function with high-dose cytarabine • Monitor for peripheral neuropathy
Cardiac toxicity	• Symptomatic or asymptomatic CHF ➤ Caution with use of anthracyclines, consider alternative treatment ➤ Caution with use of trastuzumab[g,h] (among patients with a normal ejection fraction, risk factors for CHF include receipt of an anthracycline-based regimen, baseline LVEF of 50%-54%, and currently taking hypertensive medicines)
Renal toxicity	• Calculate creatinine clearance to assess renal function • Adjust dose for glomerular filtration rate (GFR) to reduce systemic toxicity
Bone marrow suppression	• Prophylactic colony stimulating factors when dose-intensity required for response or cure (see NCCN Guidelines for Myeloid Growth Factors*) • Decreased dose of chemotherapy if palliation is the goal • See NCCN Guidelines for Cancer- and Chemotherapy-Induced Anemia*
Falls	• Consider PT evaluation in patient with history/risk of falls
Diarrhea	• Consider early aggressive rehydration • Management with octreotide if oral preparations are ineffective (see NCCN Guidelines for Palliative Care*)
Constipation	See NCCN Guidelines for Palliative Care*
Nausea/vomiting	See NCCN Guidelines for Antiemesis*
Mucositis	• Early hospitalization in patients who develop dysphagia/diarrhea • Nutritional support • See NCCN Task Force Report: Prevention and Management of Mucositis in Cancer Care (http://www.nccn.org/JNCCN/PDF/mucositis_2008.pdf).

*For the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.
[f]Monitor the patient's functional status, comorbidities, social circumstances, pain, nutritional status, and distress.
[g]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.
[h]Romond E, Perez E, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005;35:1673-1684.

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



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DISEASE-SPECIFIC ISSUES RELATED TO AGE

Bladder Cancer

- BCG treatment for superficial bladder carcinoma has decreased efficacy in the very old (age > 80 y).[1,2]
- Age alone should not be a criterion for decisions regarding cystectomy, radiation, and chemotherapy in the elderly.[3,4]
- The improvement in disease-specific survival from neoadjuvant chemotherapy is preserved with age.[4]

[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.
[2] Herr HW. Age and outcome of superficial bladder cancer treated with bacille Calmette-Guerin therapy. Urology 2007;70:65-68.
[3] Chamie K, Hu B, Devere White RW, Ellison LM. Cystectomy in the elderly: does the survival benefit in younger patients translate to the octogenarians? BJU Int 2008;102:284-290.
[4] Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 2003;349:859-866.

Breast Cancer

- Older adults (age ≥ 65 y) with breast cancer enrolled in cooperative group trials of adjuvant chemotherapy derive similar benefits (disease-free and overall survival) compared with younger patients. However, older patients have an increased risk of side effects and treatment-related mortality.[1]
- A select group of older adults enroll 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 aged 65 y and older and only 2% (159/6487) of patients were aged 70 y or older.[1]
- In the adjuvant treatment of breast cancer, single-agent capecitabine is inferior to cyclophosphamide, methotrexate, and fluorouracil (CMF) or doxorubicin and cyclophosphamide (AC) in patients aged 65 y or older. Unplanned subset analysis suggested that the greatest difference was seen in women with hormone receptor-negative tumors.[2]
- Patients aged 70 y or older with stage I ER-positive breast cancer who undergo a lumpectomy with negative margins and are receiving endocrine therapy may consider omission of radiation therapy. Omission of radiation therapy was associated with a modest increased risk of local recurrence (4% vs. 1% at 5 y; 9% vs. 2% at 10 y); however, there was no difference in overall survival or distant metastatic disease.[3,4]
- Women older than 75 y receive less-aggressive treatment and have higher mortality from early-stage breast cancer than younger women.[5-7]
- In the absence of definitive data demonstrating superior survival from the performance of axillary lymph node dissection, axillary lymph node dissection may be considered optional in patients who have particularly favorable tumors, patients for whom the selection of adjuvant systemic therapy is unlikely to be affected, the elderly, or those with serious comorbid conditions.[8-10]
(See NCCN Guidelines for Breast Cancer; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

[1] Muss HB, Woolf S, Berry D, et al. Adjuvant chemotherapy in older and younger women with lymph node-positive breast cancer. JAMA 2005;293:1073-1081.
[2] Muss HB, Berry DA, Cirrincione CT, et al. Adjuvant chemotherapy in older women with early-stage breast cancer. N Engl J Med 2009;360:2055-2065.
[3] Hughes KS, Schnaper LA, Berry D, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. N Engl J Med 2004;351:971-977.
[4] Hughes KS, Schnaper LA, Cirrincione C, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 or older with early breast cancer [abstract]. J Clin Oncol 2010;28(Suppl 15):Abstract 507.
[5] Bouchardy C, Rapiti E, Fioretta G, et al. Undertreatment strongly decreases prognosis of breast cancer in elderly women. J Clin Oncol 2003;21:3580-3587.
[6] Schonberg MA, Marcantonio ER, Li D, et al. Breast cancer among the oldest old: tumor characteristics, treatment choices, and survival. J Clin Oncol 2010;28:2038-2045.
[7] Yood MU, Owusu C, Buist DSM, et al. Mortality impact of less-than-standard therapy in older breast cancer patients. J Am Coll Surg 2008;206:66-75.
[8] Martelli G, Miceli R, Daidone MG, et al. Axillary dissection versus no axillary dissection in elderly patients with breast cancer and no palpable axillary nodes: results after 15 years of follow-up. Ann Surg Oncol 2011;18:125-133.
[9] Rudenstam CM, Zahrieh D, Forbes JF, et al. Randomized trial comparing axillary clearance versus no axillary clearance in older patients with breast cancer: first results of International Breast Cancer Study Group Trial 10-93. J Clin Oncol 2006;24:337-344.
[10] Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 2011;305:569-575.

DISEASE-SPECIFIC ISSUES RELATED TO AGE

Central Nervous System (CNS) Cancers

- Patients older than 70 y with glioblastoma who are treated surgically with gross total resection achieve a greater overall survival 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]
- Postsurgical radiation alone is effective in improving outcomes in patients older than 70 y with glioblastoma and shorter course regimens are reasonable to consider.[3,4]
- The addition of temozolomide concurrently with radiation therapy followed by at least 6 months of adjuvant temozolomide improves survival in patients between ages 60 and 70 y.[5] Concurrent chemotherapy with radiation for patients older than 70 y with glioblastoma multiforme is of unclear benefit but is likely to be helpful in "fit" elderly based on single-institution retrospective data.[6]
- In recurrent glioblastoma, bevacizumab likely improves quality of life (and possibly overall survival) in patients aged 55 y or older.[7]
- Patients older than 60 y with primary CNS lymphoma should be treated primarily with chemotherapy, reserving radiation for salvage therapy.[8,9]

[1] Martinez R, Janka M, Soldner F, Behr R. Gross total resection of malignant glioma in elderly patients: implications in survival. Zentrabl Neurchir. 2007;68:176-181.
[2] Vuorinen V, Hinkka S, Farkkila M, Jaaskelainen J. Debulking or biopsy of malignant glioma in elderly people. A randomized study. Acta Neurochir 2003;145:5-10.
[3] Keime-Guibert F, Chinot O, Taillandier L, et al. Radiotherapy for glioblastoma in the elderly. N Engl J Med 2007;356:1527-1535.
[4] Roa W, Brasher PM, Bauman G, et al. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized trial. J Clin Oncol 2004;22:1583-1588.
[5] Stupp R, Hegi M, Mason W, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomized phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol 2009;10:459-466.
[6] Scott J, Suh J, Elson P, et al. Aggressive treatment is appropriate for glioblastoma multiforme patients 70 years old or older: a retrospective review of 206 cases. Neuro-Oncol 2011;13:428-436.
[7] Nghiemphu PL, Liu W, Lee Y, et al. Bevacizumab and chemotherapy for recurrent glioblastoma: a single-institution experience. Neurology 2009;72:1217-1222.
[8] Gavrilovic I, Hormigo A, Yahalom J, et al. Long term follow-up of high-dose methotrexate-based therapy with and without whole brain irradiation for newly diagnosed primary CNS lymphoma. J Clin Oncol 2006;24:4570-4574.
[9] Zhu JJ, Gerstner ER, Engler DA, et al. High-dose methotrexate for elderly patients with primary CNS lymphoma. Neuro Oncol 2009;11:211-215.

DISEASE-SPECIFIC ISSUES RELATED TO AGE

Colorectal Cancer

Surgery:

- Age alone should not be a contraindication for curative surgery in early-stage colon cancer and in resectable metastatic colon cancer. Careful pre-operative planning and nonemergent 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 and overall survival) with 5-FU-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 (17% of patients older than 70 y) did not show a benefit in disease-free or overall survival with the addition of oxaliplatin to 5-FU-based therapy in patients older than 70 y. Due to the lack of prospective randomized data, adjuvant oxaliplatin-based therapy in adults aged ≥ 70 y should be considered on an individual patient basis.[7]

Metastatic Disease:

- Older adults derive the same relative benefit as younger patients (in terms of disease-free and overall survival) with 5-FU-based therapy for metastatic treatment. Older adults are at increased risk for hematologic toxicities.[8]
- Stop-and-go or maintenance monotherapy strategies during combination chemotherapy may be desirable for elderly patients to minimize toxicity.[9]
- A prospective study of dose-reduced oxaliplatin in addition to 5-FU-based therapy in older (median age, 75 y) and frail patients failed to show a statistically significant benefit in progression-free survival. The addition of oxaliplatin to 5-FU-based therapy led to a numerical improvement in progression-free survival that was of borderline statistical significance. Patients treated with capecitabine compared with 5-FU had a higher risk of grade 3 or higher toxicity and no improvement in quality-of-life.[10]
- Retrospective analyses suggest acceptable toxicity profiles with anti-EGFR antibodies in elderly patients, although data are limited. Similar benefits with anti-EGFR antibodies are seen in young and elderly patients.[11,12]
- Elderly patients derive similar clinical benefit from the use of bevacizumab with chemotherapy in the metastatic setting as younger patients, but have higher rate of toxicities, mainly arterial thromboembolic events.[13,14]

1 Stocchi L, Nelson H, Young-Fadok TM, et al. Safety and advantages of laparoscopic vs. open colectomy in the elderly: matched-control study. Dis Colon Rectum 2000;43:326-332.
2 Ong ES, Alassas M, Dunn KB, Rajput A. Colorectal cancer surgery in the elderly: acceptable morbidity? Am J Surg 2008;195:344-348.
3 Schiffmann L, Ozcan S, Schwarz F, et al. Colorectal cancer in the elderly: surgical treatment and long-term survival. Int J Colorectal Dis 2008;23:601-610.
4 Fong Y, Blumgart LH, Fortner JG, Brennan MF. Pancreatic or liver resection for malignancy is safe and effective for the elderly. Ann Surg 1995;222:426-434.
5 Adam R, Frilling A, Elias D, et al. Liver resection of colorectal metastases in elderly patients. Br J Surg 2010;97:366-376.
6 Sargent DJ, Goldberg RM, Jacobson SD, et al. A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients. N Engl J Med 2001;345:1091-1097.
7 Jackson McCleary NA, Meyerhardt J, Green E, et al. Impact of older age on the efficacy of newer adjuvant therapies in >12,500 patients (pts) with stage II/III colon cancer: findings from the ACCENT Database [abstract]. J Clin Oncol 2009;27(Suppl 15):Abstract 4010.
8 Folprecht G, Cunningham D, Ross P, et al. Efficacy of 5-fluorouracil-based chemotherapy in elderly patients with metastatic colorectal cancer: a pooled analysis of clinical trials. Ann Oncol 2004;15:1330-1338.
9 Figer A, Perez-Staub N, Carola E, et al. FOLFOX in patients aged between 76 and 80 years with metastatic colorectal cancer: an exploratory cohort of the OPTIMOX1 study. Cancer 2007;110:2666-2671.
10 Seymour MT, Thompson LC, Wasan HS, et al. Chemotherapy options in elderly and frail patients with metastatic colorectal cancer (MRC FOCUS2): an open-label, randomised factorial trial. Lancet 2011;377:1749-1759.
11 Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 2007;25:1658-1664.
12 Bouchahda M, Macarulla T, Spano JP, et al. Cetuximab efficacy and safety in a retrospective cohort of elderly patients with heavily pretreated metastatic colorectal cancer. Crit Rev Oncol Hematol 2008;67:255-262.
13 Cassidy J, Saltz LB, Giantonio BJ, et al. Effect of bevacizumab in older patients with metastatic colorectal cancer: pooled analysis of four randomized studies. J Cancer Res Clin Oncol 2010;136:737-743.
14 Kozloff MF, Berlin J, Flynn PJ, et al. Clinical outcomes in elderly patients with metastatic colorectal cancer receiving bevacizumab and chemotherapy: results from the BRiTE observational cohort study. Oncology 2010;78:329-339.

DISEASE-SPECIFIC ISSUES RELATED TO AGE

Head and Neck Cancers

- Elderly patients with head and neck cancer seem to have similar efficacy outcomes with surgery but higher complication rates, which increase with comorbidities.[1,2]
- Patients aged > 70 y with squamous cell carcinoma of the head and neck (SCCHN) who are treated with radiation therapy experience similar overall survival in comparison to younger patients. Older adults are at increased risk for acute mucosal toxicities; however, no significant differences in late toxicities were seen in older patients compared with those younger than 70 y (median of 3 y of follow-up).[3]
- Regarding primary therapy for head and neck cancer, data in patients older than 70 y are insufficient to draw firm conclusions regarding a survival advantage of adding concurrent chemotherapy to radiation therapy.[4]
- 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 y.[5]
- 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 y.[6] That available evidence in patients older than 64 y does not allow firm conclusions to be drawn regarding a survival benefit of adding concurrent cetuximab to radiation.
- 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 y.[7]
- Few patients older than 70 y have been included in induction chemotherapy trials. There is limited data on the efficacy and toxicity of such an approach in this subset of patients.[8,9]
- In the adjuvant therapy of resected SCCHN, too few patients older than 70 y have been evaluated to support or reject the addition of cisplatin to radiation therapy.[10,11]
- Retrospective studies suggest an increase in toxicity with chemotherapy when used alone and when used in combination with radiation therapy in elderly patients.[12,13]

[1] Sanabria A, Carvalho AL, Melo RL, et al. Predictive factors for complications in elderly patients who underwent head and neck oncologic surgery. Head Neck 2008;30:170-177.
[2] Zabrodsky M, Calabrese L, Tosoni A, et al. Major surgery in elderly head and neck cancer patients: immediate and long-term surgical results and complication rates. Surg Oncol 2004;13:249-255.
[3] Pignon T, Horiot JC, Van den Bogaert W, et al. No age limit for radical radiotherapy in head and neck tumours. Eur J Cancer 1996;32A:2075-2081.
[4] Pignon JP, le Maitre A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92:4-14.
[5] Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 2003;349:2091-2098.
[6] Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol 2010;11:21-28.
[7] Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116-1127.
[8] Vermorken JB, Remenar E, van Herpen C, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med 2007;357:1695-1704.
[9] Posner MR, Hershock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 2007;357:1705-1715.
[10] Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350:1937-1944.
[11] Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004;350:1945-1952.
[12] Machtay M, Moughan J, Trotti A, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. J Clin Oncol 2008;26:3582-3589.
[13] Argiris A, Li Y, Murphy BA, et al. Outcome of elderly patients with recurrent or metastatic head and neck cancer treated with cisplatin-based chemotherapy. J Clin Oncol 2004;22:262-268.

DISEASE-SPECIFIC ISSUES RELATED TO AGE

Kidney Cancer

- Sorafenib and sunitinib have similar efficacy in younger and older patients. Some adverse events, including fatigue, occur with increased frequency.[1,2,5,6,8]
- 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.[4]
- Interferon is not recommended for first-line treatment. It has increased toxicity in patients aged 65 y or older compared with temsirolimus, including asthenia, nausea, fever and neutropenia.[3,5,7]

[1]Bukowski RM, Stadler WM, McDermott DF, et al. Safety and efficacy of sorafenib in elderly patients treated in the North American advanced renal cell carcinoma sorafenib expanded access program. Oncology 2010;78:340-347.
[2]Gore ME, Szczylik C, Porta C, et al. Safety and efficacy of sunitinib for metastatic renal-cell carcinoma: an expanded-access trial. Lancet Oncol 2009;10:757-763.
[3]Bajetta E, Ravaud A, Bracarda S, et al. Efficacy and safety of first-line bevacizumab (BEV) plus interferon-{alpha}2a (IFN) in patients (pts) >=65 years with metastatic renal cell carcinoma (mRCC) [abstract]. J Clin Oncol 2008;26(Suppl 15):Abstract 5095.
[4]Osanto S, Hutson TE, Calvo E, et al. Efficacy and safety of everolimus in elderly patients (pts) with metastatic renal cell carcinoma (mRCC) [abstract]. J Clin Oncol 2010;28(Suppl 15):Abstract 4608.
[5]Bellmunt J, Negrier S, Escudier B, et al. The medical treatment of metastatic renal cell cancer in the elderly: position paper of a SIOG Taskforce. Crit Rev Oncol Hematol 2009;69:64-72.
[6]Eisen T, Oudard S, Szczylik C, et al. Sorafenib for older patients with renal cell carcinoma: subset analysis from a randomized trial. J Natl Cancer Inst 2008;100:1454-1463.
[7]Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007;356:2271-2281.
[8]Hutson TE, Bukowski RM, Rini BI, et al. A pooled analysis of the efficacy and safety of sunitinib in elderly patients (pts) with metastatic renal cell carcinoma (mRCC) [abstract]. J Clin Oncol 2011;29(Suppl 15):Abstract 4604.

DISEASE-SPECIFIC ISSUES RELATED TO AGE

Multiple Myeloma

- Choice of treatment might be dependent on the side-effect profile but also the ability to travel for IV therapy.
- Older adults with multiple myeloma receiving MPT (melphalan, prednisone, and thalidomide) versus 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, although studies are conflicting and varying doses of thalidomide have been used.[1-9]
- MPT is associated with higher response rate and overall survival than transplant intermediate-dose melphalan (MEL 100).[2]
- In elderly patients receiving a thalidomide-based regimen, deep vein thrombosis (DVT) prophylaxis is recommended. Low-molecular-weight heparin (LMWH) is superior to warfarin or aspirin.[10]
- VMP (bortezomib, melphalan, and prednisone) in comparison to MP is associated with an increased response rate and overall survival at the cost of increased toxicity (peripheral neuropathy, cytopenias, fatigue). The survival benefit is maintained across age groups.[11,12]
- VMP vs VTP (bortezomib, thalidomide, and prednisone) have similar response rates and overall survival but differing side-effect profiles [VMP (hematologic toxicity, infection) and VTP (cardiac complications)]. Rates of neuropathy were similar in both groups.[13]
- VMPT (bortezomib, melphalan, prednisone, and thalidomide) followed by maintenance VT (bortezomib and thalidomide) vs. VMP is associated with higher response rate but does not improve overall survival. Weekly bortezomib is associated with a decreased rate of peripheral neuropathy without a decrement in response.[14]
- High-dose dexamethasone is associated with an increased risk of mortality and severe hematologic toxicities compared with melphalan/prednisone.[15]
- Lenalidomide plus low-dose dexamethasone (in comparison to lenalidomide plus high-dose dexamethasone) is associated with an improvement in overall survival and lower toxicity (less DVT, infections, and fatigue).[16]

[1] Beksac M, Haznedar R, Firatli-Tuglular T, et al. Addition of thalidomide to oral melphalan/prednisone in patients with multiple myeloma not eligible for transplantation: results of a randomized trial from the Turkish Myeloma Study Group. Eur J Haematol 2011;86:16-22.
[2] Facon T, Mary JY, Hulin C, et al. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. Lancet 2007;370:1209-1218.
[3] Hulin C, Facon T, Rodon P, et al. Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial. J Clin Oncol 2009;27:3664-3670.
[4] Kapoor P, Rajkumar SV, Dispenzieri A, et al. Melphalan and prednisone versus melphalan, prednisone and thalidomide for elderly and/or transplant-ineligible patients with multiple myeloma: a meta-analysis. Leukemia 2011;25:1523-1524.
[5] Ludwig H, Hajek R, Tothova E, et al. Thalidomide-dexamethasone compared with melphalan-prednisolone in elderly patients with multiple myeloma. Blood 2009;113:3435-3442.
[6] Palumbo A, Bringhen S, Caravita T, et al. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. Lancet 2006;367:825-831.
[7] Palumbo A, Bringhen S, Liberati AM, et al. Oral melphalan, prednisone, and thalidomide in elderly patients with multiple myeloma: updated results of a randomized controlled trial. Blood 2008;112:3107-3114.
[8] Waage A, Gimsing P, Fayers P, et al. Melphalan and prednisone plus thalidomide or placebo in elderly patients with multiple myeloma. Blood 2010;116:1405-1412.
[9] Wijermans P, Schaafsma M, Termorshuizen F, et al. Phase III study of the value of thalidomide added to melphalan plus prednisone in elderly patients with newly diagnosed multiple myeloma: the HOVON 49 Study. J Clin Oncol 2010;28:3160-3166.
[10] Palumbo A, Cavo M, Bringhen S, et al. Aspirin, warfarin, or enoxaparin thromboprophylaxis in patients with multiple myeloma treated with thalidomide: a phase III, open-label, randomized trial. J Clin Oncol 2011;29:986-993.
[11] Mateos MV, Richardson PG, Schlag R, et al. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. J Clin Oncol 2010;28:2259-2266.
[12] San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med 2008;359:906-917.
[13] Mateos MV, Oriol A, Martinez-Lopez J, et al. Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial. Lancet Oncol 2010;11:934-941.
[14] Palumbo A, Bringhen S, Rossi D, et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial. J Clin Oncol 2010;28:5101-5109.
[15] Facon T, Mary JY, Pegourie B, et al. Dexamethasone-based regimens versus melphalan-prednisone for elderly multiple myeloma patients ineligible for high-dose therapy. Blood 2006;107:1292-1298.
[16] Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol 2010;11:29-37.

DISEASE-SPECIFIC ISSUES RELATED TO AGE

Non-Small Cell Lung Cancer

Surgery[1-6]

- Few prospective studies.
- Retrospective analyses demonstrate that older patients who are selected for surgery tolerate it well.
- Caution with pneumonectomy in older adults.

Adjuvant Chemotherapy[7-8]

- The benefits of adjuvant chemotherapy are similar with age.

Locally Advanced Disease[9-12]

- Combined modality therapy: while efficacy is maintained, older adults (especially those with a Karnofsky performance status < 90) are more likely to have side effects (esophagitis, pneumonitis, myelosuppression).

Advanced Disease[13-22]

- As in younger patients, chemotherapy is associated with improved QOL in comparison to best supportive care.
- Emerging data are confirming the survival benefit of doublet chemotherapy in comparison to single-agent treatment.
- Use bevacizumab with caution in patients aged 70 y or older. Toxicities are increased in older adults (caution with myelosuppression). See NCCN Guidelines for Myeloid Growth Factors for the growth factor support (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

[1] Cangemi V, Volpino P, D'Andrea N, et al. Lung cancer surgery in elderly patients. Tumori 1996;82:237-241.
[2] Naunheim KS, Kesler KA, D'Orazio SA, et al. Lung cancer surgery in the octogenarian. Eur J Cardiothorac Surg 1994;8:453-456.
[3] Jack CI, Lye M, Lesley F, et al. Surgery for lung cancer: age alone is not a contraindication. Int J Clin Pract 1997;51:423-426.
[4] Morandi U, Stefani A, Golinelli M, et al. Results of surgical resection in patients over the age of 70 years with non small-cell lung cancer. Eur J Cardiothorac Surg 1997;11:432-439.
[5] Ishida T, Yokoyama H, Kaneko S, et al. Long-term results of operation for non-small cell lung cancer in the elderly. Ann Thorac Surg 1990;50:919-922.
[6] Mizushima Y, Noto H, Sugiyama S, et al. Survival and prognosis after pneumonectomy for lung cancer in the elderly. Ann Thorac Surg 1997;64:193-198.
[7] Pepe C, Hasan B, Winton TL, et al. Adjuvant vinorelbine and cisplatin in elderly patients: National Cancer Institute of Canada and Intergroup Study JBR.10. J Clin Oncol 2007;25:1553-1561.
[8] Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group. BMJ 1995;311:899-909.
[9] Movsas B, Scott C, Sause W, et al. The benefit of treatment intensification is age and histology-dependent in patients with locally advanced non-small cell lung cancer (NSCLC): a quality-adjusted survival analysis of radiation therapy oncology group (RTOG) chemoradiation studies. Int J Radiat Oncol Biol Phys 1999;45:1143-1149.
[10] Werner-Wasik M, Scott C, Cox JD, et al. Recursive partitioning analysis of 1999 Radiation Therapy Oncology Group (RTOG) patients with locally-advanced non-small-cell lung cancer (LA-NSCLC): identification of five groups with different survival. Int J Radiat Oncol Biol Phys 2000;48:1475-1482.
[11] Langer CJ, Hsu C, Curran WJ, et al. Elderly patients (pts) with locally advanced non-small cell lung cancer (LA-NSCLC) benefit from combined modality therapy: secondary analysis of Radiation Therapy Oncology Group (RTOG) 94-10. Proc Am Soc Clin Oncol 2002;21:Abstract 1193.
[12] Schild SE, Stella PJ, Geyer SM, et al. The outcome of combined-modality therapy for stage III non-small-cell lung cancer in the elderly. J Clin Oncol 2003;21:3201-3206.
[13] Kelly K, Giarritta S, Akerley W, et al. Should older patients (pts) receive combination chemotherapy for advanced stage non-small cell lung cancer (NSCLC)? An analysis of Southwest Oncology Trials 9509 and 9308 [asbtract]. J Clin Oncol 2001;20(Suppl):Abstract 1313.
[14] Langer CJ, Manola J, Bernardo P, et al. Cisplatin-based therapy for elderly patients with advanced non-small-cell lung cancer: implications of Eastern Cooperative Oncology Group 5592, a randomized trial. J Natl Cancer Inst 2002;94:173-181.
[15] Langer CJ, Vangel M, Schiller J, et al. Age-specific subanalysis of ECOG 1594: fit elderly patients (70-80 YRS) with NSCLC do as well as younger pts (<70). Proc Am Soc Clin Oncol 2003;22:Abstract 2571.
[16] Lilenbaum RC, Herndon JE, List MA, et al. Single-agent versus combination chemotherapy in advanced non-small-cell lung cancer: the cancer and leukemia group B (study 9730). J Clin Oncol 2005;23:190-196.
[17] Ramalingam SS, Dahlberg SE, Langer CJ, et al. Outcomes for elderly, advanced-stage non small-cell lung cancer patients treated with bevacizumab in combination with carboplatin and paclitaxel: analysis of Eastern Cooperative Oncology Group Trial 4599. J Clin Oncol 2008;26:60-65.
[18] Gridelli C. The ELVIS trial: a phase III study of single-agent vinorelbine as first-line treatment in elderly patients with advanced non-small cell lung cancer. Elderly Lung Cancer Vinorelbine Italian Study. Oncologist 2001;6(Suppl 1):4-7.
[19] Frasci G, Lorusso V, Panza N, et al. Gemcitabine plus vinorelbine yields better survival outcome than vinorelbine alone in elderly patients with advanced non-small cell lung cancer. A Southern Italy Cooperative Oncology Group (SICOG) phase III trial. Lung Cancer 2001;34(Suppl 4):65-69.
[20] Gridelli C, Perrone F, Gallo C, et al. Chemotherapy for elderly patients with advanced non-small-cell lung cancer: the Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. J Natl Cancer Inst 2003;95:362-372.
[21] Kudoh S, Takeda K, Nakagawa K, et al. Phase III study of docetaxel compared with vinorelbine in elderly patients with advanced non-small-cell lung cancer: results of the West Japan Thoracic Oncology Group Trial (WJTOG 9904). J Clin Oncol 2006;24:3657-3663.
[22] Quoix E, Zalcman G, Oster JP, et al. Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. Lancet 2011;378:1079-1088.

Senior Adult Oncology Version 2.2012

DISEASE-SPECIFIC ISSUES RELATED TO AGE

Prostate Cancer

- For treatment of clinically localized or locally advanced prostate cancer, see NCCN Guidelines for Prostate Cancer*.
- There are no age-related differences in docetaxel efficacy in patients with castration-resistant prostate cancer. Growth factor support should be considered in patients aged 65 y or older to decrease the risk of neutropenic complications.[1,2] See NCCN Guidelines for Myeloid Growth Factors*.
- There are no age-related differences in cabazitaxel efficacy in patients with castration-resistant prostate cancer. Growth factor support is strongly recommended in patients aged 65 y or older to decrease the risk of neutropenic complications in the elderly.[3,4] See NCCN Guidelines for Myeloid Growth Factors*.

*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

[1] Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502-1512.
[2] Sinibaldi VJ. Docetaxel treatment in the elderly patient with hormone refractory prostate cancer. Clin Interv Aging 2007;2:555-560.
[3] Pal SK, Twardowski P, Sartor O. Critical appraisal of cabazitaxel in the management of advanced prostate cancer. Clin Interv Aging 2010;5:395-402.
[4] de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010;376:1147-1154.

COMPREHENSIVE GERIATRIC ASSESSMENT

Functional status[i]
- Activities of daily living (ADLs): eating, dressing, continence, grooming, transferring, using the bathroom
- Instrumental activities of daily living (IADLs): using transportation, managing money, taking medications, shopping, preparing meals, doing laundry, doing housework, using telephone
- Performance status
- Falls
- Gait speed[1]

Socioeconomic issues: see page 165
Psychosocial distress: see NCCN Guidelines for Distress Management*

Comorbidities
- May affect treatment decisions in 4 ways:
  - Cancer treatment may interact with comorbidity to impact functional status or worsen the comorbidity. This includes any drug-drug interactions.
  - Cancer treatment may be too risky because of the type and severity of comorbidity.
  - Cancer treatment may not impact future life expectancy due to risk of morbidity[j] associated with comorbid condition. The effect of comorbidity on life expectancy should be evaluated before patient receives treatment.
  - Comorbidity may affect treatment outcome.
- Number and severity of comorbidities should be assessed.
  - Adult Comorbidity Evaluation Index (ACE-27)[2]
  - Charlson Comorbidity Index (CCI)[3]
  - Cumulative Illness Rating Scale (CIRS)[4]
  - OARS multidimensional functional assessment questionnaire[5]

Cognitive function
- Dementia
  - Mini Mental State Examination (MMSE)[6,7]
  - Montreal Cognitive Assessment (MoCA)[8] (http://www.mocatest.org/)
- Depression
  - Geriatric Depression Scale (GDS)[9,10]
  - See NCCN Guidelines for Distress Management*
- Delirium
  - Confusion Assessment Method and/or Memorial Delirium Assessment Scale[11,12]
  - See NCCN Guidelines for Palliative Care* and Distress Management*

Polypharmacy
- Medication review for duplication and appropriate use should be performed at every visit
  - Medication Appropriateness Index[13]
  - Beers criteria[14]
  - START/STOPP criteria[15,16]
- Review drug interactions[17]
- Special considerations for over/underuse, duration of therapy, and dosage when using these classes of medications[18,19]
  - Benzodiazepines
  - Anticholinergics
  - Antipsychotics
  - Opioids
  - Corticosteroids

*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

[i] See Procedure for Functional Assessment Screening in Elderly Persons (page 178).
[j] Mortality can be predicted using weight, body mass index, nutrition, fatigue, and existing medical conditions.

COMPREHENSIVE GERIATRIC ASSESSMENT

Nutritional Status
- Body mass index
- Weight loss
- Nutritional deficiency: Mini-Nutritional Assessment (MNA)[20,21]

Osteoporosis
- Dexa scan
- See NCCN Task Force Report: Bone Health in Cancer Care (http://www.nccn.org/JNCCN/PDF/2009_Bone_Health_TF.pdf)

REFERENCES

[1]Studenski S, Perera S, Patel K, et al. Gait speed and survival in older adults. JAMA 2011;305:50-58.
[2]Piccirillo JF, Tierney RM, Costas I, et al. Prognostic importance of comorbidity in a hospital-based cancer registry. JAMA 2004;291:2441-2447.
[3]Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-383.
[4]Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. J Am Geriatr Soc 1968;16:622-626.
[5]Fillenbaum GG, Smyer MA. The development, validity, and reliability of the OARS multidimensional functional assessment questionnaire. J Gerontol 1981;36:428-434.
[6]Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc 1992;40:922-935.
[7]Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the Mini-Mental State Examination by age and educational level. JAMA 1993;269:2386-2391.
[8]Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53:695-699.
[9]Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982;17:37-49.
[10]D'Ath P, Katona P, Mullan E, et al. Screening, detection and management of depression in elderly primary care attenders: the acceptability and performance of the 15 item Geriatric Depression Scale (GDS15) and the development of short versions. Fam Pract 1994;11:260-266.
[11]Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med 1990;113:941-948.
[12]Lawlor PG, Nekolaichuk C, Gagnon B, et al. Clinical utility, factor analysis, and further validation of the memorial delirium assessment scale in patients with advanced cancer: assessing delirium in advanced cancer. Cancer 2000;88:2859-2867.
[13]Samsa GP, Hanlon JT, Schmader KE, et al. A summated score for the medication appropriateness index: development and assessment of clinimetric properties including content validity. J Clin Epidemiol 1994;47:891-896.
[14]Fick DM, Cooper JW, Wade WE, et al. Updating the Beers criteria for potentially inappropriate medications use in older adults: results of a US consensus panel of experts. Arch Intern Med 2003;163:2716-2724.
[15]Barry PJ, Gallagher P, Ryan C, O'Mahony D. START (screening tool to alert doctors to the right treatment) – an evidence-based screening tool to detect prescribing omissions in elderly patients. Age Ageing 2007;36:632-638.
[16]Gallagher P and O'Mahony D. STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions): application to acutely ill elderly patients and comparison with Beers' criteria. Age Ageing 2008;37:673-679.
[17]Riechelmann RP, Saad ED. A systemic review on drug interactions in oncology. Cancer Invest 2006;24:704-712.
[18]Hilmer SN, Mager DE, Simonsick EM, et al. A drug burden index to define the functional burden of medications in older people. Arch Intern Med 2007;167:781-787.
[19]Chew ML, Mulsant BH, Pollock BG, et al. Anticholinergic activity of the 107 medications commonly used by older adults. J Am Geriatr Soc 2008;56:1333-1341.
[20]Vellas B, Guigoz Y, Garry PJ, et al. The Mini Nutritional Assessment (MNA) and its use in grading the nutritional state of elderly patients. Nutrition 1999;15:116-122.
[21]Rubenstein LZ, Harker JO, Salva A, et al. Screening for undernutrition in geriatric practice: developing the Short-Form Mini-Nutritional Assessment (MNA-SF). J Gerontol A Biol Sci Med Sci 2001;56:M366-372.

PROCEDURE FOR FUNCTIONAL ASSESSMENT SCREENING IN ELDERLY PERSONS

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

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

Text continued from p. 163

Comprehensive Geriatric Assessment

Older patients can be classified into 3 categories: 1) young old patients are aged 65 to 75 years; 2) old patients are aged 76 to 85 years; and 3) oldest old patients are older than 85 years.[11] Proper selection of patients is the key to administering effective and safe cancer treatment. The challenge of managing the older cancer patient is to assess whether the expected benefits of treatment are superior to the risk in a population with decreased life expectancy and decreased tolerance to stress.

Chronologic age alone is not reliable in estimating life expectancy, functional reserve, or the risk of treatment complications.[12] Although a physician cannot predict the exact life expectancy of an individual patient, they can provide an estimate of whether a patient is likely to live longer or shorter than an average person of similar age. Life expectancy at a given age can be estimated using life table data as suggested by Walter and Covinsky.[13] For example, approximately 25% of the healthiest 75-year-old women will live more than 17 years, 50% will live at least 12 years, and 25% will live less than 7 years. Lee et al.[14] developed and validated a potentially useful tool for clinicians to estimate the 4-year mortality risk. Patients can be stratified into 3 groups of varying risk of mortality (high, intermediate, or low) based on the prognostic index, which incorporates demographic variables (age and sex), self-reported comorbid conditions, and functional measures.[14] Carey et al.[15] 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. In a pooled analysis of individual data from 9 selected cohorts, Studenski et al.[16] reported that gait speed was associated with survival in older adults.

Comprehensive geriatric assessment (CGA) is a multidisciplinary in-depth evaluation to assess life expectancy and risk of morbidity from cancer in elderly patients.[17–19] CGA includes assessment tools to predict the functional age of elderly 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. The feasibility of CGA has been shown in elderly patients with cancer.[20–22] Balducci and Extermann[20] studied CGA in the older cancer patient, including an evaluation of functional status, comorbidity, socioeconomic conditions, cognitive and emotional function, nutritional status, polypharmacy, and geriatric syndromes. Ingram et al.[21] used a self-administered CGA, including demographics, comorbid conditions, functional status, pain, financial well-being, social support, emotional state, spiritual well-being, and quality of life, to characterize older cancer patients. Repetto et al.[22] showed that CGA adds substantial information on the functional assessment of elderly cancer patients (aged ≥ 65 years). Among patients with a good performance status, 13% had 2 or more comorbidities; 9.3% and 37.7% had limitations in activities of daily living (ADLs) or instrumental activities of daily living (IADLs), respectively.

CGA components (comorbid conditions, functional status, geriatric syndromes, and nutritional status) have been associated with the type of cancer treatment and survival in elderly patients with cancer.[23–27] For example, in women aged 65 years or older diagnosed with stage I through III primary breast cancer, the all-cause and breast cancer–specific death rate at 5 and 10 years was consistently approximately 2 times higher in women with 3 or more cancer-specific CGA deficits, regardless of age and stage of disease.[26] In another prospective study of 375 consecutive elderly patients with cancer (ELCAPA study), a multivariate analysis showed that a lower ADL score and malnutrition were independently associated with cancer treatment changes.[27]

Although CGA is helpful for physicians to develop a coordinated plan for cancer treatment and to guide appropriate interventions to the patient's problems, it can be time-consuming and may not be practical for all patients. Hurria et al.[28,29] developed a brief but comprehensive geriatric assessment of older patients with cancer. A multicenter study involving 500 older patients (median age, 73 years) with cancer showed that this brief geriatric assessment (including functional status, comorbidity, cognition, psychological status, social functioning and support, and nutritional status) is largely self-administered and can be completed by most older patients without assistance.[28] The geriatric assessment also identified deficits and problems that may impact morbidity and mortality.[29] Recent results from the CALGB 360401 study showed the feasibility of including this brief, primarily self-administered geriatric assessment tool in future cooperative group clinical trials.[30] Over-

cash et al.[31,32] developed an abbreviated CGA that could be helpful in screening for elderly patients who would benefit from an entire CGA.

Functional Status

Functional status in older patients with cancer can be evaluated based on their ability to complete ADLs and IADLs.[33,34] IADLs encompass complex skills that are necessary for maintaining independence in the community, and ADLs encompass more basic functions required to maintain independence in the home. In older patients with cancer, independence in IADLs has been associated with improved treatment tolerance and improved survival.[23–25,35] In addition to ADL and IADL scales, other screening tests (discussed later) have also been used to determine the functional status in elderly cancer patients.

A quick screening test to assess mobility is the "timed up and go" (TUG) test. Older individuals are asked to get up from an armchair without using their arms, walk 10 feet forward at their usual pace, turn around, walk back to the chair, and then sit down again. This tool can be use to assess overall motor function, and the score has been predictive of the risk of falls in older adults.

Lachs et al.[36] developed a screening tool to assess vision, hearing, arm and leg mobility, urinary incontinence, nutrition, mental status, depression, disabilities in the ADLs and IADLs, home environment, and social support. This screening test is performed by a physician (or office staff), and may be very useful for assessing whether a CGA is necessary.

Saliba et al.[37,38] developed a useful questionnaire called the *Vulnerable Elders Survey* (VES-13) that can predict the probability of death and functional decline in older patients. A score of 3 or more on the VES-13 indicates that patients are vulnerable. Patients can quickly fill out this survey at home or in the office. Saliba et al.[37] tested the questionnaire in 6205 Medicare beneficiaries aged 65 years and older. The VES-13 assesses whether elderly patients are at risk for functional decline or death. The advantage of this questionnaire is that it minimizes the amount of time required to examine patients in the office. The survey assesses age, self-rated health, limitation in physical function, and functional disabilities. Recently, Luciani et al.[39] reported that the VES-13 is highly predictive of impaired functional status and can be considered a useful preliminary means of assessing older patients with cancer before undertaking a full CGA.

In the future, laboratory tests may be used to assess which elderly patients are at increased risk for functional decline or mortality. Cohen et al.[40] showed that high levels of interleukin-6 and D-dimer were associated with mortality and functional dependence in home-dwelling individuals aged 71 years and older. Higher levels of interleukin-6 and C-reactive protein have been associated with slower walking speed and poor grip strength in adults older than 70 years.[41] In addition, cognitive decline has been found to be associated with elevated levels of D-dimer.[42] Thus, assessment of markers of inflammation and coagulation (e.g., interleukin-6, D-dimer) may be used to predict the physiologic age of elderly patients.

Comorbidities

Older adults have an increased prevalence of comorbidities, which can impact cancer prognosis and treatment tolerance.[43,44] Cardiovascular problems, including congestive heart failure (CHF), diabetes, renal insufficiency, dementia, depression, anemia, and osteoporosis, are some frequently encountered comorbid conditions in elderly cancer patients.

Specific comorbidities have been shown to have an impact on prognosis and treatment outcome in patients with cancer.[45–47] For example, in a series of 5077 men (median age, 69.5 years) with localized or locally advanced prostate cancer, neoadjuvant hormonal therapy was significantly associated with an increased risk of all-cause mortality (26.3% vs. 11.2%) among men with a history of coronary artery disease, CHF, or myocardial infarction after a median follow-up of 5.1 years.[45] In a randomized adjuvant chemotherapy trial of 3759 patients with high-risk stage II and III colon cancer, those with diabetes mellitus experienced a significantly higher rate of overall mortality and cancer recurrence. At 5 years, the disease-free (48% vs. 59%), overall (57% vs. 66%), and recurrence-free survival rates (56% vs. 64%) were significantly worse for patients with diabetes than for those without.[46] In the SEER database analysis of elderly patients (aged ≥ 66 years) diagnosed with stages I through III breast cancer, those with diabetes had increased rate of hospitalizations for any chemotherapy toxicity and higher all-cause mortality.[47] In elderly cancer patients with comorbidities, the interaction of cancer treatment with comorbidity may impact functional status or worsen the comorbidity. Cancer treatment may be too risky because of the type and severity of comorbidity, and, finally, cancer or cancer treatment may

not have any impact on life expectancy because of the risk of morbidity or mortality associated with the comorbid condition. The effect of comorbidity on life expectancy should be evaluated before initiation of treatment.

The guidelines recommend that the number and severity of comorbidities should be assessed. The adult comorbidity evaluation-27 (ACE-27) index,[48] Charlson Comorbidity Index (CCI),[49] Cumulative Illness Rating Scale (CIRS),[50] and OARS Multidimensional Functional Assessment Questionnaire[51] are commonly used indices to determine the risk of mortality associated with comorbidity in elderly patients. ACE-27,[52,53] CCI,[54–56] and CIRS[57,58] have also been used to determine treatment tolerance in elderly cancer patients. In a study of 310 elderly patients (aged ≥ 70 years) with head and neck cancer, comorbidity measured using the ACE-27 index was an indicator of overall survival.[59] In a randomized trial that compared vinorelbine alone or in combination with gemcitabine in elderly 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).[53] In a phase III trial comparing platinum-doublet therapy as first-line treatment in patients with stage IIIB or IV NSCLC, those with severe comorbidities (as measured with CIRS) benefited from and tolerated platinum-doublet chemotherapy as well as those with no comorbidities.[56] However, the former group had a higher risk of neutropenic fever and death from neutropenic infections.

Polypharmacy

Polypharmacy can be defined in various ways, including the use of an increased number of medications (≥ 5), more than is clinically indicated; the use of potentially inappropriate medications; medication underuse; and medication duplication.[60,61] Although polypharmacy can be an issue across all age groups, it can be a more serious problem in elderly patients because of 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.[62–64]

The use of multiple medications can lead to increased incidences of adverse drug reactions (which can lead to functional decline and geriatric syndromes), drug–drug interactions, and nonadherence.[60,65,66] Among patients receiving systemic anticancer therapy for solid tumors, one or more drug–drug interactions were observed in 27% of patients, which increased to 31% among patients receiving palliative care only.[66,67] Older patients, those with comorbid conditions, those with brain tumors, and those taking many medications are at greater risk for drug interactions.[67]

Alterations in pharmacokinetics and pharmacodynamics of drug metabolism in elderly patients can also contribute to adverse drug interactions.[60] Most of the commonly prescribed medications, such as opioids, antidepressants, antibiotics, and antipsychotics, and anticancer drugs induce or inhibit cytochrome P450 enzymes. In a retrospective analysis, Popa et al.[68] assessed the impact of polypharmacy on toxicity from chemotherapy in 290 elderly patients (aged ≥ 70 years). Results showed that cytochrome P450 inhibition may contribute to nonhematologic toxicities, whereas hematologic toxicities may be associated with protein binding interactions. The role of protein binding and cytochrome P450 inhibition should be further explored.

The use of one or more potentially inappropriate medications among elderly 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 elderly cancer patients (aged ≥ 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%.[71] Although polypharmacy did not increase the risk of chemotherapy-related toxicity in this cohort, it was associated with a higher frequency of hospitalization and early discontinuation of chemotherapy.[71]

Evaluation of Polypharmacy: The guidelines recommend that medication review for duplication and appropriate use be performed at every visit. Beers criteria and the Medication Appropriateness Index (MAI) are 2 of the most common approaches used to evaluate potentially inappropriate medication use in older patients. The screening tool of older persons' prescriptions (STOPP) and the screening tool to alert doctors to right treatment (START) criteria were 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 elderly cancer patients.[72,73] The criteria are appropriate for persons older than 65 years, and provide a rating of severity for adverse outcomes and a descriptive summary of the prescribing information associated with the medication. The updated 2003 Beers criteria have been used to evaluate polypharmacy in older patients with cancer both in an oncology-specific acute care unit (oncology-acute care for elders [OACE]; n = 47, with a median age of 73.5 years) and in the outpatient setting (n = 154, with a median age of 74 years).[74,75] The Beers criteria–based polypharmacy was observed in 21% and 11% of patients, respectively. Both of these studies included 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.[74] In the outpatient study, 50% of patients required specific interventions after geriatric management evaluation.[75]

Medication Appropriateness Index: The MAI was developed to measure appropriate prescribing based on a 10-item list and a 3-point rating scale.[76] Samsa et al.[77] subsequently modified the MAI to include a single summated MAI score per medication, which showed acceptable reliability in assessing medication appropriateness among 1644 medications prescribed to 208 elderly veterans from the same clinic. This modified MAI seems to be a valid and relatively reliable measure to detect medication appropriateness and inappropriateness in the community pharmacy setting, and in ambulatory elderly patients on multiple medications.[78,79] MAI scores were significantly lower for medications with a high potential for adverse effects than for those with a low potential (1.8 vs. 2.9).[78] Higher MAI scores were also associated with lower self-related health scores in older adults.[80] MAI has not been evaluated extensively in elderly cancer patients.

STOPP/START Criteria: The STOPP/START criteria were established by a Delphi consensus process involving 18 experts in geriatric pharmacotherapy from Ireland and the United Kingdom.[81] The STOPP criteria is composed of 65 indicators for potentially inappropriate prescribing, including drug–drug and drug–disease interactions, therapeutic duplication, and drugs that increase the risks of geriatric syndromes, whereas the START criteria incorporate 22 evidence-based indicators to identify prescribing omissions in older people.[82,83] In a randomized trial of 400 hospitalized patients (aged ≥ 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 using STOPP/START criteria with recommendations provided to their attending physicians, compared with a control group assigned to routine pharmaceutical care.[84] Significant improvements in prescribing appropriateness were sustained for 6 months after discharge.

Nutritional Status

Nutritional deficiency or malnutrition is a common and serious condition in older patients. Although some of the malnutrition is attributed to the underlying illness, in most patients it is from inadequate intake of calories. The Mini-Nutritional Assessment (MNA) was designed and validated to provide a single, rapid assessment of nutritional status of elderly patients in outpatient settings.[85,86] The MNA is composed of simple measurements and brief questions that help identify people at risk for malnutrition before severe changes in weight or albumin levels occur. Rubenstein et al.[87] developed a shortened version of the MNA, which also has good diagnostic accuracy. Special attention should also be given to vitamin D deficiency, because it may be related to osteoporosis and fractures.[88]

Cognitive Function

Geriatric patients with cancer who are cognitively impaired have an increased risk of functional dependence and a higher incidence of depression, and are at greater risk for death. Cognitive function was also predictive of medication adherence across diagnoses, regardless of the complexity of regimen.[89] In addition, the association between cognitive impairment and the ability to weigh the risks and benefits of cancer treatment decisions must be considered. Cognitively impaired patients should be cared for by an experienced multidisciplinary geriatric oncology team and receive good supportive care throughout the treatment.[90] Anticholinergics, antipsychotics, benzodiazepines, corticosteroids, and opioids can be associated with cognitive impairment in older adults.[91] Special considerations for overuse or unde-

ruse, duration of therapy, and dosage should be in place with the use of these classes of medications. Hilmer et al.[92] developed a drug burden index that is a useful evidence-based tool for assessing the effect of medications on the physical and cognitive performance in elderly people.

Dementia and delirium are among the most common causes of cognitive impairment.[93] See Geriatric Syndromes on this page for the assessment of dementia and delirium in older cancer patients.

Socioeconomic Issues

Social ties have been identified as significant predictors of mortality in older adults.[94,95] In a study of 2835 women diagnosed with breast cancer, socially isolated women had an elevated risk of mortality after a breast cancer diagnosis.[96] An evaluation of social support is an integral part of geriatric assessment. The patient's treatment goals should be discussed with them. In addition, the patient's living conditions, presence and adequacy of caregiver, and financial status should also be taken into consideration. Consultation with a social worker should be encouraged. Consultation with a financial expert to discuss the cost and coverage options of treatment would also be beneficial.

Geriatric Syndromes

Dementia, delirium, depression, distress, osteoporosis, falls, fatigue, and frailty are some of the most common syndromes in elderly cancer patients.[97] Elderly patients with cancer experience a higher prevalence of geriatric syndromes compared with those without cancer. In 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.[98] In this cohort, the prevalence of hearing trouble, urinary incontinence, falls, depression, and osteoporosis were significantly higher in patients with cancer than in those without.

Dementia: Dementia is a permanent cognitive impairment and is often present in elderly patients as a comorbid condition. In a SEER database analysis, elderly patients (aged ≥ 67 years) with colon cancer and dementia were less likely to receive invasive diagnostic methods or therapies with curative intent.[99] Preexisting dementia was also associated with high mortality, mostly from noncancer causes in patients aged 68 years or older diagnosed with breast, colon, or prostate cancer.[100]

The Blessed Orientation-Memory-Concentration test (BOMC), Mini-Mental State Examination (MMSE), or Montreal Cognitive Assessment (MoCA) can be used to screen for cognitive impairment in older adults.[101–104] The BOMC is a 6-item derivative of the Blessed Information-Memory-Concentration test.[103] The 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.[101,102] However, the MMSE is not adequate for mild cognitive impairment and does not predict future decline. The 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.[104] The MoCA has been shown to be superior as a prognostic indicator over the MMSE in patients with brain metastases.[105,106] In a feasibility study of the MoCA in patients with brain metastases, cognitive impairment was detected in 80% of the patients using this test compared with 30% using the MMSE.[105] Among the 28 patients with a normal MMSE, 71% had cognitive impairment according to the MoCA.

The use of antipsychotic medications in patients with dementia is associated with higher mortality rates.[107–109] Antipsychotic drugs should be used with caution even when short-term therapy is being considered.[109]

Delirium: Delirium is an acute decline in attention and cognition. It is the most common and underrecognized problem in older adults and can pose serious complications in patients with advanced cancer.[110] Dementia is the leading factor for delirium, and approximately two-thirds of cases of delirium occur in older patients with dementia.[111] It can contribute to poorer clinical outcome and affects communication between patients and physicians.

Several screening tools are available to identify patients with delirium. The Confusion Assessment Method (CAM) is a screening and diagnostic tool based on 4 important features of delirium: acute onset and fluctuating course, inattention, disorganized thinking, and altered level of consciousness.[112,113] The Memorial Delirium Assessment Scale (MDAS) is a 10-item validated instrument developed for repeated use to quantify the severity of delirium symptoms in patients with advanced cancer.[114] The Nursing Delirium Screening Scale (Nu-DESC) is an

observational 5-item scale that has been validated in the oncology inpatient setting and is associated with high sensitivity and specificity.[115] Medications that can contribute to delirium should be used with caution in elderly patients with cancer.[116,117] See the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Distress Management for the management of dementia and delirium (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

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.[118] The GDS was originally developed by Yesavage et al.[118] as 30-item scale. Recently, shortened versions of the GDS have been found be equally accurate and less time-consuming in screening for depression in older adults.[119,120] Cancer-related fatigue and depression frequently occur together; therefore, patients reporting fatigue should probably be assessed for depression.[121–123]

Distress: Psychological distress is common among patients with cancer. Hurria et al.[124] reported that significant distress was identified in 41% of patients aged 65 years or older with cancer, and that poorer physical function was the best predictor of distress. Screening tools have been found to be effective and feasible in reliably identifying distress and the psychosocial needs of patients.[125–127] The Distress Thermometer (DT) and the accompanying 36-item problem list is a well-known screening tool, specifically developed for cancer patients by the NCCN Distress Management Panel (see the NCCN Guidelines for Distress Management, available online at www.NCCN.org).[128,129] 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 (HADS).[127] Patients can quickly complete this distress assessment tool in the waiting room, and the results can alert the physician to potential problems. This tool identifies whether cancer patients have problems in 5 different categories: practical, family, emotional, spiritual/religious, and physical.

Frailty: Frailty is a biologic syndrome of decreased reserve and resistance to stressors, causing vulnerability to adverse outcomes.[130] Frail patients are at risk for falling, disability, hospitalization, and death. The Cardiovascular Health Study (CHS) developed a screening tool to identify frail patients.[131] Frail patients have 3 or more of the following criteria: unintentional weight loss (≥ 10 lb in past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and/or low physical activity.[131] Fit, frail, and pre-frail patients had different 5-year mortality rates and different risks of developing functional dependence at 3 and 7 years. The CHS screening tool was tested in 5317 men and women aged 65 years and older.

Fatigue: Cancer-related fatigue is a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning. In advanced cancer, the prevalence of fatigue is greater than 50% to 70%.[132] 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.[133] 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.[134,135] In contrast to normal fatigue, cancer-related fatigue is refractory to sleep and rest, perhaps because cancer patients have aberrant sleep patterns. It is reasonable to expect that fatigue may precipitate functional dependence, especially in patients who are already dependent in IADLs.[136–138]

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

Falls: Falls are one of the most common geriatric syndromes. Risk factors include older age, muscle weakness, and impairments in gait, balance, vision, cognition, and ADLs.[139] In a prospective study of inci-

dences of falls in patients with advanced cancer, 52% of patients fell during a follow-up of up to 6 months, regardless of age. The median time to fall was 85 and 80 days for those younger than 65 years and those aged 65 years or older, respectively.[140] Evidence from a meta-analysis of randomized trials and a systematic review identified interventions, such as multifactorial falls risk assessment and management, exercise, environmental modifications, and education, that are very effective in preventing falls in older adults, and also in reducing both risk and rate of falling.[141] Multifactorial risk assessment and management was the most effective intervention for both the risk of falling and the monthly rate of falls. Exercise programs were effective in reducing the risk of falling but did not have a beneficial effect in reducing the monthly fall rate.[141]

The American Geriatrics Society/British Geriatrics Society Clinical Practice Guideline for Prevention of Falls in Older Persons recommend a multifactorial risk assessment followed by multicomponent interventions to address the identified risks and to prevent falls in elderly patients aged 75 years or older with 2 or more falls in the past 12 months, or difficulty with walking or with balance or gait.[142] Recommended interventions include minimizing the number of medications; providing a tailored exercise program to improve strength, balance, gait, and coordination; treating vision impairment (including cataracts); managing postural hypotension, heart rate, and rhythm abnormalities, and addressing foot and footwear problems; providing vitamin D supplementation; modifying the home environment; and providing education and necessary information.[142]

Osteoporosis: Osteoporosis and its associated increase in fracture is a major risk factor in cancer patients, especially in women undergoing chemotherapy or hormonal therapy for breast cancer and in men undergoing 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 using dual energy x-ray absorptiometry (DEXA) scan. Management of bone health has become an integral part of comprehensive cancer care. Elderly patients should be made aware of the impact of cancer therapies on bone health and should adhere to treatment recommendations for maintaining bone health.[143] The NCCN task force report on bone health in cancer care discusses effective screening and therapeutic options for the management of treatment-related bone loss.[144]

Approach to Decision-Making in Older Patients With Cancer

The risk of morbidity from cancer is generally established according to the stage at diagnosis, aggressiveness of the tumor, and risk of recurrence and progression. After initial screening and CGA, patients with a low risk of dying or suffering from cancer during their lifetime can receive symptom management and supportive care as detailed in the appropriate NCCN Guidelines for Supportive Care (see list of NCCN Guidelines, available online, at www.NCCN.org). Patients in the moderate- or high-risk group can be further evaluated to assess their functional dependency, decision-making capacity, overall goals, and desire for proposed treatment.[145,146]

Irrespective of age, a person who is functionally independent and without serious comorbidities should be a good candidate for most forms of cancer treatment. 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 (see list of NCCN Guidelines, available online, at www.NCCN.org). Patients who are dependent in some IADLs, with or without severe comorbidities, are at increased risk of treatment complications. For these patients with intermediate functional impairment who have milder problems (e.g., dependence in one or more IADL, milder comorbidity, depression, minor memory disorder, mild dementia, inadequate caregiver), treatment may still be administered with special individualized precautions, including attempts to reverse the problem and cautious dosing of treatment.[147,148] In patients without decision-making capacity, the guidelines recommend considering consultation with an ethics committee.

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

ive Care are recommended for all patients (see list of NCCN Guidelines, available online, at www.NCCN.org).

Surgery

In general, age is not a primary consideration for surgical risk, although the physiologic status of the patient must be assessed. Performance status and comorbidities of the older patient are more important factors than age when considering surgical treatment options.[149] Special efforts should be made to prevent or avoid emergency surgery, because it carries increased risk of complications. After surgery, physical and/or occupational therapy should be considered to expedite the patient's return to their preoperative functional level.

The surgical task force report from the International Society of Geriatric Oncology (SIOG) reported that in many malignancies (breast, gastric, and liver), the surgical outcomes in older patients with cancer were not significantly different from those of their younger counterparts.[150] The Preoperative Assessment of Cancer in Elderly (PACE) was developed to determine the suitability of older patients for surgical intervention.[151] PACE incorporates CGA, the brief fatigue inventory (BFI), performance status, and American Society Anesthesiologists (ASA) grade. In an international prospective study, 460 consecutive older patients completed PACE before surgery.[152,153] 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 postsurgical complications. Disability determined based on ADL, IADL, and performance status was associated with an extended hospital stay. This study showed that PACE is a useful tool that will enable physicians to evaluate older cancer patients' fitness for surgery. The reliability of this tool must be confirmed in large prospective trials as applied to specific cancer types in elderly patients.

RT

RT (external beam RT or brachytherapy) can be offered either in the curative or palliative setting.[154] Hypofractionated RT may be an alternative treatment option in patients who are unable to tolerate conventional-dose RT.[155] Available data from the literature indicate that RT is highly effective and well tolerated, and that age is not a limiting factor in elderly cancer patients.[156–158] Concurrent chemoradiation, however, should be used with extreme caution; dose modification of chemotherapy may be necessary to reduce toxic side effects. Nutritional support and pain control for RT-included mucositis are recommended for patients receiving RT.

Chemotherapy

Several retrospective studies have reported that the toxicity of chemotherapy is not more severe or prolonged in persons older than 70 years.[159–163] However, the results of these studies cannot be generalized for the following reasons:

- Only a few patients were aged 80 years or older; therefore, minimal information is available on the oldest patients.
- The older patients involved in these studies were highly selected based on 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 show that age alone is not a contraindication to cancer chemotherapy. Therefore, patient selection is extremely important to maximize the benefits of adjuvant chemotherapy in older patients with breast cancer, NSCLC, and colon cancer.

Tolerance to Chemotherapy

Age has been associated with pharmacokinetic and pharmacodynamic changes and with increased susceptibility of normal tissues to toxic complications. In general, all of these changes increase the risks of chemotherapy.[164,165] 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 et al.[166] devised the MAX2 index for estimating the average per-patient risk for toxicity from chemotherapy. In a retrospective analysis, Shayne et al.[167] 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 undergoing adjuvant chemotherapy.[167] In another retrospective analysis of elderly patients (aged ≥ 65 years) with invasive breast cancer, the type of adjuvant chemotherapy regimen was a better predictor of toxicity than increased age or comorbidity score.[55] An anthracycline-based regimen resulted in greater grade 3 or 4 toxicity, hospitalization, and/or febrile neutropenia, whereas treatment delays because of myelosuppression were more frequent with a cyclophosphamide-containing regimen. Among elderly patients with ovarian cancer, those receiving standard-dose chemotherapy were more likely to experience cumulative toxicity and delays in therapy.[56]

Other investigators have developed tools incorporating components of CGA to assess the individual risk of severe toxicity from chemotherapy in older patients.[35,168,169] Extermann et al.[168] 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. With this model, diastolic blood pressure, IADLs, lactate dehydrogenase, and the type of therapy are the best predictors of hematologic toxicity, whereas performance status, cognitive function, nutritional status, and the type of therapy are the best predictors of nonhematologic toxicity. Hurria et al.[169] developed a scoring algorithm for predicting chemotherapy toxicity in older adults with cancer. The following factors were predictive of grade 3 to 5 chemotherapy toxicity: 1) age of 72 years or older, 2) cancer type (gastrointestinal or genitourinary), 3) standard dosing of chemotherapy, 4) polychemotherapy, 5) hemoglobin (male: < 11 g/dL; female: < 10 g/dL), 6) creatinine clearance less than 34 mL/min (Jelliffe formula using ideal weight),[170] 7) hearing impairment described as fair or worse, 8) one or more falls in past 6 months, 9) limited in walking one block, 10) the need for assistance with taking medications, and 11) decreased social activities because of physical or emotional health.[169]

Adherence to Therapy

Adherence to the prescribed regimen, especially oral therapy, is essential to derive maximal clinical benefit. Older adults are at increased risk for poor adherence to oral therapy for a variety of reasons, including cognitive impairment, comorbid conditions, polypharmacy, higher risk of side effects from drug interactions, limited insurance coverage, social isolation, and inadequate social support.[171] Several studies have evaluated the adherence to adjuvant therapy in older patients with estrogen receptor–positive breast cancer.[172–175] In one study, the discontinuation rate was 49% before the completion of 5 years, with women aged 75 years or older showing an increase in the number of cardiopulmonary comorbidities at 3 years, and those who had received breast-conserving surgery without RT being at higher risk of discontinuation.[174] In a cohort of 161 elderly women receiving oral adjuvant chemotherapy with capecitabine for breast cancer (CALGB 49907 study), 25% of the patients took fewer than 80% of the planned doses.[175] Nonadherence was more likely among women with node-negative disease and mastectomy. Although nonadherence was not associated with shorter relapse-free survival in this study (maybe because of limited sample size), Hershman et al.[176] recently reported that early discontinuation and nonadherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. Therefore, interventions designed to educate older patients about the benefits and risks of oral therapy may help reduce nonadherence.

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 seem to be at special risk for severe and prolonged myelosuppression and mucositis; increased risk of cardiomyopathy; and increased risk of central and peripheral neuropathy. In addition, they are also at risk for infection (with or without neutropenia), dehydration, electrolyte disorders, and malnutrition, either as a side effect of the

chemotherapy or directly from the tumor. Chemotherapy can also affect cognition, function, balance, vision, hearing, continence, and mood.[93] The combination of these complications enhances the risk of delirium and functional dependence. These complications (that may interfere with treatment) must be detected and corrected to achieve maximum benefit from chemotherapy. Prevention and/or amelioration of some of the common chemotherapy-related complications are discussed.

Cardiac Toxicity: Anthracyclines are associated with increased cardiac toxicity resulting in CHF. Other antineoplastic drugs may have additional effect on anthracycline-induced cardiac toxicity.[177] Risk factors for anthracycline-induced cardiotoxicity 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.[178,179]

Trastuzumab has also been associated with cardiac dysfunction and CHF in patients with metastatic breast cancer.[180] Other trials, including the NSABP B-31[181] and NCCTG N9831 studies,[182] which evaluated trastuzumab in combination with doxorubicin and cyclophosphamide followed by paclitaxel in patients with HER2-positive breast cancer, identified older age (≥ 50 years), lower left ventricular ejection fraction, and the use antihypertensive medications as risk factors for cardiac dysfunction in patients receiving trastuzumab. However, in the long-term follow-up of the Herceptin Adjuvant (HERA) trial, the incidence of severe CHF, left ventricular dysfunction, 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.[183] A combined review of cardiac data from the NSABP B-31 and NCCTG N9831 trials also showed that the incidence of symptomatic heart failure events was 2.0% in patients treated with adjuvant trastuzumab, and most of these patients recovered with appropriate treatment.[184]

In a recently published single-center retrospective analysis of elderly patients (aged ≥ 70 years; n = 45) with breast cancer, Serrano et al.[185] reported an increased incidence of cardiotoxicity among those with a history of cardiac disease and/or diabetes treated with trastuzumab. Asymptomatic cardiotoxicity was observed in 12.5% of patients with early-stage breast cancer and 24% of those with advanced breast cancer, and 8.9% of all patients with advanced breast cancer developed symptomatic CHF.

Emerging data from clinical studies (BCIRG 006 and BCIRG 007) 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 and metastatic HER2-positive breast cancer.[186,187] However, the median age of all patients in both trials was 50 to 52 years. Additional data regarding the tolerability of these regimens in older adults are needed.

In patients aged 65 years or older with both HER2-positive and HER2-negative early-stage breast cancer, the US Oncology Research Trial 9735 showed that non–anthracycline-based adjuvant chemotherapy with docetaxel and cyclophosphamide was associated with a disease-free and overall survival benefit compared with doxorubicin plus cyclophosphamide.[188] In this study, 160 of the 1016 enrolled patients (16%) were aged 65 years or older.

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.[189–191]

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 (carboplatin, oxaliplatin, methotrexate, bleomycin) and drugs that are converted to active (idarubicin, daunorubicin) or toxic metabolites (high-dose cytarabine).[11] Dose adjustment to the measured GFR should be considered for these drugs to decrease systemic toxicity.

Renal insufficiency is common in elderly cancer patients, particularly in those receiving nephrotoxic drugs and those with genitourinary cancers or 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. A SIOG task force provides several recommendations for the clinical management of older cancer patients with renal insufficiency.[192] Dose adjustments and calculation of creatinine clearance to assess renal function are recommended for all patients.

Neurotoxicity: Neurotoxicity is also a dose-limiting toxicity associated with chemotherapy.[193] Vinca alkaloids, cisplatin, and taxanes induce peripheral

neurotoxicity. Methotrexate, cytarabine, and ifosfamide are associated with central neurotoxic side effects. Purine analogs (e.g., fludarabine, cladribine, pentostatin) are associated with life-threatening neurotoxicity at significantly higher doses than the recommended clinical dose.[194] High-dose cytarabine can cause an acute cerebellar syndrome. Patient age (> 60 years); drug dose and schedule; and renal and hepatic dysfunction are the most important risk factors for cytarabine-induced cerebellar toxicity.[195,196]

Management of neurotoxicity mainly consists of dose reductions or lower dose-intensities. Older patients are particularly susceptible to the toxicity of cytarabine-based regimens because of 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. Alternative regimens with nonneurotoxic drugs should be considered, particularly in patients with significant hearing loss.

Myelosuppression: Available data from various studies have shown that the risk of myelosuppression increases substantially by age 65 years.[197–202] The risk of myelosuppression is decreased by 50% when using growth factors.[203–205] 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. Several prospective studies of older patients with large cell lymphoma have shown that older age is a risk factor for neutropenic infections in patients treated with regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone).[205–211] In patients aged 60 years or older undergoing induction or consolidation chemotherapy for acute myeloid leukemia (AML), the prophylactic use of hematopoietic growth factors results in faster recovery of neutrophil and shorter hospitalization but does not impact overall survival.[212,213]

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.[214] 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.[215,216] Despite these caveats, the use of growth factors seems to be the best established strategy to improve treatment in this group of patients.[217] The EORTC issued similar recommendations for the prophylactic use of G-CSF in older patients with cancer.[218] The NCCN Guidelines for Myeloid Growth Factors address the use of G-CSFs in patients with solid tumors and nonmyeloid malignancies (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

Anemia: Anemia has been shown to be a risk factor for chemotherapy-related toxicity, and is one of the factors responsible for reduction in volume of distribution, which may result in increased peak concentration and increased toxicity of drugs.[219] Anemia is also associated with cardiovascular disease, CHF, coronary death, and dementia.[220–223]

In patients with severe anemia, blood transfusions are necessary to prevent serious clinical consequences. There is increasing controversy regarding the use of erythropoietic stimulating agents (ESAs). ESAs have been shown to decrease the need for transfusion in patients receiving chemotherapy.[224] It also seems beneficial to complement the administration of erythropoietin with oral or parenteral iron, although this is not specific for elderly patients. However, recent randomized studies have reported decreased survival and poorer tumor control among cancer patients receiving erythropoietic drugs for correcting anemia and targeting hemoglobin levels at 12 g/dL or greater.[225] The use of ESAs in patients with cancer is also associated with increased risks of venous thromboembolism (VTE) and mortality.[226] The risks of shortened survival and of disease progression have not been excluded when ESAs are dosed to achieve hemoglobin levels of less than 12 g/dL.

Based on the results of these trials, in July 2008 the FDA strengthened its warnings to alert physicians of increased risk of tumor progression and shortened survival in patients with advanced breast, cervical, head and neck, lymphoid, and non–small cell lung cancers. Physicians were advised to use the lowest dose necessary to avoid transfusion. In addition, 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 elderly cancer patients should be managed as outlined in the NCCN Guidelines for Cancer- and Chemotherapy-Induced Anemia (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

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. Although 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 for the treatment of CIT in patients with nonmyeloid malignancies.[227] 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.[228]

Diarrhea: Diarrhea is a well-recognized side effect associated with several chemotherapeutic agents, and is particularly associated with regimens containing 5-fluorouracil (5-FU) and irinotecan. Chemotherapy-induced diarrhea can lead to discontinuation of chemotherapy and poorer clinical outcomes. Loss of fluid associated with persistent and severe diarrhea can lead to dehydration, renal insufficiency, and electrolyte imbalance. Older adults with chemotherapy-induced diarrhea should be treated with early rehydration. ASCO guidelines for the treatment of chemotherapy-induced diarrhea[229] recommend comprehensive evaluation at the onset of diarrhea to determine the severity. Based on the results from various clinical trials, the ASCO guidelines recommend loperamide therapy for mild to moderate diarrhea and octreotide (subcutaneous or intravenous if the patient is severely dehydrated) treatment for severe diarrhea or for chemotherapy-induced diarrhea that is refractory to loperamide therapy.

Mucositis: Oral and gastrointestinal mucositis are significant complications of radiotherapy and chemotherapy. The risk of mucositis increases with age. The Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology developed guidelines for preventing, evaluating, and treating oral and gastrointestinal mucositis.[230] An NCCN task force also published a comprehensive approach to the management of mucositis in patients with cancer.[231] Once mucositis has occurred, patients should be kept well hydrated with intravenous fluids and hospitalization, if necessary. Until recently, no pharmacologic agents have been shown to effectively treat mucositis. In 2004, the FDA approved palifermin (human keratinocyte growth factor) for the treatment of oral mucositis in patients with hematologic malignancies undergoing myelotoxic therapy requiring hematopoietic stem cell support.[232] Rosen et al.[233] reported that palifermin was well tolerated and resulted in significant reduction of oral mucositis in patients with metastatic colorectal cancer treated with 5-FU–based chemotherapy. However, the safety and efficacy of palifermin is yet to be firmly established in nonhematologic malignancies. A new time-released preparation of glutamine has shown promising results in the management of oral mucositis in patients with breast cancer undergoing anthracycline-based chemotherapy.[234]

Targeted Therapies

Recently, the emergence of targeted therapies such as monoclonal antibodies and tyrosine kinase inhibitors has revolutionized the treatment and improved outcomes of a variety of malignancies. Limited but increasing data are available on the toxicity of these targeted therapies in older adults with cancer, and their use should be individualized.[235] In patients who are not able to tolerate cytotoxic chemotherapy, the risk/benefit ratio should be considered before targeted therapy is initiated. 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. See the next section on Disease-Specific Issues for the efficacy and tolerability of specific targeted therapies in elderly cancer patients.

Disease-Specific Issues

Because the biologic characteristics of certain cancers are different in older patients compared with their younger counterparts, and partly because of the decreased tolerance of treatment by older patients, chemotherapy should be individualized based on the

nature of the disease and the performance status of the patient. Disease-specific issues related to age in some cancer types are discussed.

AML: Older patients with AML may have decreased sensitivity to chemotherapy because of increased prevalence of multidrug resistance and unfavorable cytogenetic profiles.[236] In view of the seriousness of the complications of AML treatment, the panel recommends that older patients with AML be treated according to the NCCN Guidelines for AML in centers skilled in the management and supportive care of AML (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

Bladder Cancer: Intravesical immunotherapy with Bacillus Calmette-Guérin (BCG) has decreased efficacy, particularly in patients older than 80 years.[237,238] 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 aged 61 to 70 years treated with BCG (P = .0002).[237] Age was an independent risk factor for response after taking into account the disease stage and grade and the patient's sex and prior treatment.[237] In the second study, the percent free from disease at 5 years after BCG therapy was 27% and 37% (P = .005) for patients aged 70 years or older and those younger than 70 years, respectively.[238]

Age alone should not be a criterion for making decisions regarding cystectomy, RT, and chemotherapy in elderly 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 overall survival than treatment with RT in all age groups.[239] Although the overall survival benefit was significantly higher in the radical cystectomy arm for patients aged 70 to 79 years (33 vs. 19 months), the survival benefit was smaller in patients aged 80 years or older (18 vs.15 months). In patients aged 80 years or older, radical cystectomy with PLND showed a small overall survival benefit compared with bladder preservation with RT (21 vs.15 months, respectively).[239] 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.[240] Median survival was 46 and 77 months, respectively (P = .06), for patients assigned to cystectomy and cystectomy plus neoadjuvant chemotherapy, and the survival benefit was preserved with age.[240]

Breast Cancer: Breast cancer in older women is associated with a more favorable tumor biology because of the high prevalence of hormone receptor–positive, HER2-negative, slowly proliferating tumors.[241,242] However, women older than 75 years receive less-aggressive treatment and have higher mortality rates from early-stage breast cancer than younger women.[243–245]

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 improved disease-free or overall survival compared with 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.[246] Elderly patients with early-stage and clinically node-negative breast cancer also did not benefit from ALND in terms of breast cancer mortality or survival.[247,248] In the absence of definitive evidence showing superior survival associated with ALND, this procedure can be considered optional for elderly patients with particularly favorable tumors, those with serious comorbid conditions, and those for whom the selection of adjuvant systemic therapy is unlikely to be affected.

RT as a component of breast conserving-therapy is not always necessary in selected women aged 70 years or older with stage I breast cancer. In a study that randomized women (aged ≥ 70 years) with clinical stage I estrogen receptor–positive breast cancer to receive lumpectomy and tamoxifen with whole-breast RT or lumpectomy and tamoxifen for 5 years, no differences were seen in overall survival or breast cancer–specific survival.[249,250] However, locoregional recurrence was higher among women who did not receive RT (4% vs. 1% for those who received RT).

Older women with stage I through III breast cancer derive similar clinical benefits from adjuvant chemotherapy compared with younger patients. However, older patients have an increased risk of treatment-related side effects and mortality.[251] Adjuvant chemotherapy with CMF (cyclophosphamide, methotrexate,

and 5-FU) or doxorubicin plus cyclophosphamide was superior to capecitabine alone.[252] The 3-year relapse-free survival rates were 68% and 85%, respectively, for the capecitabine group and the standard chemotherapy group ($P < .001$).The corresponding overall survival rates were 86% and 91%, respectively ($P = .02$).[252] The benefit was pronounced in women with hormone receptor–negative tumors ($P < .001$).

Trastuzumab is approved for the treatment of patients with HER2-positive early-stage and metastatic breast cancer. However, few elderly patients (aged ≥ 70 years) have been included in the pivotal trastuzumab trials.[253,254] Cardiac toxicity has been a concern in patients receiving trastuzumab-based therapy,[181] and age is a risk factor for CHF in patients receiving trastuzumab-based regimens. In elderly patients (aged ≥ 70 years), trastuzumab-related cardiotoxicity was associated with a history of cardiac disease and diabetes[185] (see Cardiac Toxicity on page 188).

Central Nervous System Cancers

Glioblastoma Multiforme: Surgery is the primary treatment option for patients with newly diagnosed glioblastoma multiforme. Available evidence suggests that gross total resection is associated with greater overall survival in patients aged 70 years or older.[255,256] In a small, randomized study involving patients aged 65 years or older (n = 30), the estimated median survival time was longer after open craniotomy and resection of the tumor (171 days compared with 85 days after the stereotactic biopsy; $P = .035$).[255] For patients aged 65 years or older, gross total resection was associated with a longer survival compared with biopsy and subtotal resection in a retrospective analysis.[256] 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 is unclear. 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 3 components (RT, chemotherapy, and surgery) was associated with best overall survival.[257]

Postoperative RT alone or in combination with temozolomide has been effective in improving clinical outcomes in elderly patients.[258–260] At a median follow-up of 21 weeks in a small randomized study of patients aged 70 years or older (n = 85), median survival was longer for those who received postoperative RT plus supportive care than for those who received supportive care alone (29 and 17 weeks, respectively).[259] 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. In another randomized trial, overall survival times were similar for postoperative standard RT (5.1 months) and shorter-course RT (5.6 months) for elderly patients (aged ≥ 60 years; n = 100).[258] However, among those who completed RT as planned, more patients who received standard RT required a posttreatment increase in corticosteroid dosage (49% compared with only 23% of those who received shorter-course RT). These results suggest that postoperative shorter-course RT is a reasonable treatment option for patients aged 70 years or older.

In a phase III randomized trial, the addition of temozolomide concurrently with RT followed by 6 months of adjuvant temozolomide improved survival rates in patients between ages 60 and 70 years with newly diagnosed glioblastoma multiforme.[260] At 5-year follow-up, overall survival 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. However, the benefit of concurrent chemoradiation therapy is unclear in patients older than 70 years, but it is likely to be helpful in selected "fit" patients.[261]

Bevacizumab, an anti–vascular endothelial growth factor receptor (VEGFR) antibody, resulted in a significant improvement in progression-free and overall survival in patients aged 55 years or older and with poor performance status, in a single-institution retrospective analysis.[262] VEGFR expression was also significantly higher in patients aged 55 years or older, implying that bevacizumab could be beneficial for this group of patients with recurrent glioblastoma multiforme.[262]

Primary Central Nervous System Lymphoma: Methotrexate-based chemotherapy is associated with superior outcome in elderly patients with primary central nervous system (CNS) lymphoma. In patients older than 60 years, high-dose methotrexate-based chemotherapy with or without whole-brain RT resulted in a median overall survival of 29 months.[263] However, a striking increase in neurotoxicity was seen in patients older than 60 years compared with

younger patients (75% vs. 26%). In a more recent retrospective analysis, Ney et al.[264] also reported similar median overall survival (25 months) in elderly patients treated with chemotherapy alone. In another retrospective review of 31 elderly patients (aged ≥ 70 years), high-dose methotrexate induced an overall radiographic response rate of 97%; the progression-free and overall survival rates were 7 and 37 months, respectively.[265] These results indicate that patients aged 60 years or older with primary CNS lymphoma should be treated initially with chemotherapy, with whole-brain RT reserved for those with recurrent or refractory disease, given the increase in neurotoxicity.

Colorectal Cancers: Age alone should not be a contraindication for curative surgery in elderly patients with early-stage and resectable colorectal cancer.[266–268] 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 type of adjuvant or palliative treatment than on age.[266] In the metastatic setting, Adam et al.[269] compared the outcome of liver resection for colorectal metastases between elderly and younger patients, and reported 3-year overall survival rates of 57% and 60%, respectively ($P < .001$). The overall survival was similar among patients aged 70 to 75, 75 to 80, or at least 80 years (58%, 55%, and 54%, respectively; $P = .160$). Careful preoperative planning and nonemergent surgery are more likely to result in optimal outcomes.[269]

In the adjuvant setting, older patients derive similar benefit from 5-FU–based chemotherapy to that of younger patients.[10,270] However, older patients may be at an increased risk for hematologic toxicities. In a pooled analysis of adjuvant chemotherapy trials, the relative benefit of overall survival from adjuvant chemotherapy was similar across all age groups, with no increased incidence of toxicities among patients aged 70 years or older, except for leukopenia in one study.[10] The 5-year overall survival rate was 71% for those who received adjuvant chemotherapy compared with 64% for those who were untreated. However, after 5 years, the absolute benefit of chemotherapy was smaller in patients aged 70 years or older because of competing causes of deaths. Pooled analyses of data from adjuvant trials using newer regimens containing oxaliplatin did not show significant benefit in disease-free or overall survival compared with 5-FU and leucovorin in patients aged 70 years or older.[271] Scant data are available among patients older than 80 years. Because of the lack of data from prospective randomized studies, adjuvant chemotherapy with newer regimens should be considered on an individual basis for patients aged 70 years or older.

For patients with metastatic disease, 5-FU–based palliative chemotherapy resulted in equal overall survival (10.8 and 11.3 months, respectively; $P = .31$) and progression-free survival (5.5 and 5.3 months, respectively; $P = .01$) in elderly (aged ≥ 70 years) and younger patients with metastatic colorectal cancer.[272] Infusional 5-FU was more effective than bolus 5-FU in both age groups. A recent prospective randomized trial (MRC FOCUS2) reported some improvement in median progression-free survival with the addition of reduced-dose oxaliplatin to 5-FU–based chemotherapy in elderly and frail patients with metastatic colorectal cancer, but the difference was not significant (5.8 vs. 4.5 months; $P = .07$).[273] The replacement of 5-FU with capecitabine resulted in higher risk of grade 3 or higher toxicity and no improvement in quality of life. In the OPTIMOX-1 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 as the standard oxaliplatin-based regimen (FOLFOX4) regimen in patients aged between 76 and 80 years with metastatic colorectal cancer,[274] implying that stop-and-go strategies or maintenance 5-FU–based chemotherapy may be desirable for elderly patients with metastatic disease to minimize toxicities.

Bevacizumab[275,276] and the anti–epidermal growth factor receptor (EGFR) antibodies cetuximab[277–279] and panitumumab[280,281] have also been evaluated for the treatment of elderly patients with metastatic colorectal cancer. 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 elderly patients (aged ≥ 70 years) with metastatic colorectal cancer, and the efficacy was similar to that observed in younger patients with acceptable tolerability.[277,278] Response rates and progression-free survival were significantly higher for elderly patients (aged ≥ 70 years) with wild-type *KRAS* mutations than for those

with *KRAS* mutations.[278] In a phase II clinical trial, cetuximab was safe and moderately active when used as a first-line single agent in fit elderly patients with metastatic colorectal cancer.[279]

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 progression-free survival regardless of age (hazard ratio, 0.51 and 0.60, respectively, for patients younger than 65 years and older than 65 years).[280] Progression-free survival, overall survival, and overall response rates were similar in elderly and younger patients. In this study, the efficacy of panitumumab is confined to patients with wild-type *KRAS* mutations.[281] The safety and efficacy of bevacizumab in elderly patients (aged ≥ 65 years) were comparable to those of younger patients.[275,276] In the BRiTE (Bevacizumab Regimens: Investigation of Treatment Effects and Safety) study, the median progression-free survival was similar across all age cohorts. However, median overall survival and survival beyond progression declined with age.[276] In a retrospective analysis, the addition of bevacizumab to chemotherapy significantly improved progression-free and overall survival in patients aged 65 years or older with metastatic colorectal cancer.[275] However, it is associated with higher rate of arterial thromboembolic events in elderly patients.

Head and Neck Cancers: Surgery is associated with good clinical outcomes and acceptable complication rates in elderly patients; however, complication rates increase with comorbidities.[53,282] In a retrospective analysis of elderly patients (aged ≥ 70 years), 63% and 54% experienced clinically important surgical and/or medical complications.[282] Bilateral neck dissection, male sex, presence of 2 or more comorbidities, and advanced stage of disease were associated with postoperative complications.[53]

Elderly patients (aged ≥ 70 years) with squamous cell carcinoma of the head and neck (SCCHN) who are treated with RT experience similar overall survival to younger patients.[283] Although no significant differences in late toxicities were seen between older patients and those younger than 70 years (median follow-up of 3 years), severe grade 3 and 4 functional acute toxicity was significantly more frequent in older patients (67% for patients aged 65 years or older compared with 49% in younger patients).[283] Few patients older than 70 years have been included in trials evaluating induction chemotherapy, and limited data exist on the efficacy and toxicity of this approach in this subset of patients.[284,285] Randomized trials and meta-analyses have reported that concurrent chemoradiation offers greater benefit than RT or induction chemotherapy alone.[286,287] In a prospective randomized study that included 255 patients aged 60 years or older, 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.[286] In the meta-analysis of chemotherapy in head and neck cancer (MACH-NC), concurrent chemoradiation offered a significant overall survival benefit of 4.5% at 5 years compared with RT alone in patients with nonmetastatic SCCHN. 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 and laryngeal dysfunction) after concurrent chemoradiation.[288] Data in patients older than 70 years are insufficient 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 data are limited on the benefit of adding cisplatin to RT.

Cisplatin-based chemotherapy is associated with increased toxicity in elderly patients with recurrent head and neck cancer.[289] In a review of 2 phase III randomized trials conducted by ECOG that evaluated cisplatin with paclitaxel or 5-FU, objective response rates (28% vs. 33%; $P = .58$) and median time to progression (5.25 vs. 4.8 months; $P = .69$) were similar for older and younger patients, respectively.[289] However, the incidences of severe nephrotoxicity, diarrhea, and thrombocytopenia were higher among elderly patients.

Cetuximab has been evaluated in only few patients with head and neck cancer. For patients with locally advanced SCCHN, limited evidence exists regarding the benefit of adding cetuximab to RT in patients older than 64 years.[290] Available evidence for this group of patients does not allow firm conclusions to be drawn regarding a survival advantage of concurrent cetuximab plus RT. Limited evidence is also

available regarding the benefit of adding cetuximab to chemotherapy in the treatment of patients older than 64 years with recurrent or metastatic SCCHN.[291]

Kidney Cancer: Surgical resection remains an effective treatment for patients with localized renal cell carcinoma (RCC). However, in a recent study, Lane et al.[292] reported that surgical management of clinically localized renal cortical tumors was not associated with increased survival in patients aged 75 years or older. 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 elderly patients with localized RCC should be individualized based on predicted life expectancy.

Recently, several targeted therapies, including bevacizumab,[293] tyrosine kinase inhibitors (sorafenib[294,295] and sunitinib[296,297]), and mammalian target of rapamycin (mTOR) inhibitors (everolimus[298] and temsirolimus[299]) have been evaluated in elderly 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 overall (46 vs. 50 weeks; $P = .4$) and progression-free survivals (42 vs. 35 weeks; $P = .8$) were similar for patients aged 70 years or older and patients younger than 70 years with advanced RCC.[295] Incidences of the 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.[295] In a pooled analysis of 6 clinical trials that evaluated the efficacy and safety of sunitinib in patients with metastatic RCC, the median progression-free (9 and 11 months, respectively; $P = .0830$) and overall survivals (23.3 and 23.7 months, respectively; $P = .5441$) were similar in patients younger than 70 years and those aged 70 years or older.[297] The incidences of adverse events were also similar, although some (fatigue, decreased appetite/weight, cough, peripheral edema, thrombocytopenia, and anemia) were more common in elderly patients.

Temsirolimus was associated with improved overall ($P = .008$) and progression-free survivals ($P < .001$) compared with interferon among patients with metastatic RCC and poor prognosis.[299] In a multicenter, randomized phase III trial, the median overall survival was 10.9 months for temsirolimus group compared with 7.3 and 8.4 months, respectively, in the groups treated with interferon-α 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 elderly patients because of its increased toxicity. In a subgroup analysis of a phase III trial evaluating the safety and efficacy of everolimus in patients with metastatic RCC, median progression-free survivals were 5.36 and 5.13 months, respectively ($P < .001$), for patients aged 65 years or older and 70 years or older.[298] Older patients were at increased risk of adverse events, including stomatitis, anemia, and infection.

Multiple Myeloma: In elderly patients with newly diagnosed multiple myeloma, induction chemotherapy with the combination of melphalan, prednisone, and thalidomide (MPT) was associated with significantly superior response rates, progression-free survival, time-to-treatment progression, and event-free survival compared with melphalan and prednisone (MP) in randomized studies.[300–307] However, overall survival benefit for MPT was reported only in 2 of these studies. In the IFM 99-06 trial, which compared MPT, MP, and reduced-intensity autologous stem cell transplant, median overall survival times were 51.6, 33.2, and 38.3 months, respectively; the MPT regimen was associated with a significantly better overall survival than the MP regimen ($P = .0006$) or reduced-intensity autologous stem cell transplant ($P = .027$).[302] In the IFM 01/01 trial, median overall survival times were 44 and 29 months, respectively ($P = .028$), for elderly patients (aged ≥ 75 years) treated with MPT and MP.[303] However, MPT was associated with significant toxicity (constipation, fatigue, VTE, neuropathy, cytopenias, and infection).[307] Deep vein thrombosis (DVT) prophylaxis with low-molecular-weight heparin (LMWH) is recommended for elderly patients receiving thalidomide-based regimens. In a phase III randomized trial, aspirin and fixed low-dose warfarin showed similar safety and efficacy in reducing thromboembolic complications compared with LMWH in patients with myeloma treated with a thalidomide-based regimen, except in elderly patients, in whom LMWH was more effective than warfarin.[308]

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 high-dose therapy and the survival benefit was seen across all age groups.[309,310] However, the rates of adverse events (peripheral neuropathy, cytopenias, and fatigue) were higher among patients in the VMP group than those in the MP group. The subgroup analyses of the VISTA trial showed that VMP resulted in longer overall survival among patients younger than 75 years than in those aged 75 years or older (3-year overall survival rates were 74.1% and 55.5%, respectively; $P = .011$).[310] In another randomized trial, in the induction phase, bortezomib, thalidomide, and prednisone (VTP) and VMP resulted in similar response rates (partial response rates were 81% and 80%, respectively) and overall survival, with different side-effect profiles.[311] Incidences of infection were higher in the VMP group, and VTP was associated with higher incidences of cardiac events. In the maintenance setting, complete response rates were higher with bortezomib and thalidomide (44%) than with bortezomib and prednisone (39%); however, peripheral neuropathy was higher with bortezomib and thalidomide.[311] In a 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 progression-free survival compared with VMP alone but did not result in an improvement in overall survival.[312] The 3-year overall survival rates were 89% and 87%, respectively, for VMPT followed by VT and for VMP ($P = .77$). VMPT followed by VT was also associated with higher-grade 3 or 4 toxicities (neutropenia, cardiologic, and thromboembolic events).

Dexamethasone-based regimens are associated with increased mortality and severe hematologic toxicities compared with MP in elderly patients with newly diagnosed multiple myeloma not eligible for high-dose therapy.[313,314] In a large randomized trial (IFM 95-01) comparing MP with dexamethasone-based regimens (dexamethasone, alone or in combination with melphalan or interferon), although no difference was seen in overall survival among the 4 treatment groups, the response rate was significantly higher in patients receiving dexamethasone and melphalan, and progression-free-survival 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, and hemorrhage, severe diabetes, and gastrointestinal and psychiatric complications in the dexamethasone arms) were significantly higher than with MP.[313] The results of a recent randomized trial suggest that the low-dose dexamethasone used in combination with lenalidomide is associated with better short-term overall survival and lower toxicity than high-dose dexamethasone and lenalidomide in patients with newly diagnosed myeloma.[314]

Non-Hodgkin's Lymphoma: In randomized clinical trials, the outcome in older patients who received full-dose anthracycline-based therapy was comparable to that of younger patients. However, the complete response rates drop to 45% in patients aged 70 years or older.[315] Age and serum interleukin-6 levels have been identified as independent prognostic factors for complete response and failure-free survival in patients with diffuse large B-cell lymphoma (DLBCL).[316–320] Rituximab (an anti-CD20 monoclonal antibody) has been well tolerated and effective in the treatment of elderly patients with DLBCL, with no apparent increase in toxicity. Several randomized trials involving older adults exclusively have shown that the addition of rituximab to CHOP improves survival in patients with advanced-stage DLBCL.[211,321–323]

Hepatitis B virus (HBV) reactivation has been reported to occur in patients treated with chemotherapy with or without rituximab; treatment with rituximab alone is also a risk for HBV reactivation.[324] Antiviral prophylaxis has been shown to prevent chemoimmunotherapy-associated HBV reactivation.[325–327] Because of the significant of risk of HBV reactivation associated with rituximab, the panel recommends that elderly patients receiving rituximab should be monitored for HBV reactivation as outlined in the NCCN Guidelines for Non-Hodgkin's Lymphoma (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

NSCLC: Surgery is the standard treatment for patients with localized NSCLC. Retrospective studies have shown that age alone is not a contraindication for surgery, and that surgery is well tolerated in carefully selected patients.[328–332] Long-term follow-up of elderly patients (aged ≥ 70 years) showed that the mortality and prognosis were similar to those of

younger patients.[328] The postoperative mortality and 5-year survival rates were 3% and 48%, respectively, for elderly patients. However, pneumonectomy was associated with a higher mortality rate in patients aged 70 or older compared with younger patients (22% and 3.2%, respectively; $P < .005$).[333] Therefore, pneumonectomy should be performed with caution in elderly patients.

Older patients with completely resected NSCLC treated with adjuvant chemotherapy derive similar survival benefits to younger patients.[334–336] A pooled analysis of 4584 patients from 5 trials of adjuvant cisplatin-based chemotherapy showed that elderly patients had a survival benefit similar to that of their younger counterparts, without significant toxicity.[336] 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.[335]

Combined modality therapy is feasible and effective in elderly patients with locally advanced disease; however, it is associated with more toxicities (esophagitis, pneumonitis, and myelosuppression), especially in patients with poor performance status (Karnofsky performance status < 90).[337,338] Langer et al.[337] reported that concurrent chemotherapy with once-daily RT was beneficial to elderly patients with locally advanced NSCLC. Median survival time was 22.4 months for patients treated with concurrent chemotherapy with daily RT compared with 16.4 months for patients treated with concurrent chemotherapy with twice-daily RT, and 10.8 months for those treated with sequential chemotherapy and daily RT. Short-term toxicities were more pronounced in the elderly patients. Schild et al.[338] also reported that elderly and younger patients derived similar survival benefit from concurrent chemoradiation therapy. The 2- and 5-year survival rates were 36% and 13%, respectively, in elderly patients with locally advanced disease compared with 39% and 18%, respectively, in patients younger than 70 years ($P = .4$). Pneumonitis and myelosuppression were more pronounced in the elderly patients. In some studies, combined modality treatment was associated with excess toxicity and no survival benefit for the elderly.[339,340]

Chemotherapy is associated with improved quality of care compared with best supportive care in elderly patients with advanced disease.[341,342] In the ELVIS study, vinorelbine plus best supportive care was superior to best supportive care alone in terms of both survival and quality of life.[341] Median and 1-year survivals 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 elderly patients with good performance status derive similar clinical benefit from combination chemotherapy to younger patients; however, the incidences of toxicities are higher among elderly patients.[337,343,344] The 2 trials that have compared the combination of vinorelbine and gemcitabine with single-agent vinorelbine or gemcitabine in elderly patients with advanced NSCLC have shown conflicting results.[345,346] 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 elderly patients with NSCLC,[345] whereas 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.[346] Emerging data are confirming the survival benefit of 2-drug regimens compared with 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 significantly longer survival in patients aged 70 years or older (performance status 0–2) with advanced NSCLC than single-agent therapy with vinorelbine or gemcitabine, despite an increased risk of side effects (e.g., febrile neutropenia, asthenia, toxic death rate) with combination therapy.[347] Median overall survivals were 10.3 and 6.2 months, respectively, and the 1-year survival rates were 44.5% and 25.4%, respectively.

Bevacizumab[348] and erlotinib, an EGFR inhibitor,[349,350] have been evaluated in elderly patients with advanced NSCLC. In a subset analysis of a phase III study (ECOG 4599), elderly patients with NSCLC who were randomized to paclitaxel and carboplatin with bevacizumab experienced a higher degree of toxicity and no improvement in overall survival compared with those who received paclitaxel and carboplatin.[348] Bevacizumab should be used with caution in older patients. Erlotinib, although active and relatively well tolerated in chemotherapy-näive elderly patients (aged ≥ 70 years) with advanced NSCLC, is associ-

ated with higher incidences of interstitial lung disease and toxicity-related discontinuation (5% and 12%, respectively),[348] compared with only 1% and 5%, respectively, observed in the erlotinib arm of the BR.21 trial, in which the median age was only 62 years. A recent subgroup analysis of the BR.21 trial also confirmed that elderly patients experienced greater toxicity and prolonged dose interruptions compared with younger patients, even though survival and quality-of-life benefits were similar for both groups.[350]

Prostate Cancer: Management of elderly patients with prostate cancer is similar to that of younger patients.[351] Treatment options are based on anticipated life expectancy of individual patients and whether they are symptomatic. See the NCCN Guidelines for Prostate Cancer for the management of patients with localized or locally advanced disease (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

Docetaxel-based chemotherapy has been effective in elderly patients with metastatic castration-resistant prostate cancer.[352,353] In the subgroup analysis of the TAX 327 trial, the survival benefit of 3-weekly docetaxel with prednisone compared with mitoxantrone with prednisone was seen across all age groups; median overall survival was 18.1 months for patients aged 69 years or older compared with 17.6 months for patients aged 68 years or younger.[354] The hazard ratios for younger and older patients were 0.81 and 0.77, respectively. The hazard ratio was 0.80 with the age cutoff of 75 years.

Recently, cabazitaxel has shown activity in patients with metastatic castration-resistant prostate cancer that has progressed on docetaxel-based chemotherapy.[355] In a randomized phase III trial, cabazitaxel with prednisone improved overall survival compared with mitoxantrone plus prednisone. The survival benefit was seen across all age groups.[356] The hazard ratios for overall survival were 0.62 and 0.81, respectively, for older (age ≥ 65 years) and younger patients. Growth factor support is strongly recommended for patients aged 65 years or older receiving cabazitaxel because of the increased risk of neutropenia in these patients.

Summary

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

Chronologic age is not reliable in estimating life expectancy, functional reserve, or the risk of treatment complications. Whether cancer treatment is appropriate may be best determined through careful assessment of the older patient. CGA can be used to assess life expectancy and risk of morbidity from cancer in elderly patients, in turn enabling physicians to develop a coordinated plan for cancer treatment and guide interventions tailored to the patient's problems.

References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010;60:277–300.
2. Altekruse SF, Kosary CL, Krapcho M, et al., eds. SEER Cancer Statistics Review, 1975–2007: National Cancer Institute. Bethesda, MD, based on November 2009 SEER data submission, posted to the SEER web site, 2010. Available at: http://seer.cancer.gov/csr/1975_2007/. Accessed January 12, 2012.
3. Smith BD, Smith GL, Hurria A, et al. Future of cancer incidence in the United States: burdens upon an aging, changing nation. J Clin Oncol 2009;27:2758–2765.
4. Balducci L, Beghe C. Cancer and age in the USA. Crit Rev Oncol Hematol 2001;37:137–145.
5. Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. J Clin Oncol 2004;22:4626–4631.
6. Saltzstein SL, Behling CA. 5- and 10-year survival in cancer patients aged 90 and older: a study of 37,318 patients from SEER. J Surg Oncol 2002;81:113–116; dicussion 117.
7. Extermann M. Management issues for elderly patients with breast cancer. Curr Treat Options Oncol 2004;5:161–169.
8. Chen H, Cantor A, Meyer J, et al. Can older cancer patients tolerate chemotherapy? A prospective pilot study. Cancer 2003;97:1107–1114.
9. Christman K, Muss HB, Case LD, Stanley V. Chemotherapy of metastatic breast cancer in the elderly. The Piedmont Oncology Association experience [see comment]. JAMA 1992;268:57–62.
10. Sargent DJ, Goldberg RM, Jacobson SD, et al. A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients. N Engl J Med 2001;345:1091–1097.
11. Balducci L. Management of cancer in the elderly. Oncology (Williston Park) 2006;20:135–143.
12. Wedding U, Honecker F, Bokemeyer C, et al. Tolerance to chemotherapy in elderly patients with cancer. Cancer Control 2007;14:44–56.

13. Walter LC, Covinsky KE. Cancer screening in elderly patients: a framework for individualized decision making. JAMA 2001;285:2750–2756.
14. Lee SJ, Lindquist K, Segal MR, Covinsky KE. Development and validation of a prognostic index for 4-year mortality in older adults. JAMA 2006;295:801–808.
15. Carey EC, Walter LC, Lindquist K, Covinsky KE. Development and validation of a functional morbidity index to predict mortality in community-dwelling elders. J Gen Intern Med 2004;19:1027–1033.
16. Studenski S, Perera S, Patel K, et al. Gait speed and survival in older adults. JAMA 2011;305:50–58.
17. Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. J Clin Oncol 2007;25:1824–1831.
18. Pal SK, Katheria V, Hurria A. Evaluating the older patient with cancer: understanding frailty and the geriatric assessment. CA Cancer J Clin 2010;60:120–132.
19. Rodin MB, Mohile SG. A practical approach to geriatric assessment in oncology. J Clin Oncol 2007;25:1936–1944.
20. Balducci L, Extermann M. Management of cancer in the older person: a practical approach. Oncologist 2000;5:224–237.
21. Ingram SS, Seo PH, Martell RE, et al. Comprehensive assessment of the elderly cancer patient: the feasibility of self-report methodology. J Clin Oncol 2002;20:770–775.
22. Repetto L, Fratino L, Audisio RA, et al. Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients: an Italian Group for Geriatric Oncology Study. J Clin Oncol 2002;20:494–502.
23. Maione P, Perrone F, Gallo C, et al. Pretreatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non-small-cell lung cancer receiving chemotherapy: a prognostic analysis of the multicenter Italian lung cancer in the elderly study. J Clin Oncol 2005;23:6865–6872.
24. Koroukian SM, Xu F, Bakaki PM, et al. Comorbidities, functional limitations, and geriatric syndromes in relation to treatment and survival patterns among elders with colorectal cancer. J Gerontol A Biol Sci Med Sci 2010;65:322–329.
25. Winkelmann N, Petersen I, Kiehntopf M, et al. Results of comprehensive geriatric assessment effect survival in patients with malignant lymphoma. J Cancer Res Clin Oncol 2011;137:733–738.
26. Clough-Gorr KM, Thwin SS, Stuck AE, Silliman RA. Examining five- and ten-year survival in older women with breast cancer using cancer-specific geriatric assessment. Eur J Cancer 2011; July7[Epub ahead of print].
27. Caillet P, Canoui-Poitrine F, Vouriot J, et al. Comprehensive geriatric assessment in the decision-making process in elderly patients with cancer: ELCAPA Study. J Clin Oncol 2011;29:3636–3642.
28. Hurria A, Gupta S, Zauderer M, et al. Developing a cancer-specific geriatric assessment: a feasibility study. Cancer 2005;104:1998–2005.
29. Hurria A, Mohile S, Lichtman S, et al. Geriatric assessment of older adults with cancer: baseline data from a 500 patient multicenter study [abstract]. J Clin Oncol 2009;27(Suppl 15):Abstract 9546.
30. Hurria A, Cirrincione CT, Muss HB, et al. Implementing a geriatric assessment in cooperative group clinical cancer trials: CALGB 360401. J Clin Oncol 2011:1290–1296.
31. Overcash JA, Beckstead J, Extermann M, Cobb S. The abbreviated comprehensive geriatric assessment (aCGA): a retrospective analysis. Crit Rev Oncol Hematol 2005;54:129–136.
32. Overcash JA, Beckstead J, Moody L, et al. The abbreviated comprehensive geriatric assessment (aCGA) for use in the older cancer patient as a prescreen: scoring and interpretation. Crit Rev Oncol Hematol 2006;59:205–210.
33. Katz S, Ford AB, Moskowitz RW, et al. Studies of illness in the aged. The index of ADL: a standardized measure of biological and psychosocial function. JAMA 1963;185:914–919.
34. Lawton MP. Scales to measure competence in everyday activities. Psychopharmacol Bull 1988;24:609–614.
35. Freyer G, Geay JF, Touzet S, et al. Comprehensive geriatric assessment predicts tolerance to chemotherapy and survival in elderly patients with advanced ovarian carcinoma: a GINECO study. Ann Oncol 2005;16:1795–1800.
36. Lachs MS, Feinstein AR, Cooney LM, et al. A simple procedure for general screening for functional disability in elderly patients. Ann Intern Med 1990;112:699–706.
37. Saliba D, Elliott M, Rubenstein LZ, et al. The Vulnerable Elders Survey: a tool for identifying vulnerable older people in the community. J Am Geriatr Soc 2001;49:1691–1699.
38. Min L, Yoon W, Mariano J, et al. The vulnerable elders-13 survey predicts 5-year functional decline and mortality outcomes in older ambulatory care patients. J Am Geriatr Soc 2009;57:2070–2076.
39. Luciani A, Ascione G, Bertuzzi C, et al. Detecting disabilities in older patients with cancer: comparison between comprehensive geriatric assessment and vulnerable elders survey-13. J Clin Oncol 2010;28:2046–2050.
40. Cohen HJ, Harris T, Pieper CF. Coagulation and activation of inflammatory pathways in the development of functional decline and mortality in the elderly. Am J Med 2003;114:180–187.
41. Taaffe DR, Harris TB, Ferrucci L, et al. Cross-sectional and prospective relationships of interleukin-6 and C-reactive protein with physical performance in elderly persons: MacArthur studies of successful aging. J Gerontol A Biol Sci Med Sci 2000;55:M709–715.
42. Wilson CJ, Cohen HJ, Pieper CF. Cross-linked fibrin degradation products (D-dimer), plasma cytokines, and cognitive decline in community-dwelling elderly persons. J Am Geriatr Soc 2003;51:1374–1381.
43. Extermann M. Interaction between comorbidity and cancer. Cancer Control 2007;14:13–22.
44. Pal SK, Hurria A. Impact of age, sex, and comorbidity on cancer therapy and disease progression. J Clin Oncol 2010;28:4086–4093.
45. Nanda A, Chen MH, Braccioforte MH, et al. Hormonal therapy use for prostate cancer and mortality in men with coronary artery disease-induced congestive heart failure or myocardial infarction. JAMA 2009;302:866–873.
46. Meyerhardt JA, Catalano PJ, Haller DG, et al. Impact of diabetes mellitus on outcomes in patients with colon cancer. J Clin Oncol 2003;21:433–440.
47. Srokowski TP, Fang S, Hortobagyi GN, Giordano SH. Impact of diabetes mellitus on complications and outcomes of adjuvant chemotherapy in older patients with breast cancer. J Clin Oncol 2009;27:2170–2176.
48. Piccirillo JF, Tierney RM, Costas I, et al. Prognostic importance of comorbidity in a hospital-based cancer registry. JAMA

2004;291:2441–2447.

49. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–383.
50. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. J Am Geriatr Soc 1968;16:622–626.
51. Fillenbaum GG, Smyer MA. The development, validity, and reliability of the OARS multidimensional functional assessment questionnaire. J Gerontol 1981;36:428–434.
52. Breccia M, Latagliata R, Stagno F, et al. Charlson comorbidity index and adult comorbidity evaluation-27 scores might predict treatment compliance and development of pleural effusions in elderly patients with chronic myeloid leukemia treated with second-line dasatinib. Haematologica 2011;96:1457–1461.
53. Sanabria A, Carvalho AL, Melo RL, et al. Predictive factors for complications in elderly patients who underwent head and neck oncologic surgery. Head Neck 2008;30:170–177.
54. Frasci G, Lorusso V, Panza N, et al. Gemcitabine plus vinorelbine versus vinorelbine alone in elderly patients with advanced non-small-cell lung cancer. J Clin Oncol 2000;18:2529–2536.
55. Hurria A, Brogan K, Panageas KS, et al. Patterns of toxicity in older patients with breast cancer receiving adjuvant chemotherapy. Breast Cancer Res Treat 2005;92:151–156.
56. Fader AN, von Gruenigen V, Gibbons H, et al. Improved tolerance of primary chemotherapy with reduced-dose carboplatin and paclitaxel in elderly ovarian cancer patients. Gynecol Oncol 2008;109:33–38.
57. Gronberg BH, Sundstrom S, Kaasa S, et al. Influence of comorbidity on survival, toxicity and health-related quality of life in patients with advanced non-small-cell lung cancer receiving platinum-doublet chemotherapy. Eur J Cancer 2010;46:2225–2234.
58. Ngeow J, Leong SS, Gao F, et al. Impact of comorbidities on clinical outcomes in non-small cell lung cancer patients who are elderly and/or have poor performance status. Crit Rev Oncol Hematol 2010;76:53–60.
59. Sanabria A, Carvalho AL, Vartanian JG, et al. Comorbidity is a prognostic factor in elderly patients with head and neck cancer. Ann Surg Oncol 2007;14:1449–1457.
60. Tam-McDevitt J. Polypharmacy, aging, and cancer. Oncology (Williston Park) 2008;22:1052–1055, discussion 1055, 1058, 1060.
61. Maggiore RJ, Gross CP, Hurria A. Polypharmacy in older adults with cancer. Oncologist 2010;15:507–522.
62. Sokol KC, Knudsen JF, Li MM. Polypharmacy in older oncology patients and the need for an interdisciplinary approach to side-effect management. J Clin Pharm Ther 2007;32:169–175.
63. Puts MT, Costa-Lima B, Monette J, et al. Medication problems in older, newly diagnosed cancer patients in Canada: how common are they? A prospective pilot study. Drugs Aging 2009;26:519–536.
64. Lees J, Chan A. Polypharmacy in elderly patients with cancer: clinical implications and management. Lancet Oncol 2011;12:1249–1257.
65. Riechelmann RP, Saad ED. A systematic review on drug interactions in oncology. Cancer Invest 2006;24:704–712.
66. Riechelmann RP, Tannock IF, Wang L, et al. Potential drug interactions and duplicate prescriptions among cancer patients. J Natl Cancer Inst 2007;99:592–600.
67. Riechelmann RP, Zimmermann C, Chin SN, et al. Potential drug interactions in cancer patients receiving supportive care exclusively. J Pain Symptom Manage 2008;35:535–543.
68. Popa M, Wallace K, Brunello A, Extermann M. The impact of polypharmacy on toxicity from chemotherapy in elderly patients: focus on cytochrome P-450 inhibition and protein binding effects [abstract]. J Clin Oncol 2008;26(Suppl 15):Abstract 9505.
69. Steinman MA, Landefeld SC, Rosenthal GE, et al. Polypharmacy and prescribing quality in older people. J Am Geriatr Soc 2006;54:1516–1523.
70. Currow DC, Stevenson JP, Abernethy AP, et al. Prescribing in palliative care as death approaches. J Am Geriatr Soc 2007;55:590–595.
71. Maggiore RJ, Gross CP, Hardt M, et al. Polypharmacy, potentially inappropriate medications, and chemotherapy-related adverse events among older adults with cancer [abstract]. J Clin Oncol 2011;29(Supp 1):Abstract e19501.
72. Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. Arch Intern Med 1997;157:1531–1536.
73. Fick DM, Cooper JW, Wade WE, et al. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. Arch Intern Med 2003;163:2716–2724.
74. Flood KL, Carroll MB, Le CV, Brown CJ. Polypharmacy in hospitalized older adult cancer patients: experience from a prospective, observational study of an oncology-acute care for elders unit. Am J Geriatr Pharmacother 2009;7:151–158.
75. Lichtman SM, Boparai MK. Geriatric medication management: evaluation of pharmacist interventions and potentially inappropriate medication (PIM) use in older (>=65 years) cancer patients [asbtract]. J Clin Oncol 2009;27(Suppl):Abstract 9507.
76. Hanlon JT, Schmader KE, Samsa GP, et al. A method for assessing drug therapy appropriateness. J Clin Epidemiol 1992;45:1045–1051.
77. Samsa GP, Hanlon JT, Schmader KE, et al. A summated score for the medication appropriateness index: development and assessment of clinimetric properties including content validity. J Clin Epidemiol 1994;47:891–896.
78. Schmader K, Hanlon JT, Weinberger M, et al. Appropriateness of medication prescribing in ambulatory elderly patients. J Am Geriatr Soc 1994;42:1241–1247.
79. Kassam R, Martin LG, Farris KB. Reliability of a modified medication appropriateness index in community pharmacies. Ann Pharmacother 2003;37:40–46.
80. Hanlon JT, Artz MB, Pieper CF, et al. Inappropriate medication use among frail elderly inpatients. Ann Pharmacother 2004;38:9–14.
81. Gallagher P, Baeyens JP, Topinkova E, et al. Inter-rater reliability of STOPP (Screening Tool of Older Persons' Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment) criteria amongst physicians in six European countries. Age Ageing 2009;38:603–606.
82. Gallagher P, O'Mahony D. STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions): application to acutely ill elderly patients and comparison with Beers' criteria. Age Ageing 2008;37:673–679.
83. Barry PJ, Gallagher P, Ryan C, O'Mahony D. START (screening tool to alert doctors to the right treatment)—an evidence-based screening tool to detect prescribing omissions in elderly patients. Age Ageing 2007;36:632–638.

84. Gallagher PF, O'Connor MN, O'Mahony D. Prevention of potentially inappropriate prescribing for elderly patients: a randomized controlled trial using STOPP/START criteria. Clin Pharmacol Ther 2011;89:845–854.
85. Guigoz Y, Lauque S, Vellas BJ. Identifying the elderly at risk for malnutrition. The Mini Nutritional Assessment. Clin Geriatr Med 2002;18:737–757.
86. Vellas B, Guigoz Y, Garry PJ, et al. The Mini Nutritional Assessment (MNA) and its use in grading the nutritional state of elderly patients. Nutrition 1999;15:116–122.
87. Rubenstein LZ, Harker JO, Salva A, et al. Screening for undernutrition in geriatric practice: developing the short-form mini-nutritional assessment (MNA-SF). J Gerontol A Biol Sci Med Sci 2001;56:M366–372.
88. Bjorkman MP, Sorva AJ, Risteli J, Tilvis RS. Low parathyroid hormone levels in bedridden geriatric patients with vitamin D deficiency. J Am Geriatr Soc 2009;57:1045–1050.
89. Stilley CS, Bender CM, Dunbar-Jacob J, et al. The impact of cognitive function on medication management: three studies. Health Psychol 2010;29:50–55.
90. Extermann M. Older patients, cognitive impairment, and cancer: an increasingly frequent triad. J Natl Compr Canc Netw 2005;3:593–596.
91. Chew ML, Mulsant BH, Pollock BG, et al. Anticholinergic activity of 107 medications commonly used by older adults. J Am Geriatr Soc 2008;56:1333–1341.
92. Hilmer SN, Mager DE, Simonsick EM, et al. A drug burden index to define the functional burden of medications in older people. Arch Intern Med 2007;167:781–787.
93. Naeim A, Reuben D. Geriatric syndromes and assessment in older cancer patients. Oncology (Williston Park) 2001;15:1567–1577.
94. Seeman TE, Kaplan GA, Knudsen L, et al. Social network ties and mortality among the elderly in the Alameda County Study. Am J Epidemiol 1987;126:714–723.
95. Tomaka J, Thompson S, Palacios R. The relation of social isolation, loneliness, and social support to disease outcomes among the elderly. J Aging Health 2006;18:359–384.
96. Kroenke CH, Kubzansky LD, Schernhammer ES, et al. Social networks, social support, and survival after breast cancer diagnosis. J Clin Oncol 2006;24:1105–1111.
97. Flood KL, Carroll MB, Le CV, et al. Geriatric syndromes in elderly patients admitted to an oncology-acute care for elders unit. J Clin Oncol 2006;24:2298–2303.
98. Mohile SG, Fan L, Reeve E, et al. Association of cancer with geriatric syndromes in older Medicare beneficiaries. J Clin Oncol 2011;29:1458–1464.
99. Gupta SK, Lamont EB. Patterns of presentation, diagnosis, and treatment in older patients with colon cancer and comorbid dementia. J Am Geriatr Soc 2004;52:1681–1687.
100. Raji MA, Kuo YF, Freeman JL, Goodwin JS. Effect of a dementia diagnosis on survival of older patients after a diagnosis of breast, colon, or prostate cancer: implications for cancer care. Arch Intern Med 2008;168:2033–2040.
101. Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the Mini-Mental State Examination by age and educational level. JAMA 1993;269:2386–2391.
102. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc 1992;40:922–935.
103. Kawas C, Karagiozis H, Resau L, et al. Reliability of the Blessed Telephone Information-Memory-Concentration Test. J Geriatr Psychiatry Neurol 1995;8:238–242.
104. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53:695–699.
105. Olson RA, Chhanabhai T, McKenzie M. Feasibility study of the Montreal Cognitive Assessment (MoCA) in patients with brain metastases. Support Care Cancer 2008;16:1273–1278.
106. Olson RA, Iverson GL, Carolan H, et al. Prospective comparison of two cognitive screening tests: diagnostic accuracy and correlation with community integration and quality of life. J Neurooncol 2011;105:337–344.
107. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA 2005;294:1934–1943.
108. Kales HC, Valenstein M, Kim HM, et al. Mortality risk in patients with dementia treated with antipsychotics versus other psychiatric medications. Am J Psychiatry 2007;164:1568–1576; quiz 1623.
109. Rochon PA, Normand SL, Gomes T, et al. Antipsychotic therapy and short-term serious events in older adults with dementia. Arch Intern Med 2008;168:1090–1096.
110. Bush SH, Bruera E. The assessment and management of delirium in cancer patients. Oncologist 2009;14:1039–1049.
111. Inouye SK. Delirium in older persons. N Engl J Med 2006;354:1157–1165.
112. Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med 1990;113:941–948.
113. Wei LA, Fearing MA, Sternberg EJ, Inouye SK. The Confusion Assessment Method: a systematic review of current usage. J Am Geriatr Soc 2008;56:823–830.
114. Lawlor PG, Nekolaichuk C, Gagnon B, et al. Clinical utility, factor analysis, and further validation of the memorial delirium assessment scale in patients with advanced cancer: assessing delirium in advanced cancer. Cancer 2000;88:2859–2867.
115. Gaudreau JD, Gagnon P, Harel F, et al. Fast, systematic, and continuous delirium assessment in hospitalized patients: the nursing delirium screening scale. J Pain Symptom Manage 2005;29:368–375.
116. Gaudreau JD, Gagnon P, Harel F, et al. Psychoactive medications and risk of delirium in hospitalized cancer patients. J Clin Oncol 2005;23:6712–6718.
117. Gaudreau JD, Gagnon P, Roy MA, et al. Opioid medications and longitudinal risk of delirium in hospitalized cancer patients. Cancer 2007;109:2365–2373.
118. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982;17:37–49.
119. D'Ath P, Katona P, Mullan E, et al. Screening, detection and management of depression in elderly primary care attenders. I: the acceptability and performance of the 15 item Geriatric Depression Scale (GDS15) and the development of short versions. Fam Pract 1994;11:260–266.
120. Jongenelis K, Pot AM, Eisses AM, et al. Diagnostic accuracy of the original 30-item and shortened versions of the Geriatric Depression Scale in nursing home patients. Int J Geriatr Psychiatry 2005;20:1067–1074.
121. Jacobsen PB. Assessment of fatigue in cancer patients. J Natl Cancer Inst Monogr 2004:93–97.
122. Jacobsen PB, Donovan KA, Weitzner MA. Distinguishing

fatigue and depression in patients with cancer. Semin Clin Neuropsychiatry 2003;8:229–240.

123. Respini D, Jacobsen PB, Thors C, et al. The prevalence and correlates of fatigue in older cancer patients. Crit Rev Oncol Hematol 2003;47:273–279.

124. Hurria A, Li D, Hansen K, et al. Distress in older patients with cancer. J Clin Oncol 2009;27:4346–4351.

125. Zabora J, BrintzenhofeSzoc K, Jacobsen P, et al. A new psychosocial screening instrument for use with cancer patients. Psychosomatics 2001;42:241–246.

126. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–370.

127. Mitchell AJ. Pooled results from 38 analyses of the accuracy of distress thermometer and other ultra-short methods of detecting cancer-related mood disorders. J Clin Oncol 2007;25:4670–4681.

128. Hoffman BM, Zevon MA, D'Arrigo MC, Cecchini TB. Screening for distress in cancer patients: the NCCN rapid-screening measure. Psychooncology 2004;13:792–799.

129. Jacobsen PB, Donovan KA, Trask PC, et al. Screening for psychologic distress in ambulatory cancer patients. Cancer 2005;103:1494–1502.

130. Hamerman D. Toward an understanding of frailty. Ann Intern Med 1999;130:945–950.

131. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146–156.

132. Rao A, Cohen HJ. Symptom management in the elderly cancer patient: fatigue, pain, and depression. J Natl Cancer Inst Monogr 2004:150–157.

133. Minton O, Strasser F, Radbruch L, Stone P. Identification of factors associated with fatigue in advanced cancer: a subset analysis of the European Palliative Care Research Collaborative computerized symptom assessment data set. J Pain Symptom Manage, in press.

134. Demetri GD, Kris M, Wade J, et al. Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: results from a prospective community oncology study. Procrit Study Group. J Clin Oncol 1998;16:3412–3425.

135. Vogelzang NJ, Breitbart W, Cella D, et al. Patient, caregiver, and oncologist perceptions of cancer-related fatigue: results of a tripart assessment survey. The Fatigue Coalition. Semin Hematol 1997;34:4–12.

136. Berger AM, Farr L. The influence of daytime inactivity and nighttime restlessness on cancer-related fatigue. Oncol Nurs Forum 1999;26:1663–1671.

137. Hardy SE, Studenski SA. Fatigue and function over 3 years among older adults. J Gerontol A Biol Sci Med Sci 2008;63:1389–1392.

138. Luciani A, Jacobsen PB, Extermann M, et al. Fatigue and functional dependence in older cancer patients. Am J Clin Oncol 2008;31:424–430.

139. Rao SS. Prevention of falls in older patients. Am Fam Physician 2005;72:81–88.

140. Stone C, Lawlor PG, Nolan B, Kenny RA. A prospective study of the incidence of falls in patients with advanced cancer. J Pain Symptom Manage 2011;42:535–540.

141. Chang JT, Morton SC, Rubenstein LZ, et al. Interventions for the prevention of falls in older adults: systematic review and meta-analysis of randomised clinical trials. BMJ 2004;328:680–680.

142. Summary of the Updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. J Am Geriatr Soc 2011;59:148–157.

143. Balducci L. Bone complications of cancer treatment in the elderly. Oncology (Williston Park) 2010;24:741–747.

144. Gralow JR, Biermann JS, Farooki A, et al. NCCN Task Force Report: bone health in cancer care. J Natl Compr Canc Netw 2009;7(Suppl 3):S1–32; quiz S33–35.

145. Sessums LL, Zembrzuska H, Jackson JL. Does this patient have medical decision-making capacity? JAMA 2011;306:420–427.

146. Harrington SE, Smith TJ. The role of chemotherapy at the end of life: "when is enough, enough?" JAMA 2008;299:2667–2678.

147. Balducci L, Extermann M. Cancer and aging. An evolving panorama. Hematol Oncol Clin North Am 2000;14:1–16.

148. Monfardini S, Ferrucci L, Fratino L, et al. Validation of a multidimensional evaluation scale for use in elderly cancer patients. Cancer 1996;77:395–401.

149. Ramesh H, Pope D, Gennari R, Audisio R. Optimising surgical management of elderly cancer patients. World J Surg Oncol 2005;3:17.

150. Audisio RA, Bozzetti F, Gennari R, et al. The surgical management of elderly cancer patients; recommendations of the SIOG surgical task force. Eur J Cancer 2004;40:926–938.

151. Audisio RA, Ramesh H, Longo WE, et al. Preoperative assessment of surgical risk in oncogeriatric patients. Oncologist 2005;10:262–268.

152. Pope D, Ramesh H, Gennari R, et al. Pre-operative assessment of cancer in the elderly (PACE): a comprehensive assessment of underlying characteristics of elderly cancer patients prior to elective surgery. Surg Oncol 2006;15:189–197.

153. Audisio RA, Pope D, Ramesh HS, 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;65:156–163.

154. Zachariah B, Balducci L. Radiation therapy of the older patient. Hematol Oncol Clin North Am 2000;14:131–167.

155. Donato V, Valeriani M, Zurlo A. Short course radiation therapy for elderly cancer patients. Evidences from the literature review. Crit Rev Oncol Hematol 2003;45:305–311.

156. Mitsuhashi N, Hayakawa K, Yamakawa M, et al. Cancer in patients aged 90 years or older: radiation therapy. Radiology 1999;211:829–833.

157. Wasil T, Lichtman SM, Gupta V, Rush S. Radiation therapy in cancer patients 80 years of age and older. Am J Clin Oncol 2000;23:526–530.

158. Zachariah B, Balducci L, Venkattaramanabalaji GV, et al. Radiotherapy for cancer patients aged 80 and older: a study of effectiveness and side effects. Int J Radiat Oncol Biol Phys 1997;39:1125–1129.

159. Gelman RS, Taylor SG. Cyclophosphamide, methotrexate, and 5-fluorouracil chemotherapy in women more than 65 years old with advanced breast cancer: the elimination of age trends in toxicity by using doses based on creatinine clearance. J Clin Oncol 1984;2:1404–1413.

160. Ibrahim NK, Frye DK, Buzdar AU, et al. Doxorubicin-based chemotherapy in elderly patients with metastatic breast cancer. Tolerance and outcome. Arch Intern Med 1996;156:882–888.

161. Giovanazzi-Bannon S, Rademaker A, Lai G, Benson AB. Treatment tolerance of elderly cancer patients entered onto phase II clinical trials: an Illinois Cancer Center study. J Clin Oncol 1994;12:2447–2452.

162. Newcomb PA, Carbone PP. Cancer treatment and age: patient

perspectives. J Natl Cancer Inst 1993;85:1580–1584.

163. Lichtman SM, Wildiers H, Chatelut E, et al. International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. J Clin Oncol 2007;25:1832–1843.

164. Balducci L, Corcoran MB. Antineoplastic chemotherapy of the older cancer patient. Hematol Oncol Clin North Am 2000;14:193–212.

165. Hurria A, Lichtman SM. Clinical pharmacology of cancer therapies in older adults. Br J Cancer 2008;98:517–522.

166. Extermann M, Bonetti M, Sledge GW, et al. MAX2—a convenient index to estimate the average per patient risk for chemotherapy toxicity; validation in ECOG trials. Eur J Cancer 2004;40:1193–1198.

167. Shayne M, Crawford J, Dale DC, et al. Predictors of reduced dose intensity in patients with early-stage breast cancer receiving adjuvant chemotherapy. Breast Cancer Res Treat 2006;100:255–262.

168. Extermann M, Boler I, Reich R, et al. The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score: design and validation [abstract]. J Clin Oncol 2010;28(Suppl 15):Abstract 9000.

169. Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol 2011;29:3457–3465.

170. Jelliffe RW, Jelliffe SM. Estimation of creatinine clearance from changing serum-creatinine levels. Lancet 1971;2:710.

171. Maloney KW, Kagan SH. Adherence and oral agents with older patients. Semin Oncol Nurs 2011;27:154–160.

172. Demissie S, Silliman RA, Lash TL. Adjuvant tamoxifen: predictors of use, side effects, and discontinuation in older women. J Clin Oncol 2001;19:322–328.

173. Fink AK, Gurwitz J, Rakowski W, et al. Patient beliefs and tamoxifen discontinuance in older women with estrogen receptor—positive breast cancer. J Clin Oncol 2004;22:3309–3315.

174. Owusu C, Buist DS, Field TS, et al. Predictors of tamoxifen discontinuation among older women with estrogen receptor-positive breast cancer. J Clin Oncol 2008;26:549–555.

175. Partridge AH, Archer L, Kornblith AB, et al. Adherence and persistence with oral adjuvant chemotherapy in older women with early-stage breast cancer in CALGB 49907: adherence companion study 60104. J Clin Oncol 2010;28:2418–2422.

176. Hershman DL, Shao T, Kushi LH, et al. Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. Breast Cancer Res Treat 2011;126:529–537.

177. Floyd JD, Nguyen DT, Lobins RL, et al. Cardiotoxicity of cancer therapy. J Clin Oncol 2005;23:7685–7696.

178. Hershman DL, McBride RB, Eisenberger A, et al. Doxorubicin, cardiac risk factors, and cardiac toxicity in elderly patients with diffuse B-cell non-Hodgkin's lymphoma. J Clin Oncol 2008;26:3159–3165.

179. Aapro M, Bernard-Marty C, Brain EGC, et al. Anthracycline cardiotoxicity in the elderly cancer patient: a SIOG expert position paper. Ann Oncol 2011;22:257–267.

180. Suter TM, Procter M, van Veldhuisen DJ, et al. Trastuzumab-associated cardiac adverse effects in the herceptin adjuvant trial. J Clin Oncol 2007;25:3859–3865.

181. Tan-Chiu E, Yothers G, Romond E, et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. J Clin Oncol 2005;23:7811–7819.

182. Perez EA, Suman VJ, Davidson NE, et al. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. J Clin Oncol 2008;26:1231–1238.

183. Procter M, Suter TM, de Azambuja E, et al. Longer-term assessment of trastuzumab-related cardiac adverse events in the Herceptin Adjuvant (HERA) trial. J Clin Oncol 2010;28:3422–3428.

184. Russell SD, Blackwell KL, Lawrence J, et al. Independent adjudication of symptomatic heart failure with the use of doxorubicin and cyclophosphamide followed by trastuzumab adjuvant therapy: a combined review of cardiac data from the National Surgical Adjuvant breast and Bowel Project B-31 and the North Central Cancer Treatment Group N9831 clinical trials. J Clin Oncol 2010;28:3416–3421.

185. Serrano C, Cortes J, De Mattos-Arruda L, et al. Trastuzumab-related cardiotoxicity in the elderly: a role for cardiovascular risk factors. Ann Oncol, in press.

186. Slamon D, Eiermann W, Robert N, et al. Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC→T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC→TH) with docetaxel, carboplatin and trastuzumab (TCH) in her2neu positive early breast cancer patients: BCIRG 006 study [abstract]. Presented at the 2009 San Antionio Breast Cancer Symposium; December 9–13, 2009; San Antonio, Texas. Abstract 62.

187. Valero V, Forbes J, Pegram MD, et al. Multicenter phase III randomized trial comparing docetaxel and trastuzumab with docetaxel, carboplatin, and trastuzumab as first-line chemotherapy for patients with HER2-gene-amplified metastatic breast cancer (BCIRG 007 study): two highly active therapeutic regimens. J Clin Oncol 2011;29:149–156.

188. Jones S, Holmes FA, O'Shaughnessy J, et al. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology Research Trial 9735. J Clin Oncol 2009;27:1177–1183.

189. Swain SM, Whaley FS, Gerber MC, et al. Delayed administration of dexrazoxane provides cardioprotection for patients with advanced breast cancer treated with doxorubicin-containing therapy. J Clin Oncol 1997;15:1333–1340.

190. Swain SM, Whaley FS, Gerber MC, et al. Cardioprotection with dexrazoxane for doxorubicin-containing therapy in advanced breast cancer. J Clin Oncol 1997;15:1318–1332.

191. Marty M, Espie M, Llombart A, et al. Multicenter randomized phase III study of the cardioprotective effect of dexrazoxane (Cardioxane) in advanced/metastatic breast cancer patients treated with anthracycline-based chemotherapy. Ann Oncol 2006;17:614–622.

192. Launay-Vacher V, Chatelut E, Lichtman SM, et al. Renal insufficiency in elderly cancer patients: International Society of Geriatric Oncology clinical practice recommendations. Ann Oncol 2007;18:1314–1321.

193. Sul JK, Deangelis LM. Neurologic complications of cancer chemotherapy. Semin Oncol 2006;33:324–332.

194. Cheson BD, Vena DA, Foss FM, Sorensen JM. Neurotoxicity of purine analogs: a review. J Clin Oncol 1994;12:2216–2228.

195. Smith GA, Damon LE, Rugo HS, et al. High-dose cytarabine dose modification reduces the incidence of neurotoxicity in patients with renal insufficiency. J Clin Oncol 1997;15:833–839.

196. Rubin EH, Andersen JW, Berg DT, et al. Risk factors for high-dose cytarabine neurotoxicity: an analysis of a cancer and leukemia group B trial in patients with acute myeloid leukemia. J Clin Oncol 1992;10:948–953.

197. Balducci L, Repetto L. Increased risk of myelotoxicity in elderly patients with non-Hodgkin lymphoma. Cancer 2004;100:6–11.

198. Begg CB, Carbone PP. Clinical trials and drug toxicity in the elderly. The experience of the Eastern Cooperative Oncology Group. Cancer 1983;52:1986–1992.

199. Crivellari D. Results of adjuvant treatments in breast cancer patients over 70 years old: the IBCSG experience. International Breast Cancer Study Group. Tumori 2002;88(1 Suppl 1):S81–82.

200. Langer CJ, Manola J, Bernardo P, et al. Cisplatin-based therapy for elderly patients with advanced non-small-cell lung cancer: implications of Eastern Cooperative Oncology Group 5592, a randomized trial. J Natl Cancer Inst 2002;94:173–181.

201. Rocha Lima CM, Herndon JE II, Kosty M, et al. Therapy choices among older patients with lung carcinoma: an evaluation of two trials of the Cancer and Leukemia Group B. Cancer 2002;94:181–187.

202. Neubauer M, Schwartz J, Caracandas J, et al. Results of a phase II study of weekly paclitaxel plus carboplatin in patients with extensive small-cell lung cancer with Eastern Cooperative Oncology Group performance status of 2, or age > or = 70 years. J Clin Oncol 2004;22:1872–1877.

203. Doorduijn JK, van der Holt B, van Imhoff GW, et al. CHOP compared with CHOP plus granulocyte colony-stimulating factor in elderly patients with aggressive non-Hodgkin's lymphoma. J Clin Oncol 2003;21:3041–3050.

204. Osby E, Hagberg H, Kvaloy S, et al. CHOP is superior to CNOP in elderly patients with aggressive lymphoma while outcome is unaffected by filgrastim treatment: results of a Nordic Lymphoma Group randomized trial. Blood 2003;101:3840–3848.

205. Zinzani PL, Pavone E, Storti S, et al. Randomized trial with or without granulocyte colony-stimulating factor as adjunct to induction VNCOP-B treatment of elderly high-grade non-Hodgkin's lymphoma. Blood 1997;89:3974–3979.

206. Armitage JO, Potter JF. Aggressive chemotherapy for diffuse histiocytic lymphoma in the elderly: increased complications with advancing age. J Am Geriatr Soc 1984;32:269–273.

207. Bastion Y, Blay JY, Divine M, et al. Elderly patients with aggressive non-Hodgkin's lymphoma: disease presentation, response to treatment, and survival—a Groupe d'Etude des Lymphomes de l'Adulte study on 453 patients older than 69 years. J Clin Oncol 1997;15:2945–2953.

208. Bertini M, Freilone R, Vitolo U, et al. The treatment of elderly patients with aggressive non-Hodgkin's lymphomas: feasibility and efficacy of an intensive multidrug regimen. Leuk Lymphoma 1996;22:483–493.

209. Gomez H, Mas L, Casanova L, et al. Elderly patients with aggressive non-Hodgkin's lymphoma treated with CHOP chemotherapy plus granulocyte-macrophage colony-stimulating factor: identification of two age subgroups with differing hematologic toxicity. J Clin Oncol 1998;16:2352–2358.

210. O'Reilly SE, Connors JM, Howdle S, et al. In search of an optimal regimen for elderly patients with advanced-stage diffuse large-cell lymphoma: results of a phase II study of P/DOCE chemotherapy. J Clin Oncol 1993;11:2250–2257.

211. Sonneveld P, de Ridder M, van der Lelie H, et al. Comparison of doxorubicin and mitoxantrone in the treatment of elderly patients with advanced diffuse non-Hodgkin's lymphoma using CHOP versus CNOP chemotherapy. J Clin Oncol 1995;13:2530–2539.

212. Amadori S, Suciu S, Jehn U, et al. Use of glycosylated recombinant human G-CSF (lenograstim) during and/or after induction chemotherapy in patients 61 years of age and older with acute myeloid leukemia: final results of AML-13, a randomized phase-3 study. Blood 2005;106:27–34.

213. Lowenberg B, van Putten W, Theobald M, et al. Effect of priming with granulocyte colony-stimulating factor on the outcome of chemotherapy for acute myeloid leukemia. N Engl J Med 2003;349:743–752.

214. Lyman GH, Kuderer NM, Djulbegovic B. Prophylactic granulocyte colony-stimulating factor in patients receiving dose-intensive cancer chemotherapy: a meta-analysis. Am J Med 2002;112:406–411.

215. Relling MV, Boyett JM, Blanco JG, et al. Granulocyte colony-stimulating factor and the risk of secondary myeloid malignancy after etoposide treatment. Blood 2003;101:3862–3867.

216. Patt DA, Duan Z, Fang S, et al. Acute myeloid leukemia after adjuvant breast cancer therapy in older women: understanding risk. J Clin Oncol 2007;25:3871–3876.

217. Lyman GH, Kuderer N, Agboola O, Balducci L. Evidence-based use of colony-stimulating factors in elderly cancer patients. Cancer Control 2003;10:487–499.

218. Repetto L, Biganzoli L, Koehne CH, et al. EORTC cancer in the Elderly Task Force guidelines for the use of colony-stimulating factors in elderly patients with cancer. Eur J Cancer 2003;39:2264–2272.

219. Pierelli L, Perillo A, Greggi S, et al. Erythropoietin addition to granulocyte colony-stimulating factor abrogates life-threatening neutropenia and increases peripheral-blood progenitor-cell mobilization after epirubicin, paclitaxel, and cisplatin combination chemotherapy: results of a randomized comparison. J Clin Oncol 1999;17:1288–1296.

220. Metivier F, Marchais SJ, Guerin AP, et al. Pathophysiology of anaemia: focus on the heart and blood vessels. Nephrol Dial Transplant 2000;15(Suppl 3):14–18.

221. Pickett JL, Theberge DC, Brown WS, et al. Normalizing hematocrit in dialysis patients improves brain function. Am J Kidney Dis 1999;33:1122–1130.

222. Silverberg DS, Wexler D, Blum M, et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. J Am Coll Cardiol 2000;35:1737–1744.

223. Wu WC, Rathore SS, Wang Y, et al. Blood transfusion in elderly patients with acute myocardial infarction. N Engl J Med 2001;345:1230–1236.

224. Bohlius J, Wilson J, Seidenfeld J, et al. Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9353 patients. J Natl Cancer Inst 2006;98:708–714.

225. Juneja V, Keegan P, Gootenberg JE, et al. Continuing reassessment of the risks of erythropoiesis-stimulating agents in patients with cancer. Clin Cancer Res 2008;14:3242–3247.

226. Bennett CL, Silver SM, Djulbegovic B, et al. Venous

thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. JAMA 2008;299:914–924.

227. Tepler I, Elias L, Smith JW, et al. A randomized placebo-controlled trial of recombinant human interleukin-11 in cancer patients with severe thrombocytopenia due to chemotherapy. Blood 1996;87:3607–3614.

228. Vadhan-Raj S. Management of chemotherapy-induced thrombocytopenia: current status of thrombopoietic agents. Semin Hematol 2009;46:S26–32.

229. Benson AB, Ajani JA, Catalano RB, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Oncol 2004;22:2918–2926.

230. Rubenstein EB, Peterson DE, Schubert M, et al. Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. Cancer 2004;100:2026–2046.

231. Bensinger W, Schubert M, Ang KK, et al. NCCN Task Force Report: prevention and management of mucositis in cancer care. J Natl Compr Canc Netw 2008;6(Suppl 1):1–21.

232. Spielberger R, Stiff P, Bensinger W, et al. Palifermin for oral mucositis after intensive therapy for hematologic cancers. N Engl J Med 2004;351:2590–2598.

233. Rosen LS, Abdi E, Davis ID, et al. Palifermin reduces the incidence of oral mucositis in patients with metastatic colorectal cancer treated with fluorouracil-based chemotherapy. J Clin Oncol 2006;24:5194–5200.

234. Peterson DE, Jones JB, Petit RG. Randomized, placebo-controlled trial of Saforis for prevention and treatment of oral mucositis in breast cancer patients receiving anthracycline-based chemotherapy. Cancer 2007;109:322–331.

235. Gonsalves W, Ganti AK. Targeted anti-cancer therapy in the elderly. Crit Rev Oncol Hematol 2011;78:227–242.

236. Sekeres MA. Treatment of older adults with acute myeloid leukemia: state of the art and current perspectives. Haematologica 2008;93:1769–1772.

237. 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.

238. Herr HW. Age and outcome of superficial bladder cancer treated with bacille Calmette-Guerin therapy. Urology 2007;70:65–68.

239. Chamie K, Hu B, Devere White RW, Ellison LM. Cystectomy in the elderly: does the survival benefit in younger patients translate to the octogenarians? BJU Int 2008;102:284–290.

240. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 2003;349:859–866.

241. Diab SG, Elledge RM, Clark GM. Tumor characteristics and clinical outcome of elderly women with breast cancer. J Natl Cancer Inst 2000;92:550–556.

242. Eppenberger-Castori S, Moore DH Jr, Thor AD, et al. Age-associated biomarker profiles of human breast cancer. Int J Biochem Cell Biol 2002;34:1318–1330.

243. Bouchardy C, Rapiti E, Fioretta G, et al. Undertreatment strongly decreases prognosis of breast cancer in elderly women. J Clin Oncol 2003;21:3580–3587.

244. Yood MU, Owusu C, Buist DSM, et al. Mortality impact of less-than-standard therapy in older breast cancer patients. J Am Coll Surg 2008;206:66–75.

245. Schonberg MA, Marcantonio ER, Li D, et al. Breast cancer among the oldest old: tumor characteristics, treatment choices, and survival. J Clin Oncol 2010;28:2038–2045.

246. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 2011;305:569–575.

247. Rudenstam CM, Zahrieh D, Forbes JF, et al. Randomized trial comparing axillary clearance versus no axillary clearance in older patients with breast cancer: first results of International Breast Cancer Study Group Trial 10-93. J Clin Oncol 2006;24:337–344.

248. Martelli G, Miceli R, Daidone MG, et al. Axillary dissection versus no axillary dissection in elderly patients with breast cancer and no palpable axillary nodes: results after 15 years of follow-up. Ann Surg Oncol 2011;18:125–133.

249. Hughes KS, Schnaper LA, Berry D, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. N Engl J Med 2004;351:971–977.

250. Hughes KS, Schnaper LA, Cirrincione C, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 or older with early breast cancer [abstract]. J Clin Oncol 2010;28(Suppl 15):Abstract 507.

251. Muss HB, Woolf S, Berry D, et al. Adjuvant chemotherapy in older and younger women with lymph node-positive breast cancer. JAMA 2005;293:1073–1081.

252. Muss HB, Berry DA, Cirrincione CT, et al. Adjuvant chemotherapy in older women with early-stage breast cancer. N Engl J Med 2009;360:2055–2065.

253. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005;353:1659–1672.

254. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005;353:1673–1684.

255. Vuorinen V, Hinkka S, Farkkila M, Jaaskelainen J. Debulking or biopsy of malignant glioma in elderly people. A randomized study. Acta Neurochir 2003;145:5–10.

256. Martinez R, Janka M, Soldner F, Behr R. Gross total resection of malignant glioma in elderly patients: implications in survival. Zentrabl Neurchir 2007;68:176–181.

257. Scott J, Suh J, Elson P, et al. Aggressive treatment is appropriate for glioblastoma multiforme patients 70 years old or older: a retrospective review of 206 cases. Neuro Oncol 2011;13:428–436.

258. Roa W, Brasher PM, Bauman G, et al. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized trial. J Clin Oncol 2004;22:1583–1588.

259. Keime-Guibert F, Chinot O, Taillandier L, et al. Radiotherapy for glioblastoma in the elderly. N Engl J Med 2007;356:1527–1535.

260. Stupp R, Hegi M, Mason W, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomized phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol 2009;10:459–466.

261. Lanzetta G, Minniti G. Treatment of glioblastoma in elderly patients: an overview of current treatments and future perspective. Tumori 2010;96:650–658.

262. Nghiemphu PL, Liu W, Lee Y, et al. Bevacizumab and chemotherapy for recurrent glioblastoma: a single-institution experience. Neurology 2009;72:1217–1222.

263. Gavrilovic I, Hormigo A, Yahalom J, et al. Long term follow-up

of high-dose methotrexate-based therapy with and without whole brain irradiation for newly diagnosed primary CNS lymphoma. J Clin Oncol 2006;24:4570–4574.

264. Ney DE, Reiner AS, Panageas KS, et al. Characteristics and outcomes of elderly patients with primary central nervous system lymphoma: the Memorial Sloan-Kettering Cancer Center experience. Cancer 2010;116:4605–4612.

265. Zhu JJ, Gerstner ER, Engler DA, et al. High-dose methotrexate for elderly patients with primary CNS lymphoma. Neuro Oncol 2009;11:211–215.

266. Schiffmann L, Ozcan S, Schwarz F, et al. Colorectal cancer in the elderly: surgical treatment and long-term survival. Int J Colorectal Dis 2008;23:601–610.

267. Devon KM, Vergara-Fernandez O, Victor JC, McLeod RS. Colorectal cancer surgery in elderly patients: presentation, treatment, and outcomes. Dis Colon Rectum 2009;52:1272–1277.

268. Ong ES, Alassas M, Dunn KB, Rajput A. Colorectal cancer surgery in the elderly: acceptable morbidity? Am J Surg 2008;195:344–348.

269. Adam R, Frilling A, Elias D, et al. Liver resection of colorectal metastases in elderly patients. Br J Surg 2010;97:366–376.

270. Schrag D, Cramer LD, Bach PB, Begg CB. Age and adjuvant chemotherapy use after surgery for stage III colon cancer. J Natl Cancer Inst 2001;93:850–857.

271. Jackson McCleary NA, Meyerhardt J, Green E, et al. Impact of older age on the efficacy of newer adjuvant therapies in >12,500 patients (pts) with stage II/III colon cancer: findings from the ACCENT Database. J Clin Oncol 2009;27:4010.

272. Folprecht G, Cunningham D, Ross P, et al. Efficacy of 5-fluorouracil-based chemotherapy in elderly patients with metastatic colorectal cancer: a pooled analysis of clinical trials. Ann Oncol 2004;15:1330–1338.

273. Seymour MT, Thompson LC, Wasan HS, et al. Chemotherapy options in elderly and frail patients with metastatic colorectal cancer (MRC FOCUS2): an open-label, randomised factorial trial. Lancet 2011;377:1749–1759.

274. Figer A, Perez-Staub N, Carola E, et al. FOLFOX in patients aged between 76 and 80 years with metastatic colorectal cancer: an exploratory cohort of the OPTIMOX1 study. Cancer 2007;110:2666–2671.

275. Cassidy J, Saltz LB, Giantonio BJ, et al. Effect of bevacizumab in older patients with metastatic colorectal cancer: pooled analysis of four randomized studies. J Cancer Res Clin Oncol 2010;136:737–743.

276. Kozloff MF, Berlin J, Flynn PJ, et al. Clinical outcomes in elderly patients with metastatic colorectal cancer receiving bevacizumab and chemotherapy: results from the BRiTE observational cohort study. Oncology 2010;78:329–339.

277. Bouchahda M, Macarulla T, Spano JP, et al. Cetuximab efficacy and safety in a retrospective cohort of elderly patients with heavily pretreated metastatic colorectal cancer. Crit Rev Oncol Hematol 2008;67:255–262.

278. Fornaro L, Baldi GG, Masi G, et al. Cetuximab plus irinotecan after irinotecan failure in elderly metastatic colorectal cancer patients: clinical outcome according to KRAS and BRAF mutational status. Crit Rev Oncol Hematol 2011;78:243–251.

279. Sastre J, Aranda E, Gravalos C, et al. First-line single-agent cetuximab in elderly patients with metastatic colorectal cancer. A phase II clinical and molecular study of the Spanish group for digestive tumor therapy (TTD). Crit Rev Oncol Hematol 2011;77:78–84.

280. Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 2007;25:1658–1664.

281. Amado RG, Wolf M, Peeters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 2008;26:1626–1634.

282. Zabrodsky M, Calabrese L, Tosoni A, et al. Major surgery in elderly head and neck cancer patients: immediate and long-term surgical results and complication rates. Surg Oncol 2004;13:249–255.

283. Pignon T, Horiot JC, Van den Bogaert W, et al. No age limit for radical radiotherapy in head and neck tumours. Eur J Cancer 1996;32A:2075–2081.

284. Posner MR, Hershock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 2007;357:1705–1715.

285. Vermorken JB, Remenar E, van Herpen C, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med 2007;357:1695–1704.

286. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 2003;349:2091–2098.

287. Pignon JP, le Maitre A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92:4–14.

288. Machtay M, Moughan J, Trotti A, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. J Clin Oncol 2008;26:3582–3589.

289. Argiris A, Li Y, Murphy BA, et al. Outcome of elderly patients with recurrent or metastatic head and neck cancer treated with cisplatin-based chemotherapy. J Clin Oncol 2004;22:262–268.

290. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol 2010;11:21–28.

291. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116–1127.

292. Lane BR, Abouassaly R, Gao T, et al. Active treatment of localized renal tumors may not impact overall survival in patients aged 75 years or older. Cancer 2010;116:3119–3126.

293. Bajetta E, Ravaud A, Bracarda S, et al. Efficacy and safety of first-line bevacizumab (BEV) plus interferon-{alpha}2a (IFN) in patients (pts) >=65 years with metastatic renal cell carcinoma (mRCC) [abstract]. J Clin Oncol 2008;26(Suppl 15):Abstract 5095.

294. Eisen T, Oudard S, Szczylik C, et al. Sorafenib for older patients with renal cell carcinoma: subset analysis from a randomized trial. J Natl Cancer Inst 2008;100:1454–1463.

295. Bukowski RM, Stadler WM, McDermott DF, et al. Safety and efficacy of sorafenib in elderly patients treated in the North American advanced renal cell carcinoma sorafenib expanded access program. Oncology 2010;78:340–347.

296. Gore ME, Szczylik C, Porta C, et al. Safety and efficacy of sunitinib for metastatic renal-cell carcinoma: an expanded-access trial. Lancet Oncol 2009;10:757–763.

297. Hutson TE, Bukowski RM, Rini BI, et al. A pooled analysis of

the efficacy and safety of sunitinib in elderly patients (pts) with metastatic renal cell carcinoma (mRCC) [abstract]. J Clin Oncol 2011;29(Supp1):Abstract 4604.

298. Osanto S, Hutson TE, Calvo E, et al. Efficacy and safety of everolimus in elderly patients (pts) with metastatic renal cell carcinoma (mRCC) [abstract]. J Clin Oncol 2010;28(Suppl 15):Abstract 4608.

299. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007;356:2271–2281.

300. Palumbo A, Bringhen S, Caravita T, et al. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. Lancet 2006;367:825–831.

301. Palumbo A, Bringhen S, Liberati AM, et al. Oral melphalan, prednisone, and thalidomide in elderly patients with multiple myeloma: updated results of a randomized controlled trial. Blood 2008;112:3107–3114.

302. Facon T, Mary JY, Hulin C, et al. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. Lancet 2007;370:1209–1218.

303. Hulin C, Facon T, Rodon P, et al. Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial. J Clin Oncol 2009;27:3664–3670.

304. Waage A, Gimsing P, Fayers P, et al. Melphalan and prednisone plus thalidomide or placebo in elderly patients with multiple myeloma. Blood 2010;116:1405–1412.

305. Wijermans P, Schaafsma M, Termorshuizen F, et al. Phase III study of the value of thalidomide added to melphalan plus prednisone in elderly patients with newly diagnosed multiple myeloma: the HOVON 49 Study. J Clin Oncol 2010;28:3160–3166.

306. Beksac M, Haznedar R, Firatli-Tuglular T, et al. Addition of thalidomide to oral melphalan/prednisone in patients with multiple myeloma not eligible for transplantation: results of a randomized trial from the Turkish Myeloma Study Group. Eur J Haematol 2011;86:16–22.

307. Kapoor P, Rajkumar SV, Dispenzieri A, et al. Melphalan and prednisone versus melphalan, prednisone and thalidomide for elderly and/or transplant-ineligible patients with multiple myeloma: a meta-analysis. Leukemia 2011;25:1523–1524.

308. Palumbo A, Cavo M, Bringhen S, et al. Aspirin, warfarin, or enoxaparin thromboprophylaxis in patients with multiple myeloma treated with thalidomide: a phase III, open-label, randomized trial. J Clin Oncol 2011;29:986–993.

309. San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med 2008;359:906–917.

310. Mateos MV, Richardson PG, Schlag R, et al. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. J Clin Oncol 2010;28:2259–2266.

311. Mateos MV, Oriol A, Martinez-Lopez J, et al. Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial. Lancet Oncol 2010;11:934–941.

312. Palumbo A, Bringhen S, Rossi D, et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial. J Clin Oncol 2010;28:5101–5109.

313. Facon T, Mary JY, Pegourie B, et al. Dexamethasone-based regimens versus melphalan-prednisone for elderly multiple myeloma patients ineligible for high-dose therapy. Blood 2006;107:1292–1298.

314. Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol 2010;11:29–37.

315. Effect of age on the characteristics and clinical behavior of non-Hodgkin's lymphoma patients. The Non-Hodgkin's Lymphoma Classification Project. Ann Oncol 1997;8:973–978.

316. Seymour JF, Talpaz M, Cabanillas F, et al. Serum interleukin-6 levels correlate with prognosis in diffuse large-cell lymphoma. J Clin Oncol 1995;13:575–582.

317. Pedersen LM, Klausen TW, Davidsen UH, Johnsen HE. Early changes in serum IL-6 and VEGF levels predict clinical outcome following first-line therapy in aggressive non-Hodgkin's lymphoma. Ann Hematol 2005;84:510–516.

318. Wei J, Xu H, Davies JL, Hemmings GP. Increase of plasma IL-6 concentration with age in healthy subjects. Life Sci 1992;51:1953–1956.

319. Hager K, Machein U, Krieger S, et al. Interleukin-6 and selected plasma proteins in healthy persons of different ages. Neurobiol Aging 1994;15:771–772.

320. Ferrucci L, Corsi A, Lauretani F, et al. The origins of age-related proinflammatory state. Blood 2005;105:2294–2299.

321. Pfreundschuh M, Trumper L, Kloess M, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL. Blood 2004;104:634–641.

322. Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J Clin Oncol 2006;24:3121–3127.

323. Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood 2010;116:2040–2045.

324. Lau GK. Hepatitis B reactivation after chemotherapy: two decades of clinical research. Hepatol Int 2008;2:152–162.

325. Loomba R, Rowley A, Wesley R, et al. Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. Ann Intern Med 2008;148:519–528.

326. Tsutsumi Y, Kawamura T, Saitoh S, et al. Hepatitis B virus reactivation in a case of non-Hodgkin's lymphoma treated with chemotherapy and rituximab: necessity of prophylaxis for hepatitis B virus reactivation in rituximab therapy. Leuk Lymphoma 2004;45:627–629.

327. Tsutsumi Y, Tanaka J, Kawamura T, et al. Possible efficacy of lamivudine treatment to prevent hepatitis B virus reactivation due to rituximab therapy in a patient with non-Hodgkin's lymphoma. Ann Hematol 2004;83:58–60.

328. Ishida T, Yokoyama H, Kaneko S, et al. Long-term results of operation for non-small cell lung cancer in the elderly. Ann

Thorac Surg 1990;50:919–922.

329. Naunheim KS, Kesler KA, D'Orazio SA, et al. Lung cancer surgery in the octogenarian. Eur J Cardiothorac Surg 1994;8:453–456.

330. Cangemi V, Volpino P, D'Andrea N, et al. Lung cancer surgery in elderly patients. Tumori 1996;82:237–241.

331. Jack CI, Lye M, Lesley F, et al. Surgery for lung cancer: age alone is not a contraindication. Int J Clin Pract 1997;51:423–426.

332. Morandi U, Stefani A, Golinelli M, et al. Results of surgical resection in patients over the age of 70 years with non small-cell lung cancer. Eur J Cardiothorac Surg 1997;11:432–439.

333. Mizushima Y, Noto H, Sugiyama S, et al. Survival and prognosis after pneumonectomy for lung cancer in the elderly. Ann Thorac Surg 1997;64:193–198.

334. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group. BMJ 1995;311:899–909.

335. Pepe C, Hasan B, Winton TL, et al. Adjuvant vinorelbine and cisplatin in elderly patients: National Cancer Institute of Canada and Intergroup Study JBR.10. J Clin Oncol 2007;25:1553–1561.

336. Fruh M, Rolland E, Pignon JP, et al. Pooled analysis of the effect of age on adjuvant cisplatin-based chemotherapy for completely resected non-small-cell lung cancer. J Clin Oncol 2008;26:3573–3581.

337. Langer CJ, Hsu C, Curran WJ, et al. Elderly patients (pts) with locally advanced non-small cell lung cancer (LA-NSCLC) benefit from combined modality therapy: secondary analysis of Radiation Therapy Oncology Group (RTOG) 94-10 [abstract]. J Clin Oncol 2002;21(Supp1):Abstract 1193.

338. Schild SE, Stella PJ, Geyer SM, et al. The outcome of combined-modality therapy for stage III non-small-cell lung cancer in the elderly. J Clin Oncol 2003;21:3201–3206.

339. Movsas B, Scott C, Sause W, et al. The benefit of treatment intensification is age and histology-dependent in patients with locally advanced non-small cell lung cancer (NSCLC): a quality-adjusted survival analysis of radiation therapy oncology group (RTOG) chemoradiation studies. Int J Radiat Oncol Biol Phys 1999;45:1143–1149.

340. Werner-Wasik M, Scott C, Cox JD, et al. Recursive partitioning analysis of 1999 Radiation Therapy Oncology Group (RTOG) patients with locally-advanced non-small-cell lung cancer (LA-NSCLC): identification of five groups with different survival. Int J Radiat Oncol Biol Phys 2000;48:1475–1482.

341. Gridelli C. The ELVIS trial: a phase III study of single-agent vinorelbine as first-line treatment in elderly patients with advanced non-small cell lung cancer. Elderly Lung Cancer Vinorelbine Italian Study. Oncologist 2001;6(Suppl 1):4–7.

342. Kudoh S, Takeda K, Nakagawa K, et al. Phase III study of docetaxel compared with vinorelbine in elderly patients with advanced non-small-cell lung cancer: results of the West Japan Thoracic Oncology Group Trial (WJTOG 9904). J Clin Oncol 2006;24:3657–3663.

343. Kelly K, Giarritta S, Akerley W, et al. Should older patients (pts) receive combination chemotherapy for advanced stage non-small cell lung cancer (NSCLC)? An analysis of Southwest Oncology trials 9509 and 9308 [abstract]. J Clin Oncol 2001;20(Suppl):Abstract 1313.

344. Lilenbaum RC, Herndon JE, List MA, et al. Single-agent versus combination chemotherapy in advanced non-small-cell lung cancer: the cancer and leukemia group B (study 9730). J Clin Oncol 2005;23:190–196.

345. Frasci G, Lorusso V, Panza N, et al. Gemcitabine plus vinorelbine yields better survival outcome than vinorelbine alone in elderly patients with advanced non-small cell lung cancer. A Southern Italy Cooperative Oncology Group (SICOG) phase III trial. Lung Cancer 2001;34(Suppl 4):65–69.

346. Gridelli C, Perrone F, Gallo C, et al. Chemotherapy for elderly patients with advanced non-small-cell lung cancer: the Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. J Natl Cancer Inst 2003;95:362–372.

347. Quoix E, Zalcman G, Oster JP, et al. Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. Lancet 2011;378:1079–1088.

348. Ramalingam SS, Dahlberg SE, Langer CJ, et al. Outcomes for elderly, advanced-stage non small-cell lung cancer patients treated with bevacizumab in combination with carboplatin and paclitaxel: analysis of Eastern Cooperative Oncology Group Trial 4599. J Clin Oncol 2008;26:60–65.

349. Jackman DM, Yeap BY, Lindeman NI, et al. Phase II clinical trial of chemotherapy-naive patients > or = 70 years of age treated with erlotinib for advanced non-small-cell lung cancer. J Clin Oncol 2007;25:760–766.

350. Wheatley-Price P, Ding K, Seymour L, et al. Erlotinib for advanced non-small-cell lung cancer in the elderly: an analysis of the National Cancer Institute of Canada Clinical Trials Group Study BR.21. J Clin Oncol 2008;26:2350–2357.

351. Droz JP, Balducci L, Bolla M, et al. Management of prostate cancer in older men: recommendations of a working group of the International Society of Geriatric Oncology. BJU Int 2010;106:462–469.

352. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502–1512.

353. Sinibaldi VJ. Docetaxel treatment in the elderly patient with hormone refractory prostate cancer. Clin Interv Aging 2007;2:555–560.

354. Berthold DR, Pond GR, Soban F, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. J Clin Oncol 2008;26:242–245.

355. Pal SK, Twardowski P, Sartor O. Critical appraisal of cabazitaxel in the management of advanced prostate cancer. Clin Interv Aging 2010;5:395–402.

356. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010;376:1147–1154.

Individual Disclosures for the NCCN Guidelines Panel for Senior Adult Oncology

Panel Member	Clinical Research Support	Advisory Boards, Speakers Bureau, Expert Witness, or Consultant	Patent, Equity, or Royalty	Other	Date Completed
Ilene S. Browner, MD	None	None	None	None	7/22/11
Harvey Jay Cohen, MD	None	None	None	None	7/6/11
Crystal S. Denlinger, MD	AstraZeneca Pharmaceuticals LP; Genentech, Inc.; Chugai Pharmaceutical Co. Ltd.; Merrimack Pharmaceuticals Inc.; Roche Laboratories, Inc.	Vicus Therapeutics	None	None	4/1/11
Mollie deShazo, MD	None	None	None	None	7/21/11
Efrat Dotan, MD	Biocompoatibles UK Ltd.	None	None	None	11/2/11
Martine Extermann, MD, PhD	None	None	None	None	5/10/11
Apar Kishor P. Ganti, MD	Pfizer Inc.	None	None	None	4/25/11
Jimmie C. Holland, MD	None	None	None	None	10/5/11
Holly M. Holmes, MD	None	None	None	None	5/16/11
Arti Hurria, MD	Abraxis Oncology; Celgene Corporation; and GlaxoSmithKline plc	GTX	None	None	7/23/11
Mohana B. Karlekar, MD	None	None	None	None	6/22/11
Nancy L. Keating, MD, MPH	None	None	None	None	7/21/11
June M. McKoy, MD, JD, MBA	None	None	None	None	5/31/11
Bruno C. Medeiros, MD	Celgene Corporation; and Millennium Pharmaceuticals, Inc.	Celgene Corporation; Millennium Pharmaceuticals, Inc.; and Novartis AG	None	None	4/6/11
Ewa Mrozek, MD	None	None	None	None	6/23/11
Tracey O'Connor, MD	None	None	None	None	10/28/11
Stephen H. Petersdorf, MD	Genzyme Corporation	None	None	None	2/25/11
Hope S. Rugo, MD	None	None	None	None	7/5/11
Rebecca A. Silliman, MD, PhD, MPH	None	None	None	None	5/16/11
William P. Tew, MD	None	None	None	None	5/25/11
Louise C. Walter, MD	None	None	None	None	7/21/11
Alva B. Weir, III, MD	None	None	None	None	4/6/11
Tanya Wildes, MD	None	None	None	None	5/16/11

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