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NCCN Task Force Report: Breast Cancer in the Older Woman

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Target Audience

This educational activity is designed to meet the educational needs of medical, surgical and radiation oncologists and advanced practice nurses who treat and manage older patients with breast cancer.

Educational Objectives

After completion of this CE activity, participants should be able to:

- Identify data from clinical trials specifically addressing management of breast cancer in the older patient.
- Estimate life expectancy of age cohorts in the older population
- Identify specific toxicity issues in older patients
- Recommend management options for primary, adjuvant, and metastatic disease in older patients.

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NCCN Task Force Report: Breast Cancer in the Older Woman

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Key Words

NCCN Clinical Practice Guidelines, breast cancer, older woman, treatment, chemotherapy, geriatric assessment, physiologic reserve, functional reserve, comorbidity, life expectancy, breast cancer mortality, tumor biology

Abstract

Breast cancer is common in older women, and the segment of the U.S. population aged 65 years and older is growing rapidly. Consequently, awareness is increasing of the need to identify breast cancer treatment recommendations to assure optimal, individualized treatment of older women with breast cancer. However, the development of these recommendations is limited by the heterogeneous nature of this population with respect to functional status, social support, life expectancy, and the presence of comorbidities, and by the underrepresentation of older patients with breast cancer in randomized clinical trials. The NCCN Breast Cancer in the Older Woman Task Force was convened to provide a forum for framing relevant questions on topics that impact older women with early-stage, locally advanced, and metastatic breast cancer. The task force is a multidisciplinary panel of 18 experts in breast cancer representing medical oncology, radiation oncology, surgical oncology, geriatric oncology, geriatrics, plastic surgery, and patient advocacy. All task force members were from NCCN institutions and were identified and invited solely by NCCN. Members were charged with identifying evidence relevant to their specific expertise. During a 2-day meeting, individual members provided didactic presentations; these presentations were followed by extensive discussions during which areas of consensus and controversy were identified on topics such as defining the "older" breast cancer patient; geriatric assessment tools in the oncology setting; attitudes of older patients with breast cancer and their physicians; tumor biology in older versus younger women with breast cancer; implementation of specific interventions in older patients with breast cancer, such as curative surgery, surgical axillary staging, radiation therapy, reconstructive surgery, endocrine therapy, chemotherapy, HER2-directed therapy, and supportive therapies; and areas requiring future studies. (*JNCCN* 2008;6[Suppl 4]:S1–S25)

Overview and Rationale

Although breast cancer is common in older women, guidance on optimal treatment is limited by their low

enrollment in randomized clinical trials. The Surveillance Epidemiology and End Results (SEER) database shows that the median patient age for breast cancer diagnoses in the United States is 61 years.¹ According to age-specific breast cancer incidence rates from SEER, approximately 42% of cases in the United States occur in women aged 65 years or older, with women aged 75 years or older representing more than 20% of these cases. The number of women aged 65 years or older in the United States is rapidly growing. The U.S. Census Bureau projects that between 2000 and 2030, the number of individuals aged 65 years or older will approximately double, from 35 to 71 million, with older women substantially outnumbering older men (approximately 70 men for every 100 women in the year 2000).^{2,3}

Awareness of the need to identify breast cancer treatment recommendations to assure optimal, individualized treatment of older women with breast cancer is increasing. However, several obstacles to accomplishing this task exist. Functional status, social support, the presence of comorbidities, and life expectancy must be considered to maximize benefit and minimize risk for these patients. In addition, because few women older than 65 years are included in randomized clinical trials, reliable estimates of treatment efficacy and toxicity in this population are often lacking.

Excellent reviews of breast cancer in older women have been published recently.⁴⁻⁶ This report provides a forum for framing relevant questions on topics that impact older women with early-stage, locally advanced, and metastatic breast cancer. Areas of consensus and controversy are highlighted along with the relevant evidence. Important criteria needed to perform a geriatric assessment are included, along with discussions on the relevance of functional decline in particular organ systems and their impact on decisions relating to the use of specific therapies. Patient vignettes further highlight issues involved when evaluating and recommending treatment for individual patients.

Task force members are from NCCN member institutions, and include some members of the NCCN Breast Cancer Clinical Practice Guidelines in Oncology Panel⁷ (to view the most recent version of these guideline, visit the NCCN Web site at www.nccn.org) along with others with a special expertise in treating breast cancer in the older woman. A total of 18 task force members represented medical oncology, radiation oncology, surgical oncology, geriatric oncology, geriatrics, plastic surgery, and patient advocacy. All task force members were identified and invited solely by NCCN.

A formal agenda was developed by the task force chair, and individual members were assigned topics for focused didactic presentations based on high-level scientific evidence whenever possible. Substantial time was allowed for discussion after each scientific presentation. Draft versions of this report were circulated among all task force members for review and comment.

The NCCN Clinical Practice Guidelines in Oncology: Senior Adult Oncology (to view the most recent version, visit www.nccn.org) provided a means of “operationalizing” aspects of the assessment and treatment of older patients with cancer.^{8,9} Those guidelines served as a foundation for the task force to address some issues specific to the management of older patients with breast cancer. Table 1 provides major topics of discussion at the meeting and summarizes areas of controversy and consensus identified by participants. A common theme was the paucity of high-level evidence. Most data related to treatment of older women with breast cancer are retrospective, and virtually no data address some of these issues. The older women enrolled in available clinical trials tend to be highly selected, with few or no comorbidities, and thus may not represent the older population in general.

Defining “Older” Patients With Breast Cancer

Central issues confronting the task force were the needs 1) to identify treatment recommendations in the NCCN Clinical Practice Guidelines in Oncology: Breast Cancer (to view the most recent version, visit www.nccn.org) that might not be suitable for “older” patients with breast cancer and 2) to determine whether a chronologic age or dividing line could be applied (e.g., ≥ 65 or ≥ 70 years) to help identify these

patients. Some members of the task force recommended that “70 years or older” be used to define “older” patients. One reason for this specific cutoff point was that little or no data exist to make evidence-based decisions for these patients because they are dramatically underrepresented in breast cancer clinical trials. Therefore, they are most in need of expert-driven consensus recommendations.

However, these issues are confounded by the heterogeneous nature of older patients. Beyond chronologic age, important factors to include in evaluating an older patient with breast cancer are physiologic/functional reserve, comorbidities, cognitive function, available social support systems, life expectancy, and risk for breast cancer mortality.

Physiologic Reserve

The term *physiologic reserve* describes the functional limits of a particular physiologic system when that system is exposed to a stressor; hence, a consequence of a decreased physiologic reserve is a decreased ability to adapt to stressors.¹⁰ Aging-associated changes in the heart, vasculature, lungs, kidneys, and other organ systems produce a progressive decrease in physiologic reserve independent of disease processes.¹¹ Some physiologic changes associated with aging include decreased hepatic and renal volume and associated blood flow; decreased glomerular filtration rate; decreased bone marrow reserves; and impairment of gastrointestinal mucosal protective mechanisms.

Because cancer and its treatment are physiologic stressors, the decline in physiologic reserve associated with aging can impact tolerance to breast cancer treatment. Table 2 lists toxicities shown to have increased frequency/severity with specific cancer therapies when administered to older patients with diminished physiologic reserve in certain organ systems. The extent to which the pharmacokinetics/pharmacodynamics of chemotherapy drugs differ in older compared with younger populations was debated among members of the panel.^{12,18}

Comorbidities

The older population bears a greater burden of comorbidity compared with younger individuals. A population-based analysis from the National Institute on Aging/National Institutes of Health showed that hypertension, heart-related conditions, arthritis, and gastrointestinal problems were present in 42.9%, 39.1%, 34.9%, and 31.0% of the population of cancer patients

Breast Cancer in the Older Woman

Table 1 NCCN Task Force on Breast Cancer in the Older Woman: Discussion Topics

Topic	Area(s) of Consensus	Area(s) of Controversy
Defining the "older" breast cancer patient	<ul style="list-style-type: none"> The population of older women with breast cancer is heterogeneous with respect to factors such as number of comorbidities and life expectancy Most randomized, controlled trials of breast cancer include few, if any, patients ≥ 70 years 	<ul style="list-style-type: none"> Can a specific age cutoff value define the patient with breast cancer as "older"?
Geriatric assessment tools	<ul style="list-style-type: none"> Assessments of breast cancer mortality and functional reserve, including patient-related factors such as functional status, comorbidities, cognition, and psychosocial issues, should be used to individualize treatment for an older patient 	<ul style="list-style-type: none"> Which tools provide a useful means of evaluating the older cancer patient? Can a 3-5 minute assessment provide enough discrimination for an accurate assessment of functional reserve or is a more detailed and time-consuming test necessary? Can breast cancer-specific mortality be reliably determined for an individual patient in light of comorbid conditions?
Attitudes of older patients with breast cancer and their physicians	<ul style="list-style-type: none"> The attitudes and preferences of older patients and the attitudes of physicians towards older patients with breast cancer are underexplored areas that may have a major impact on treatment decision-making 	<ul style="list-style-type: none"> What are the attitudes and biases of older patients and their physicians regarding breast cancer treatments?
Tumor biology in older vs. younger women with breast cancer	<ul style="list-style-type: none"> Treatment should be individualized for a patient Tumor-related factors such as histologic grade, hormone receptor status, and HER2 receptor status should be considered 	<ul style="list-style-type: none"> Are indolent tumors more common in older vs. younger women with breast cancer? Is the heterogeneity of breast cancer less pronounced in older women? If so, how would this information impact treatment decisions? To what extent does the biology and age of the "host" influence tumor growth?
Implementation of specific interventions in the older cancer patient: Curative surgery Surgical axillary staging Radiation therapy Reconstructive surgery Endocrine therapy Chemotherapy HER2-directed therapy Supportive therapies	<ul style="list-style-type: none"> The benefit of curative surgery and endocrine therapy in receptor positive breast cancer is well established in older patients 	<ul style="list-style-type: none"> For whom, when, and how should radiation therapy, chemotherapy, HER2-directed therapy, and supportive therapies be administered in older women with breast cancer? What are the roles of axillary staging and breast reconstruction? Which endocrine therapies are optimal in older women with osteoporosis, arthritic symptoms, and cardiovascular disease or risk factors?
Studies involving older patients with cancer	<ul style="list-style-type: none"> Critical need for clinical trials focusing on older women Importance of data from prospective clinical trials involving older women with breast cancer An impediment to successful randomized controlled trials in older patients is the heterogeneous nature of the population Most randomized, controlled trials of breast cancer include few, if any, patients aged ≥ 70 years 	<ul style="list-style-type: none"> Can available data from clinical trials in older women with breast cancer be extrapolated to the community or are patients enrolled in these trials highly selected populations? What other types of studies would be useful? Should clinical trials be specific for older adults or should the focus be on developing standard therapies that are efficacious and tolerable across all age groups?

Abbreviation: HER2, human epidermal growth factor receptor 2.

aged 55 years, respectively.¹⁹ In addition, the number of comorbid conditions increased with age; approximately 10% of patients aged 55 to 64 years, 17% of pa-

tients aged 65 to 74 years, and 27% of patients aged 75 years or older were found to have 6 or more comorbidities.

Table 2 Impact of Diminished Physiologic Reserve in Patients Treated With Specific Chemotherapeutic Agents	
Cancer Therapy	Toxicity
Paclitaxel, docetaxel ^{12,13}	Neutropenia
Fluorouracil ^{14,15}	Diarrhea/mucositis
Capecitabine ¹⁶	Diarrhea
Methotrexate ¹⁷	Hematologic toxicity

Although age-related changes in physiologic reserve occur independent of comorbid conditions, the presence of one or more comorbidities can accelerate the rate of decline in physiologic reserve^{11,20} and may influence the severity of chemotherapy-related toxicity. Preexisting comorbidities common in elderly patients that may impact treatment decisions related to use of specific cytotoxic or endocrine agents include cardiovascular disease (e.g., congestive heart failure) and use of anthracyclines or trastuzumab;²¹⁻²³ kidney dysfunction and capecitabine;¹⁶ preexisting neuropathy and taxanes;²⁴ history of thromboembolism and tamoxifen (venous thromboembolism) or bevacizumab (arterial thromboembolism);^{25,26} and osteoporosis and aromatase inhibitors.^{27,28}

Life Expectancy

Estimation of survival was identified by many task force participants as a key factor in making treatment decisions for older women with breast cancer. Data from the U.S. Centers for Disease Control and Prevention updated in 2007 indicate that, although the median life expectancy of a white woman in the United States is 80.4 years, a white woman of 65 or 75 years has a life expectancy of approximately 20.0 or 12.8 years, respectively²⁹ (Figure 1). These values are lower for a black woman in the United States. However, comorbid conditions can have considerable impact on survival in the population aged 65 years and older.

Figure 2 displays estimates of life expectancies of women in the United States at 65 to 85 years of age based on whether they are classified as “healthy,” “average,” or “sick.”³⁰ Interestingly, the presence of comorbidity is shown to have the greatest impact on survival in women 65 years of age and to have progressively less effect on life expectancy for women in older age groups. This suggests that older patients may develop adaptive mechanisms to partially compensate for certain long-standing comorbidities.

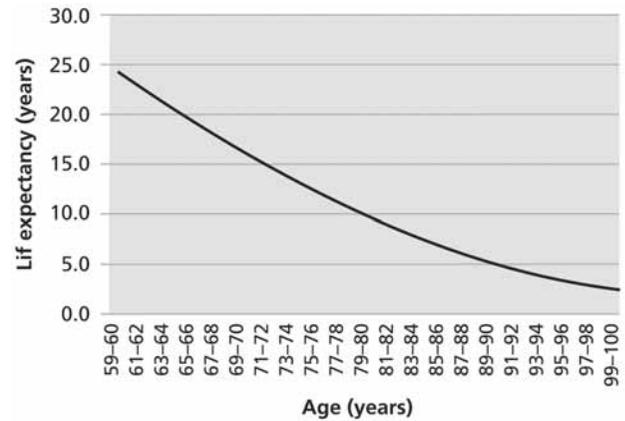


Figure 1 Life expectancy by age: U.S. white women. Data from Arias E. National Vital Statistics Report: United States Life Tables, 2003. Available at: http://www.cdc.gov/nchs/data/nvsr/nvsr54/nvsr54_14.pdf. Last accessed April 9, 2008.

Breast Cancer Mortality

Figure 3 shows age-specific breast cancer incidence rates in the United States from the SEER database for 1975 to 2003 for women aged 40 years and older.³¹ Breast cancer incidence is approximately twice as high in women aged 75 to 79 years compared with women aged 50 to 54 years. In addition, data from the U.S. National Center for Health Statistics for 2002 through 2004 show that the mortality burden from breast cancer increases with age; for example, the percentage of women in the United States aged 70 and 50 years who will die of breast cancer within 10 years is 0.9% and 0.4%, respectively.³²

Competing causes of mortality must be evaluated in women with breast cancer to assess how likely they are to die of breast cancer than another cause.³³

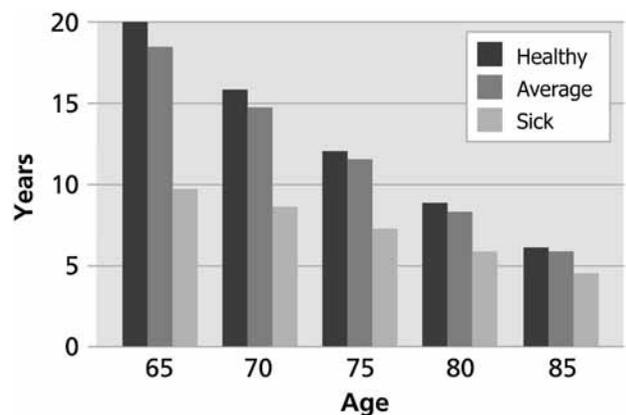


Figure 2 Life expectancy and comorbidity. Data from Extermann M, Balducci L, Lyman GH. What threshold for adjuvant therapy in older breast cancer patients? *J Clin Oncol* 2000;18:1709-1717.

Breast Cancer in the Older Woman

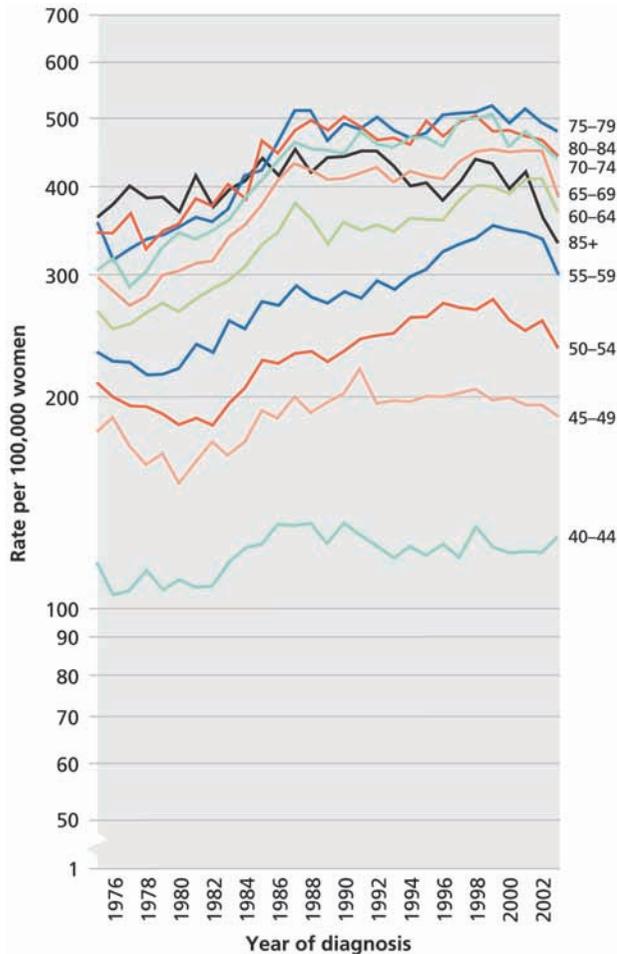


Figure 3 Trends in age-specific breast cancer incidence rates among women aged 40 years and older, 1975–2003. From Jemal A, Ward E, Thun MJ. Recent trends in breast cancer incidence rates by age and tumor characteristics among U.S. women. *Breast Cancer Res* 2007;9:R28; with permission.

Associations between age-specific breast cancer mortality rates and both patient age and breast cancer stage at diagnosis are particularly relevant to the development of clinical practice guidelines. An analysis of data from SEER for approximately 400,000 patients with breast cancer diagnosed between 1973 and 2000 found that the risk for death from the disease decreased relative to the risk for death from other causes as age at diagnosis increased. However, among patients aged 70 years or older, death from breast cancer still accounted for a significant percentage of mortality, especially in patients with high-risk disease (Figure 4).³⁴

A meta-analysis of data from randomized clinical trials of women with node-positive breast cancer (patients with higher-risk disease with few comorbid conditions) treated with adjuvant therapy showed that

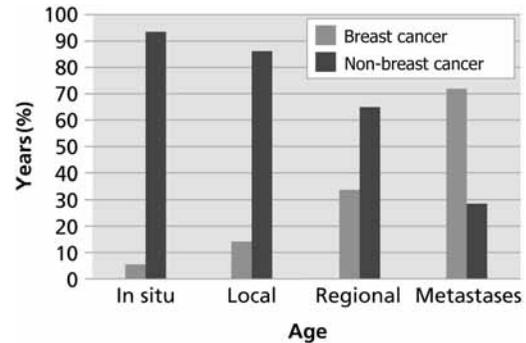


Figure 4 Cause of death for white women with breast cancer aged 70 years and older after 28-year follow-up. Data from Schairer C, Mink PJ, Carroll L, Devesa SS. Probabilities of death from breast cancer and other causes among female breast cancer patients. *J Natl Cancer Inst* 2004;96:1311–1321.

the breast cancer mortality rate in women aged 65 years and older (42%) was higher than in younger age groups (e.g., 32% in women aged ≤ 50 years and 36% in women aged 51–64 years). In this meta-analysis, the number of patients older than 65 years was limited, and the older patients had a higher disease burden than the younger patients.³⁵

Results from a large, randomized trial of women aged 70 years and older diagnosed with low-risk disease (small, hormone receptor-positive, node-negative breast cancer) support the conclusion that breast cancer mortality in this population is low. In this study, patients were treated with breast-conserving surgery and then randomly assigned to receive tamoxifen plus radiation therapy or tamoxifen alone. At a median follow-up of 8.2 years, 71% of patients were alive and only 2% had died of breast cancer (6% of total deaths were from breast cancer).^{36,37}

A population-based study of 3-year mortality rates of approximately 1000 women with breast cancer identified comorbidity as a strong predictor of survival independent of age, disease stage, tumor size, treatment, race, and social/behavioral factors. Women with 3 or more particular comorbid medical problems had a 20-fold increase in non-breast cancer–related death and a 4-fold increase in all-cause mortality compared with breast cancer patients with no comorbid conditions.³⁸

Finally, a SEER-based report of breast cancer mortality trends in the United States showed that the recent decline in breast cancer–related deaths observed for the overall population of women with breast cancer is not as significant for women aged 70 years or older compared with women younger than 70 years.³⁹

Social Support Systems

The prevalence of women who live alone is very high among women in the United States aged 75 years or older: 50% according to data from the 2000 U.S. Census Report.²

Geriatric Assessment Tools: Evaluating the Individual “Older” Patient

Although all older patients experience an age-associated decrease in physiologic reserve, marked differences in the rates of decline are observed among individuals. Therefore, the ability to tolerate treatment varies greatly; hence, the importance of estimating the functional reserve of the individual patient.¹⁰ Other issues also impact treatment decision-making in older patients with cancer, such as their life expectancy, whether they are likely to experience complications of cancer during their lifetime, and whether they are more likely to die with or of cancer.^{8,9,33}

Various geriatric assessment tools are available to provide a way to estimate the “functional reserve” of a patient, identify areas where interventions may be instituted, and predict survival.^{8,9,33,40,41} Geriatricians use the term *comprehensive geriatric assessment* (CGA) to describe a multidisciplinary evaluation of a range of independent predictors of morbidity and mortality

for older individuals, such as need for assistance with activities of daily living or instrumental activities of daily living, presence of comorbidities, nutritional status, level of cognition, psychosocial status, and whether polypharmacy is present.^{33,42}

Several short screening tests for qualitatively or quantitatively evaluating specific parameters in an older patient are also part of the CGA, including the “timed up and go” test to evaluate functional status and a short memory test to evaluate mental status (Table 3).^{8,9,33,43} Other assessment tools include the Vulnerable Elders Survey (VES-13)⁴¹ and a system developed by the Cardiovascular Health Study group to estimate frailty,^{8,9,44} although neither these nor the CGA and short screening tests were designed specifically as assessment tools for cancer patients. A short, cancer-specific, primarily self-administered geriatric assessment is currently being evaluated by the Cancer and Leukemia Group B (CALGB), and a multicenter clinical trial is underway to determine which domains in the assessment are most predictive of risk for toxicity from chemotherapy among older adults with cancer.^{45,46}

Accurate estimates of the risks of both breast cancer– and non-breast cancer–specific mortality for individual patients is an extremely important component of an overall geriatric assessment, but are difficult to determine. The Charlson Comorbidity Index

Table 3 Screening Tests	
Realm	Screening
Mental status (performance-based test)	Ask patient to remember 3 objects (e.g., tree, cat, ball) and ask them to recall them in a few minutes
Emotional status	Ask patient, “Do you often feel depressed or sad?”
Functional status	
Activities of daily living	Ask patient, “Can you get out of bed yourself?” “Can you dress yourself?”
Instrumental activities of daily living	Ask patient, “Can you make your own meals?” “Can you do your own shopping?”
“Timed up and go” test (performance-based test)	Individual is asked to get up from an armchair without using their arms, walk 10 feet forward briskly, turn around, walk back to the chair, and then sit down again; ≤ 10 seconds to complete test is considered normal.
Social support	Ask patient, “Who would be able to help you in case of illness or an emergency?”
Comorbidity	Evaluate for the presence of following conditions from the review of systems: congestive heart failure; coronary artery disease; valvular heart disease; chronic lung disease; cardiovascular disease; peripheral neuropathy; chronic renal insufficiency; hypertension; diabetes; coexisting malignancies; collagen vascular diseases; incapacitating arthritis
Nutrition	Weigh patient, measure height, body mass index, inquire about weight loss (unintentional loss of ≥ 10% of body weight in prior year; body mass index < 22 kg/m ²)
Polypharmacy	Review number and type of medications

Breast Cancer in the Older Woman

(CCI), based on 1-year mortality data from internal medicine patients admitted to an inpatient setting, is widely used in geriatrics and oncology. It provides an estimate of survival based on patient age and presence of specific comorbidities. The CCI has been validated in patients with breast cancer and shown to be a good predictor of survival over a 10-year period.⁴⁷

Another tool includes 12 prognostic indicators, including age, male sex, certain comorbidities and behaviors, several functional measures, and a simple scoring system to estimate the 4-year mortality risk for an individual patient.⁴⁸ Table 4 shows this tool with the following point system for 4-year mortality risk:

Table 4 Independent Risk Factors for 4-Year Mortality		
Risk Factor	Adjusted OR (95% CI)*	Points
Demographics		
Age (y)		
60–64	1.9 (1.4–2.5)	1
65–69	2.8 (2.1–3.7)	2
70–74	3.7 (2.8–4.9)	3
75–79	5.4 (4.1–7.1)	4
80–84	8.3 (6.3–11.0)	5
≥ 85	16.2 (12.2–21.6)	7
Male gender	2.0 (1.8–2.3)	2
Comorbidities and behaviors		
Diabetes mellitus	1.8 (1.5–2.1)	1
Cancer	2.1 (1.7–2.4)	2
Lung disease	2.3 (1.8–2.9)	2
Heart failure	2.3 (1.8–3.1)	2
BMI < 25 kg/m ²	1.7 (1.4–1.9)	1
Current smoker	2.1 (1.7–2.5)	2
Functional measures		
Bathing	2.0 (1.6–2.4)	2
Managing finances	1.9 (1.6–2.3)	2
Walking several blocks	2.1 (1.8–2.4)	2
Pushing/pulling	1.5 (1.3–1.8)	1

*Each OR was adjusted for the risk factors in the table. Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CI, confidence interval; OR, odds ratio. From Lee SJ, Lindquist K, Segal MR, Covinsky KE. Development and validation of a prognostic index for 4-year mortality in older adults. *JAMA* 2006;295:805; with permission.

0 to 5 points: 4% or less; 6 to 9 points is 15%; 10 to 13 points is 42%; and 14 or more points is 64%.

The Adjuvant! Online program provides estimates of the 10-year risks for breast cancer–related death, death from other causes, and relapse in women with stage I, II, or IIIA breast cancer.⁴⁹ The patient-specific parameters are limited to age and a comorbidity estimate. A unique feature of Adjuvant! Online is the inclusion of disease-specific parameters, such as tumor size, hormone-receptor status, tumor grade, and number of involved lymph nodes, although this program has not been specifically validated in older patients.

Specific types of organ dysfunction may be particularly important in deciding on treatment in the context of particular therapies and the specific side effects associated with them. For example, a high prevalence of renal insufficiency has been reported in older adults with cancer.^{50–52} Changes in renal function are often not well reflected in measurements of serum creatinine.^{50–52} Certain formulas for estimating individual glomerular filtration rates may provide a better assessment of renal function, although the accuracy of some of these determinations in older patients has been questioned.^{51,53,54} A detailed summary of aspects of these assessments relevant to the older cancer population⁵¹ and specific recommendations for adjustments in the dosing of cytotoxic agents administered to older cancer patients are provided elsewhere.⁵⁰ Finally, measurement of inflammatory markers (e.g., C-reactive protein), although still investigational for cancer patients, is a potentially useful way to assess functional decline and mortality in older patients.^{10,55,56}

Although no consensus was reached about the optimal geriatric assessment tool for evaluating an older woman with breast cancer, all task force members acknowledged the need for these tools. Advantages of the CGA are the multidisciplinary nature of the assessment and the wealth of information included in the tool, whereas the length of time and level of expertise needed to administer and evaluate the results are disadvantages to its use in the oncology setting. The opinion of task force members was that a simple 3- to 5-minute test incorporating several questions and a short performance evaluation with a simple scoring algorithm was the limit to what could be practically implemented in clinical practice. However, others expressed the view that longer, more thorough assessments may be important in critical situations, such as when deciding on the use of adjuvant therapy.

The advantage of Adjuvant! Online is that it is the only tool that can estimate both breast cancer–specific mortality and death from other causes for individual patients. Finally, several task force members anticipated an increasing role of gene array assays, such as Oncotype DX^{57,58} or MammaPrint,⁵⁹ for providing tumor-specific information on the risks for breast cancer recurrence and breast cancer–specific mortality for older women as a supplement to the patient-specific information obtained through more standard geriatric assessments.^{57–59}

Attitudes of Older Patients With Breast Cancer and Their Physicians

Task force members emphasized the important role of patient preference in deciding treatment for older women with breast cancer. However, few studies have explored the attitudes of these women and the psychosocial factors that influence decision-making. Results of a longitudinal cohort study of 563 women aged 67 years or older after surgical treatment of stage I and II breast cancer showed fewer concerns about body image and better mental health when treatment was concordant with patient preferences about appearance.⁶⁰ Several studies indicated that the level of acceptance of operative procedures or chemotherapy for breast cancer did not differ among older and younger patients,^{61,62} although older patients were less likely to accept an improved likelihood of survival at the cost of decreased quality of life.^{61,62}

Several studies evaluating treatment choices of older women with breast cancer found expert advice to be a key factor.^{62–65} In addition, results from a study of 613 pairs of women with breast cancer aged 67 years or older and their surgeons showed an association between level of physician-initiated communication and patient satisfaction with type of treatment received.⁶⁶ Thus, physicians must be able to provide reasonable estimates of the risk for relapse, effect of certain treatments on relapse and mortality, and side effects associated with particular treatments when counseling older women with breast cancer; these discussions must be tailored for the individual patient.

Older women with breast cancer are more likely than their younger counterparts to be diagnosed at a later stage of disease^{67,68} and less likely to undergo chemotherapy^{67–69} or breast-conserving therapy.^{68,70,71}

The attitudes of older patients and their physicians on breast cancer diagnosis and treatment probably contribute to the differences observed in patterns of care according to patient age. The greater emphasis on quality of life for older patients^{61,62} and the possible reluctance of clinicians to expose their patients to cytotoxic therapies^{67,72} may be partly responsible for fewer older women with breast cancer undergoing certain types of treatment. Furthermore, treatment recommended by some physicians may be influenced by evidence of a more indolent course of breast cancer tumors in older patients.⁶⁷

Tumor Biology in Older Versus Younger Women With Breast Cancer

Older women have characteristic differences in the biology of breast cancer compared with younger women. Breast cancers tend to have fewer adverse prognostic features in older women. The frequency of hormone receptor–positive tumors increases with the age.^{67–69,73–76} In one study, women aged 50 to 64 years were less likely to have tumors that were both estrogen receptor (ER)– and progesterone receptor (PR)–positive compared with women aged 76 years or older (39.7% vs. 54.9%, respectively; $P < .01$), although the frequency of ER-positive tumors in these populations was not significantly different (78.6% vs. 81.3%; $P = .07$).⁶⁷

Evaluations of ER concentrations by sucrose-density gradient or charcoal titrations performed on tumor samples of patients enrolled in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 and B-20 trials showed that median receptor concentration increased with patient age.⁷⁷ The frequency of human epidermal growth factor receptor 2 (HER2)-positive tumors is reported to be lower in populations of older patients with breast cancer compared with younger patients.^{67,69} Gennari et al.⁶⁷ found 32.7% of elderly patients to have HER2-positive tumors, compared with 40.8% of younger patients ($P < .01$), and Diab et al.⁶⁹ reported HER2-negative tumors in 90% and 79% of breast cancer patients aged 85 years or older and 55 to 64 years, respectively. Potential confounders of these types of analyses are the possible inaccuracies associated with the tests used to measure hormone receptor and HER2-receptor tumor status.^{78,79}

Reports have also shown that other markers of aggressive tumors, such as tumor grade, p53 levels, and S-phase fraction, are lower in breast cancers in

older patients.⁶⁹ Less-aggressive histopathologic features (e.g., less lymphovascular invasion) were reported to be associated with breast cancer in older versus younger patients,⁸⁰ and local recurrence rates after quadrantectomy and axillary dissection alone were found to decrease with increasing patient age.⁸¹

Some studies suggest that breast cancers are not less aggressive in older versus younger women.^{6,82,83} For example, in analyzing data from 2136 postmastectomy patients at a single institution who did not undergo systemic adjuvant therapy, Singh et al.⁸³ found that among women with node-negative disease, those aged 40 to 70 years had a significantly higher distant disease-free survival rate than women older than 70 years.⁸³ Additional studies are needed to evaluate the biologic properties of tumors in older and younger women with breast cancer and to investigate how host-related characteristics, such as age and the presence of comorbidities, influence tumor growth.

Implementation of Specific Interventions in the Older Cancer Patient: Benefits and Risks

Curative Surgery and Surgical Axillary Staging

The goals of surgery for older women with breast cancer are to 1) prevent chest wall or ipsilateral breast tumor recurrence, 2) prevent axillary recurrence, 3) prevent systemic recurrence, and 4) preserve the breast when possible and preferred by the patient. An overarching objective is to accomplish these 4 goals with minimal treatment. Minimal treatment in this context is distinguished from undertreatment and is defined as treatment that makes medical sense in the context of the patient and evidence-based treatment options.

In their landmark trial, Hughes et al.^{36,37} randomly assigned 636 women aged 70 years or older at diagnosis with clinical stage I (tumors ≤ 2 cm), ER-positive breast cancer to lumpectomy plus 5 years of tamoxifen or lumpectomy and whole breast irradiation plus 5 years of tamoxifen. At 8.2 years follow-up, local regional recurrence rates were approximately 1% and 7% in the arms with and without radiation therapy, respectively, and no significant differences were seen in overall or disease-free survival or need for mastectomy. Axillary recurrence was observed in only 4 patients in the tamoxifen-only group who did not undergo axillary staging, and in none of the other patient groups.

Another randomized trial showed similar results on the lack of prognostic benefit of axillary dissection

in women aged 65 to 80 years with stage I breast cancer.⁸⁴ Finally, results of a study of 241 consecutive patients aged 70 years or older with breast tumors 3 cm or smaller and clinically node-negative disease support the safety and accuracy of sentinel node biopsy in this population.⁸⁵

Two randomized trials comparing tamoxifen alone with mastectomy plus tamoxifen for older women with operable hormone receptor-positive breast cancer showed conflicting results for overall survival. No significant difference in overall survival was observed between patient groups in one of the trials,⁸⁶ whereas a significantly shorter overall survival rate was shown for patients receiving tamoxifen alone in the other trial.⁸⁷ However, results from a meta-analysis of 4 studies indicated that although surgery did not significantly increase overall survival rates, patients undergoing treatment with surgery plus tamoxifen had significantly longer progression-free survival (hazard ratio, 0.65; 95% CI, 0.53–0.81; $P = .0001$).⁸⁸

Ongoing Questions: Questions related to the surgical treatment and evaluation of older women with breast cancer posed by the task force, for which data are limited, include:

- If breast-conserving surgery is feasible in older patients with clinically positive nodes, is radiation necessary?
- If a woman desires breast preservation but the tumor is 5 cm or larger, should preoperative chemotherapy or endocrine therapy be considered?
- Should treatment recommendations for an older woman with a positive sentinel node differ in a woman older than 70 years? (Should this patient be treated with either axillary dissection or nodal irradiation?)
- Should hormone receptor status be considered when evaluating whether to perform lumpectomy without radiation therapy? (Can the results from Hughes et al.^{36,37} be applied to older women with hormone receptor-negative disease?)
- Is axillary staging using sentinel node biopsy useful in populations of older women with stage I, hormone receptor-positive tumors if chemotherapy is not considered an option for these patients?

The task force expressed a high level of consensus on the use of breast-conserving surgery as an option in older women with early-stage breast cancer.

Older patients who will benefit from mastectomy include those with contraindications to endocrine therapy who want to avoid radiation after breast conservation. For older patients who are very frail, non-surgical therapy, such as endocrine therapy alone, may be a reasonable treatment option. Breast-conserving surgery without breast radiation therapy should be restricted to patients defined using the inclusion criteria from the trial of Hughes et al.^{36,37} The task force believes that the results of the Hughes trial^{36,37} cannot be generalized to support breast-conserving surgery without radiation therapy in older women with clinically positive lymph nodes or tumors that are hormone receptor-negative or larger than 2 cm.

The need to treat women with a positive sentinel node using either axillary dissection or nodal irradiation was another general area of agreement. A more controversial issue was whether a sentinel node biopsy could be considered optional in older women with small, clinical stage I, ER-positive breast tumors.

Radiation Therapy

The meta-analyses of radiotherapy trials by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showed that the 5-year absolute reduction in local recurrences associated with radiation therapy after breast-conserving surgery was 22% in women younger than 50 years compared with 12% in those aged 60 to 69 years. No age-specific differences in local recurrence rates were found with postmastectomy radiation therapy. Absolute reductions of 17% and 18% were observed in the younger and older age groups, respectively.⁸⁹

Hughes et al.^{36,37} showed that, in women aged 70 years or older with clinical stage I, ER-positive breast cancer, adding radiation therapy to breast-conserving surgery plus tamoxifen did not change the subsequent mastectomy rate, likelihood of developing distant metastases, incidence of death from breast cancer, or overall survival. Patients not undergoing radiation therapy showed an increase in the rate of local recurrence, with an absolute benefit in local recurrences of approximately 6% with radiation versus no radiation. Survival data showed that 71% of patients were alive and only 2% of deaths were attributable to breast cancer.

An evaluation was performed using the SEER tumor registry of radiation therapy after breast-conserving surgery in the community population of women aged 70 years or older with small, node-negative, ER-positive (or receptor status unknown) breast cancer.⁹⁰

The 5-year risks for local recurrence in women undergoing radiation therapy and those who did not were very similar to those observed in the clinical trial of Hughes et al.^{36,37}

However, separate analyses showed considerably higher absolute benefits of radiation therapy for women aged 66 to 69 years, those with larger tumors, and those with ER-negative tumors. Furthermore, women aged 70 to 79 years without comorbid conditions were among the patient groups most likely to benefit from radiation therapy after breast-conserving surgery, whereas the benefits of radiation therapy were substantially fewer in older women with moderate to severe comorbidity (i.e., a CCI score ≥ 2). No data are available relating to tamoxifen use in the SEER study, and this may have impacted the local recurrence rates.

A similar study using the SEER database to evaluate use of radiation therapy after breast-conserving surgery in older women (≥ 66 years) with ductal carcinoma in situ (DCIS) showed significant benefits of radiation therapy with respect to preventing local recurrence and subsequent invasive breast cancer.⁹¹

In patients undergoing breast-conserving surgery followed by radiation therapy, the addition of a "boost" to the tumor bed has been shown to reduce local failures by approximately 40%.^{92,93} The relative benefit seems similar across age groups. However, because older patients typically have a lower failure rate than younger patients, the magnitude of the absolute benefit of the boost is lower in the older patients.⁹⁴

Two population-based studies have addressed the effectiveness of postmastectomy radiation therapy based on patient age.^{76,95} Data from the Canadian Breast Cancer Outcomes Unit Database were evaluated for cohorts aged 50 to 69 years and 70 years and older with a median postmastectomy follow-up of 8.3 years. On multivariate analysis, age was not an independent predictor of likelihood of local recurrence in the absence of radiation therapy. However, in patients with node-positive disease involving 4 or more lymph nodes, those aged 70 years and older showed a trend toward increased rates of local recurrence compared with those aged 50 to 69 years. Overall, patients aged 70 years and older had similar local recurrence rates to those aged 50 to 69 years.⁷⁶

In an analysis of SEER data of 11,594 women aged 70 years and older treated for invasive breast cancer with mastectomy with a median follow-up of 6.2 years, significant benefit from postmastectomy radiation

therapy was seen only in the group of patients with high-risk disease (i.e., low risk—T1/2, N0; high risk—T3/4 and/or N2/3).⁹⁵ Issues regarding use of radiation therapy and axillary staging in an older patient with early-stage breast cancer are presented in Case Study 1.

Ongoing Questions:

- What short-, intermediate-, and long-term toxicities are associated with radiation therapy in older patients?
- What criteria should be considered in the decision to recommend radiation therapy for an older woman?
- Because survival benefits of radiation therapy after mastectomy may not be evident for 10 to 15 years, are these benefits relevant to older patients?

Other factors influencing decisions related to radiation therapy in older women include the attitudes of patients, medical oncologists, and other referring physicians; performance status of the individual patient; and risk for local recurrence. Although the potential survival benefits of postmastectomy radiation are likely to be less relevant in older patients, other benefits of radiation therapy can include a decreased likelihood of local recurrence with increased quality of life. Finally, the potential adverse cardiovascular effects of radiation therapy, particularly when administered to the left breast, were mentioned as a factor for consideration.⁹⁶

Reconstructive Surgery

Very few studies have addressed breast reconstructive surgery after mastectomy in older women. The SEER database documents that very few women aged 65 years and older undergo breast reconstruction after surgery for breast cancer.^{97,98} Morrow et al.⁹⁷ found the percentage of patients receiving reconstruction decreased dramatically with age, with 53.0%, 36.6%, and 8.3% reconstruction rates for women aged younger than 50 years, 50 to 64 years, and 65 years and older, respectively ($P < .001$). Lower rates of breast reconstruction were also associated with lower income and African American ethnicity. Although many women in the study reported physician discussions of breast reconstruction, patient knowledge of the procedure was limited.

A retrospective study of 84 older women (81 were ≥ 65 years of age) who underwent breast reconstruction after mastectomy found more positive

outcomes and fewer complications with autologous tissue versus implant reconstruction.⁹⁹ However, all groups of the study had relatively high rates of breast-site complications, including infection.

Smoking history and obesity are critical factors that increase complication rates of reconstructive procedures, regardless of age. In addition, the presence of certain comorbidities more common in older patients, such as diabetes and hypertension, can impact decisions related to breast reconstruction. Other less-complicated alternatives to full breast reconstruction, which might be more acceptable to some older patients, include a procedure to reduce the contralateral breast¹⁰⁰ and direct-to-implant reconstruction.¹⁰¹

Ongoing Questions:

- Should all women, regardless of age, be offered the option of a consultation with a plastic surgeon (to become informed about breast reconstructive options, including explanations of the potential risks and benefits of the surgical procedures and their impact on cancer outcome) in the absence of medical contraindications?
- Should the “functional age” threshold be lower for considering reconstructive procedures compared with breast cancer therapies that have the potential to impact disease outcome?
- Are the risks associated with breast reconstructive surgery greater in older women?

The overall consensus of the task force members was that women of all age groups should be offered consultation with a reconstructive surgeon, although some participants questioned whether the risks of the procedure would ultimately outweigh the benefits for many older patients. Further investigation is required to determine if unique risks exist for older women who undergo reconstruction. Finally, several members of the task force identified a need to further investigate the attitudes of older women about breast reconstruction options.

Endocrine Therapy

Endocrine therapy is the most commonly used systemic treatment in older patients with breast cancer in both the adjuvant and metastatic settings.^{86,102,103} Although clinical studies of endocrine agents are limited in women aged 70 years and older, the median age of women enrolled in clinical trials of aromatase inhibitors as treatment for both early-stage, locally advanced, and metastatic breast cancer was often older

Case Study 1

An 82-year-old woman with hormone receptor–positive/HER2–negative clinical stage I breast cancer presents at your office. She also has hypertension, diabetes, and a history of a transient ischemic attack. Although able to perform daily activities such as bathing and dressing, she requires assistance with housework, laundry, and managing her finances. She can walk one block without difficulty, but she tires easily and is unable to walk several blocks without stopping to rest. Having chosen to undergo breast-conserving surgery, she is scheduled for a lumpectomy. She now presents to discuss the role of axillary sampling, radiation therapy, and hormonal therapy.

Discussion

The average life expectancy of an 82-year-old woman is 8.4 additional years.^a The 82-year-old woman in this case functions independently in activities of daily living (such as bathing and dressing) but requires assistance with instrumental activities of daily living (housework, laundry, and managing her finances). Comorbidity is a strong predictor of survival in women with breast cancer. In a longitudinal observational study of 936 women with breast cancer between the ages of 40 to 84, women with 3 (of 7) selected comorbid medical conditions had a 20-fold increased risk for mortality from a cause other than breast cancer and a 4 times greater risk for overall mortality.^b Based on this patient's age, functional status, and comorbid medical conditions, her 4-year risk for mortality is 40% (Table 4).^c

This woman has clinical stage I hormone receptor–positive cancer. A randomized multicenter study of 636 women aged 70 years and older with clinical stage I (tumors ≤ 2 cm) hormone receptor–positive breast cancer showed that if patients undergo a lumpectomy and receive hormonal therapy, their risk for a local recurrence over the following 8 years will be 1% if they undergo postlumpectomy radiation, and 7% if they do not. No association exists between radiation therapy and breast cancer–specific or overall mortality. Most of these patients die of causes other than breast cancer.^d

The role of sentinel lymph node biopsy or axillary surgery in older women is controversial, especially if the results will not change recommendations for adjuvant therapy (i.e., chemotherapy would not be given regardless of nodal status). In the randomized study of patients aged 70 years and older with clinical stage I breast cancer treated with lumpectomy and hormonal therapy by Hughes et al.,^e there was an axillary recurrence in 4 patients who underwent neither radiation therapy nor axillary sampling, and no patients in the other groups. A study by the International Breast Cancer Study Group randomized patients aged 60 years or older (median age, 74 years) with node-negative breast cancer to breast surgery plus axillary clearance or breast surgery alone. Of patients who underwent axillary surgery, 28% had involved nodes; 80% had hormone receptor–positive disease and were treated with tamoxifen. At a median follow-up of 6 years, no difference was seen in the rate of axillary recurrence (occurred in 2% of patients), disease-free survival, or overall survival between treatment arms.^e

In an 82-year-old patient with stage I ER-positive breast cancer, the risks of adjuvant chemotherapy would outweigh the potential benefits. The Early Breast Cancer Trialist Collaborative Group overview of randomized trials showed that the benefits of adjuvant chemotherapy decreased with increasing age. However, too few women older than 70 years were studied to determine whether adjuvant chemotherapy was associated with a survival benefit.^f

Adjuvant endocrine therapy can be considered for this patient. The benefits of adjuvant endocrine therapy in women with hormone receptor–positive breast cancer have been shown to be independent of age.^f In fact, older women experience a greater proportional reduction in breast cancer recurrence from hormonal therapy than from chemotherapy.^f Endocrine therapy options include tamoxifen or an aromatase inhibitor, with several recent randomized trials showing the benefits of an aromatase inhibitor over tamoxifen in improving disease-free survival when either prescribed upfront or sequenced after tamoxifen therapy.^{g-h} If the patient declines endocrine therapy, the role of post-lumpectomy radiation should be considered because the omission of radiation therapy has only been studied among women who underwent endocrine therapy.

The risks of tamoxifen and aromatase inhibitors differ. Patients receiving tamoxifen, compared with an aromatase inhibitor, are at an increased risk for thromboembolism, ischemic cerebrovascular events, hot flashes, endometrial cancer, and vaginal discharge. Patients receiving an aromatase inhibitor, compared with tamoxifen, are at increased risk for fracture and arthralgias. The impact of aromatase inhibitor–associated arthralgias and fractures on the functional status of older adults requires further study. A meta-analysis of 7 randomized trials showed that patients treated with an aromatase inhibitor were also at increased risk for grade 3 or 4 cardiovascular complications (absolute difference, 0.52%; relative risk [RR], 1.31; 95% CI, 1.07–1.60; $P = .007$), whereas patients treated with tamoxifen are at increased risk for thromboembolism (absolute difference, 1.17%; RR, 0.53; 95% CI, 0.42–0.65; $P < .0001$).^o

The patient described in this case has cardiovascular risk factors and a history of a transient ischemic attack. Therefore, either form of endocrine therapy has potential risks that must be discussed with her. An aromatase inhibitor is the preferred endocrine treatment in patients with a history of thromboembolism because it is associated with a lower risk for an ischemic cerebrovascular event compared with tamoxifen. However, therapy with an aromatase inhibitor has a higher risk for bone loss and cardiovascular events. As with all older adults, careful attention must be paid to cardiac risk factors and bone health. The patient's preferences also should play an integral role in the decision-making process.

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Case Study 1 Continued

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than 60 years because of the eligibility requirement of postmenopausal status.^{104–107} Furthermore, results from the EBCTCG overview showed a decrease in risk for breast cancer recurrence and death in women aged 70 years and older with early-stage ER-positive breast cancer receiving 5 years of tamoxifen, similar to that in younger patients.¹⁰⁸ In addition, a recent prospective cohort study of the efficacy of adjuvant tamoxifen in older women showed a 4% absolute increase in breast cancer-specific survival and an 11% absolute increase in overall survival in older women receiving tamoxifen at 5-year follow-up.¹⁰³

Ongoing Questions:

- Do older women with hormone receptor-positive breast cancer benefit more from endocrine therapy than younger women with the same diagnosis based on tumor biology?
- Should adjuvant endocrine therapy recommendations for older women differ from those currently in NCCN guidelines for younger postmenopausal patients?
- How do certain side effects of aromatase inhibitors (e.g., arthralgias, altered lipid levels, decreased bone density) and tamoxifen (e.g., venous thromboembolism and endometrial

carcinoma) impact treatment tolerability and adherence in older women with breast cancer?

Areas of consensus included the benefit of endocrine therapy for older patients with hormone receptor-positive breast cancer in the adjuvant and metastatic settings, and using initial endocrine therapy with postponed use of chemotherapy to treat patients of all age groups with ER-positive metastatic disease. Several points of discussion included the increased incidence of nonaromatase inhibitor-associated arthralgias in older patients as confounders of efforts to evaluate the risk for aromatase inhibitor-induced arthralgias, and the impact of cost on the choice of endocrine therapy for older patients.¹⁰⁹

Some issues to consider regarding use of endocrine therapy in older patients with early-stage breast cancer are presented in Case Study 1.

Chemotherapy

Adjuvant Setting: Evidence indicates that the risk for recurrence in patients with ER-negative disease is highest in the first 5 years after diagnosis and that the likelihood of disease recurrence for patients with ER-positive disease is comparatively lower during the first 5 years. However, a reversal in this trend is seen in

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the subsequent 5 years, with higher recurrence rates seen for patients with ER-positive disease.^{110,111} This relatively lower rate of early recurrence in patients with ER-positive disease probably depends, at least partly, on the efficacy of endocrine therapy.¹¹¹ Furthermore, the benefit of chemotherapy is most pronounced in the first 5 years.^{108,112} The early benefits of chemotherapy and endocrine therapy are appropriate considerations when deciding on adjuvant therapy for older individuals with breast cancer.

The most recently published meta-analyses of randomized trials by the EBCTCG shows that adjuvant polychemotherapy had a substantial impact on recurrence rate and breast cancer–specific mortality in women with ER-negative tumors who were younger than 50 and those 50 to 69 years of age. The absolute risk reductions in 10-year recurrence risk and breast cancer mortality are 12% and 8%, respectively, in patients younger than 50 years, and 10% and 6%, respectively, in patients aged 50 to 69 years.¹¹² Hence, the benefits of chemotherapy in patients with ER-negative disease do not seem to be influenced by age.

Earlier EBCTCG analyses showed that the benefits of polychemotherapy, although significant, were not as marked for patients with ER-positive compared with those with ER-negative disease, and patients aged 50 to 69 years received less benefit from chemotherapy than patients younger than 50 years.¹⁰⁸ In addition, the benefit of adjuvant chemotherapy with CMF (cyclophosphamide, methotrexate, fluorouracil) in

addition to tamoxifen therapy was considerably less pronounced in women with ER-positive disease who were 60 years or older enrolled in the NSABP B-14 and B-20 trials compared with the younger patient cohorts in these trials (Figure 5).⁷⁷ In a randomized study of women 65 years or older with operable, node-positive, mostly ER-positive breast cancer, a significant increase in disease-free survival was shown for those women who received adjuvant chemotherapy with epirubicin-based chemotherapy in addition to tamoxifen compared with women receiving tamoxifen alone, although no impact on survival was observed at a follow-up of 6 years.¹¹³

Retrospective studies support the use of adjuvant chemotherapy in older women with ER-negative breast cancer. The results of 2 recent analyses using the SEER database found an association between use of adjuvant chemotherapy and decreased mortality in women with node-positive, ER-negative disease.^{114,115} A retrospective review of 4 randomized clinical trials provided evidence for benefit of intensive adjuvant chemotherapy regimens with respect to disease recurrence and breast cancer mortality in women with node-positive breast cancer across all age groups.³⁵ However, in this study, the impact of ER status on patient outcome was not evaluated; only approximately 35% of the patients had ER-negative disease, the group of patients aged 65 years or older had a higher average number of positive lymph nodes, and few older patients were enrolled in the trials.

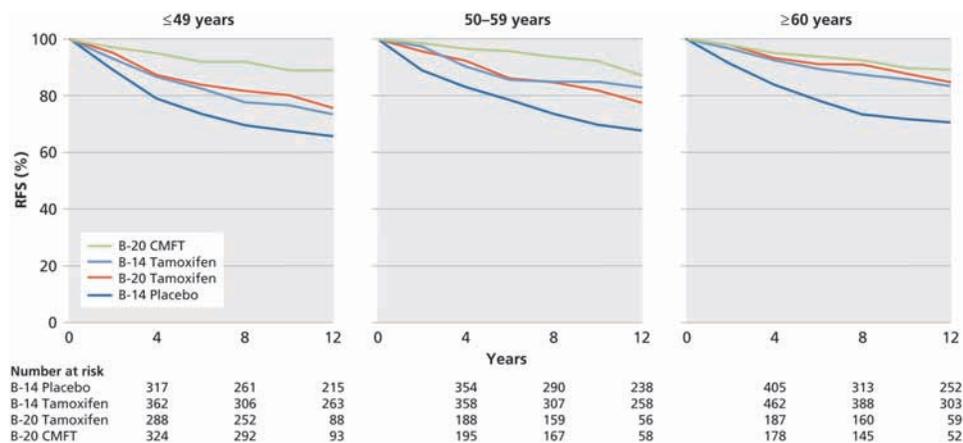


Figure 5 Relation between recurrence-free survival (RFS) in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 and B-20 trials according to age group. For patients 60 years or older (Panel 3), RFS rate differences in the tamoxifen-treated and CMFT (cyclophosphamide, methotrexate, fluorouracil + tamoxifen)-treated groups were not significant. From Fisher B, Jeong JH, Bryant J, et al. Treatment of lymph-node-negative, estrogen-receptor-positive breast cancer: long-term findings from National Surgical Adjuvant Breast and Bowel Project randomized clinical trials. *Lancet* 2004;364:858–868.

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An increased incidence of certain complications of chemotherapy, including cardiotoxicity and acute myelogenous leukemia/myelodysplastic syndromes (AML/MDS), has been reported in populations of older patients.^{21,116,117} In addition, a higher rate of treatment-related death has also been observed in older populations undergoing adjuvant chemotherapy for breast cancer,^{21,35} although the risk for chemotherapy-related toxicity in older women with breast cancer may depend more on the type of chemotherapy regimen than patient age.¹¹⁸ Some issues to consider regarding use of adjuvant chemotherapy in older patients with early-stage breast cancer are presented in Case Study 2.

Ongoing Questions:

- What estimated life expectancy would be reasonable before considering chemotherapy in an older woman?
- What incremental benefits would be required in older adults before the benefits of chemotherapy warrant the increased toxicity experience?
- How confident are physicians that benefits of chemotherapy for 60- to 69-year-old patients translate into benefits for 70- to 100-year-old patients?
- Should older patients receive lower doses of or different chemotherapy from younger patients?

The overall consensus of the task force is that the benefit-to-risk ratio of using adjuvant chemotherapy in older patients with ER-negative disease is often favorable, although other factors, such as life expectancy, impact of comorbidities, toxicities of particular agents, and personal preferences of the patient, must be considered. That the risk for recurrence of ER-negative disease is highest in the first 5 years after diagnosis further supports the usefulness of chemotherapy in many older patients with ER-negative breast cancer and justifies a life expectancy of at least 5 years as a criterion for considering chemotherapy in older patients.

Beyond absolute reduction in breast cancer recurrence or mortality, consideration of functional reserve is also important.³⁰ Furthermore, whether dose reductions or less intensive therapies given to older patients in some studies may have diminished the observed effectiveness of chemotherapy in patients with both ER-negative and -positive disease, and whether modern, more intensive regimens would show greater efficacy in these groups of patients is unclear.

No specific adjuvant chemotherapy regimens were identified as clearly preferable, although caution in using anthracyclines, reliance on less myelosuppressive therapies, careful evaluations of renal and hepatic functions, possible benefit of weekly dosing, and early use of myeloid growth factors were mentioned as important considerations. Some underexplored areas include evaluation of the pharmacokinetics and pharmacodynamics of cytotoxic agents in older versus younger patients and the interactions of chemotherapeutic drugs with other medications in the older population.

Metastatic Setting: Various biologic and clinical features, such as ER-negative tumor status, visceral dominant disease, and a short disease-free survival interval, have been identified as negative prognostic factors for women with metastatic breast cancer. Older age alone has not been shown to influence outcome.¹¹⁹ Furthermore, results from a case-control study showed no significant differences in time to disease progression and survival for women younger than 50 years, 50 to 69 years of age, and 70 years and older undergoing chemotherapy for metastatic breast cancer.¹²⁰ However, women aged 70 years and older were more likely to receive lower doses of chemotherapy. Results from a randomized study of first-line combination chemotherapy (doxorubicin/paclitaxel) versus sequential single-agent chemotherapy in women (median age, 56–58 years) with metastatic breast cancer showed no differences in overall survival or quality of life between treatment arms; however, treatment-related toxicity was higher in the combination arm.¹¹⁹

Ongoing Question:

- In the metastatic setting, is combination or sequential chemotherapy preferred for older patients?

The goals of metastatic breast cancer treatment are primarily palliative. When chemotherapy is used, sequential single agents (i.e., administering single-agent chemotherapy in tandem) are generally preferred as opposed to combination chemotherapy, because toxicity with combination regimens is likely to be more severe in the older population. In general, chemotherapy should be limited to those with hormone receptor–negative disease or those with hormone receptor–positive, endocrine therapy–refractory disease. Some members suggested that a “start low, go slow” titration to full dose could be advantageous in this setting to limit toxicity.

Case Study 2

A 73-year-old woman with triple-negative, early-stage breast cancer presents at your office. She is status post a modified radical mastectomy for a T2 N1 ER-/PR-/HER2-negative breast cancer. She has a history of hypertension but is otherwise healthy. She is independent in her daily activities, continues to work, and exercises 3 days a week. She wishes to discuss the role of adjuvant chemotherapy.

Discussion

This is an active 73-year-old woman with few comorbid medical conditions. Her average life expectancy based on data from the U.S. Census Bureau is 13.8 years.^a Her 4-year risk of mortality is estimated at 4%, based on the prognostic index developed by Lee et al.^b (Table 4). She is presenting with high-risk breast cancer that has a triple-negative phenotype (ER-/PR-/HER2-negative) and a guarded prognosis.^{c,d} The 10-year risk for breast cancer relapse and mortality is 54.9% and 44.6%, respectively, using the decision tool Adjuvant! Online.^e

Chemotherapy is the only adjuvant treatment option known to decrease the risk for relapse and mortality from a triple-negative breast cancer. Data from the Early Breast Cancer Collaborative Group show that the benefit from adjuvant chemotherapy decreases with increasing age. The biologic basis for this finding is unclear. A possible explanation is that older adults are most likely to experience treatment delays, dose reductions, or early discontinuation of chemotherapy, thereby limiting the efficacy of adjuvant treatment.^f In addition, younger women may obtain a greater benefit from adjuvant chemotherapy because of the associated ovarian ablation effects (most relevant in ER-positive tumors).

In contrast to the data from the Early Breast Cancer Collaborative Group, the CALGB clinical trial for node-positive breast cancer showed that both older and younger patients derived similar benefits from regimens that contained “more versus less” chemotherapy; however, only 8% of patients in this trial were aged 65 years or older and only 2% were aged 70 years or older.^g Data from the SEER registry linked to Medicare claims showed that receipt of adjuvant chemotherapy in women 66 years or older was associated with a 15% reduction in mortality. The benefits of treatment were most pronounced in patients who had high-risk disease.^h

The potential risks of adjuvant chemotherapy increase with age. Data from 3 CALGB clinical trials of anthracycline-based regimens showed that the risk for treatment-related death ($P = .0022$) and the need for early discontinuation of therapy ($P < .0001$) increased with age. The risk for treatment-related death in patients aged 65 years or older compared with patients 50 years or older was 1.5% versus 0.2%, respectively. In addition, the risk for AML or MDS increased with increasing age ($P < .001$).ⁱ In adults aged 66 years or older with nonmetastatic breast cancer, observational data from the SEER–Medicare database show that the absolute 10-year risk for developing AML was 1.8% for patients who underwent adjuvant chemotherapy versus 1.2% for those who did not ($P < .001$).^j Another observational study from the SEER–Medicare database showed that women aged 66 to 70 years who underwent an anthracycline-based chemotherapy regimen were at increased risk for developing congestive heart failure. Absolute risks for developing congestive heart failure at 10 years were as follows:

- 38.4% of patients who received an anthracycline
- 32.5% of patients who received a non-anthracycline
- 29% of patients who underwent no chemotherapy

No significant difference in the incidence of heart failure were seen among women aged 71 to 80 years.^j The authors postulated that perhaps only a healthier group of adults aged 71 to 80 years received anthracyclines or that these older adults received lower cumulative doses of anthracyclines. Comorbid medical conditions associated with an increased risk for congestive heart failure included coronary artery disease, emphysema, diabetes, hypertension, and peripheral artery disease.^j

Concern about the association of anthracyclines and cardiac toxicity led to the development of nonanthracycline adjuvant treatment options. Jones et al.^k reported on the efficacy of adjuvant chemotherapy with 4 cycles of AC (doxorubicin and cyclophosphamide) versus 4 cycles of TC (docetaxel and cyclophosphamide). The updated study shows a benefit in disease-free and overall survival among patients receiving TC. The efficacy of third-generation regimens, such as AC followed by paclitaxel versus TC, has not been compared. A subset analysis of TC therapy toxicity according to age showed that older adults are at increased risk for febrile neutropenia.^l As an individual ages, bone marrow reserve decreases, resulting in an age-related increased risk for myelosuppression with combination chemotherapy.

Few studies have evaluated the efficacy of single-agent or single-sequential-agent chemotherapy in older adults. A study in older women with node-positive breast cancer showed that the addition of single-agent epirubicin to tamoxifen decreased the risk for relapse compared with tamoxifen alone (relative risk for relapse with tamoxifen alone, 1.93; 95% CI, 1.7–2.17; $P = .005$). No significant difference in overall survival has been observed.^m Randomized data have also shown that dose-dense AC for 4 cycles followed by paclitaxel for 4 cycles yielded outcomes equivalent to a dose-dense

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Case Study 2 Continued

single-sequential-agent approach (doxorubicin for 4 cycles followed by paclitaxel for 4 cycles followed by cyclophosphamide for 4 cycles).^o Therefore, if a concern exists about the myelosuppressive effects of combination chemotherapy, a single-sequential-agent approach can be used.

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The preferred approach for patients with ER-positive disease is initial single-agent endocrine therapy followed sequentially with other single-agent endocrine therapy at disease progression. This strategy allows chemotherapy and its associated side effects to be delayed as long as possible. Use of HER2-targeted agents (e.g., trastuzumab, lapatinib) in older women with HER2-positive breast cancer without chemotherapy or hormone therapy may be beneficial to avoid certain treatment-related side effects.

Trastuzumab Therapy for HER2-Positive Disease:

The degree of benefit from adjuvant trastuzumab in older patients with HER2-positive disease cannot be estimated from published results because very few of these patients were enrolled in the randomized trastuzumab trials.^{121–125} For example, 16.0% of patients in the NSABP (B-31)/NCCTG(9831) joint analysis were aged 60 years or older, and only approximately 6% of patients were older than 65 years. Evaluation of the efficacy of trastuzumab in the metastatic setting has also been largely restricted to younger patients (e.g.,

mean age of patients was 54 years in both the pivotal trial of trastuzumab plus chemotherapy¹²⁶ and the trial of trastuzumab monotherapy¹²⁷).

Safety analyses from the NSABP B-31 study identified older age as a risk factor for trastuzumab-related cardiotoxicity.^{23,128,129} Increased age was identified as a risk factor for congestive heart failure (CHF) at a follow-up of 5 years (2.3% for < 50 years; 5.1% for 50–59 years; and 5.4% for ≥ 60 years; $P = .03$).²³ In addition, use of hypertensive medications, lower baseline left ventricular ejection fraction (LVEF), and lower LVEF after treatment with doxorubicin/cyclophosphamide therapy were also identified as being significantly associated with higher rates of CHF (CHF rates with or without use of hypertensive medications were 6.8% and 3.0%, respectively; $P = .02$).

Ongoing Question:

- Which older patients with early-stage HER2-positive breast cancer should undergo trastuzumab therapy in the adjuvant setting?

The task force agreed that the therapeutic index of adjuvant trastuzumab does not preclude adjuvant trastuzumab in most fit elderly women, given the small numbers of cardiac-related deaths observed in clinical trials and the increased risk for relapse in patients with HER2-positive disease.¹³⁰ Nevertheless, the general consensus was that little evidence exists on which to base tailored recommendations for adjuvant trastuzumab in the older patient. The use of adjuvant trastuzumab is related to that of adjuvant chemotherapy, because task force participants did not advocate using trastuzumab in the absence of chemotherapy in the adjuvant setting. Some members stated that a positive HER2 tumor status in an older patient with early-stage ER-positive disease could shift the decision-making balance toward use of chemotherapy. Some issues to consider regarding use of HER2-directed therapy for patients with early-stage HER2-positive breast cancer are presented in Case Study 3.

Supportive Therapies

Cancer treatment-related complications are more common in older patients with breast cancer undergoing certain types of chemotherapy regimens.^{21,118} Supportive care measures include therapies to minimize chemotherapy-related neutropenia and anemia. A meta-analysis of randomized studies evaluating primary prophylaxis with granulocyte-colony stimulating factors (G-CSF) versus placebo or untreated controls in patients undergoing chemotherapy indicated that G-CSF therapy was associated with decreased incidences of febrile neutropenia and early death, and a higher relative dose-intensity of chemotherapy.¹³¹ Although the decreased risk for febrile neutropenia was found to be independent of age in this meta-analysis, only the trials involving patients with lymphoma included substantial populations of older individuals.

Results of 2 population-based studies have suggested that colony-stimulating factor support during chemotherapy may increase the risk for AML/MDS in women with breast cancer^{132,133} (e.g., increase in absolute risk from 1.04% to 1.77%¹³³), although results from another epidemiologic study did not support this conclusion.¹¹⁷ Confounding this issue is the slightly increased risk for MDS/AML observed in some studies of older women with breast cancer that has been associated with use of certain cytotoxic drug regimens.^{21,117,132}

Treatment-related anemia is a side effect of many myelosuppressive chemotherapies. Evidence from a

multivariable logistic regression model indicates that age of 65 years or older is a risk factor for development of anemia during adjuvant treatment of breast cancer.¹³⁴ In addition, the volume of distribution of a cytotoxic drug may be affected by the concentration of erythrocytes, because certain agents bind to red blood cells (e.g., anthracyclines).¹⁷ However, in a randomized, placebo-controlled study of women with metastatic breast cancer, decreased overall survival was associated with erythropoietic-stimulating agent (ESA) use to maintain high hemoglobin levels.¹³⁵

Use of aromatase inhibitors is also associated with loss of bone mineral density and increased risk for bone fracture. Therefore, bone health should be monitored in women undergoing this therapy and followed by appropriate interventions in women at risk for osteopenia, osteoporosis, and fracture.^{136,137} The use of the potent bisphosphonates is also valuable in patients with bone metastasis from breast cancer.^{7,136}

Ongoing Questions:

- What target hemoglobin level should be recommended for older patients with breast cancer?
- Should transfusion or growth factor support be used preferentially to maintain this hemoglobin level?

No consensus was reached concerning optimal hemoglobin levels for older women with breast cancer. The 2009 recommendations from the NCCN Clinical Practice Guidelines in Oncology: Cancer- and Treatment-Related Anemia Panel do not support using ESAs for treating cancer-related anemia for solid tumors; short-term use of ESAs is recommended only for the treatment of anemia caused by myelosuppressive chemotherapy.¹³⁸ Long-term longitudinal survivorship studies are needed to evaluate the functional and medical effects of treatments in these patients, especially on the bone marrow and heart.

Studies Involving Older Patients With Cancer

A common theme linking each of the previous topics is the paucity of data from randomized clinical trials on older patients with breast cancer. The underrepresentation of cancer patients aged 65 years and older in clinical trials has been well documented.^{139–141}

In a retrospective study covering 1995–2002, the ages of cancer patients enrolled in registration trials submitted to the FDA for drug approval were evaluated.¹⁴⁰

Case Study 3

A 71-year-old woman with hypertension and diabetes is diagnosed with a T2 N1, hormone-receptor–negative, HER2-positive breast cancer. She is status post a modified radical mastectomy. Multiple gated acquisition scan shows a normal ejection fraction. She presents to discuss adjuvant treatment.

Discussion

The patient is an older adult who has potentially curable HER2-positive breast cancer. She also has hypertension and diabetes, illnesses that commonly accompany aging. (In a study of more than 7600 patients aged 55 years, 43% had hypertension and 13% had diabetes.³) Randomized trials have previously shown the benefits of adjuvant trastuzumab combined with chemotherapy in reducing the risk for relapse and mortality from HER2-positive breast cancer, although the low number of older adults included in these clinical trials and the exclusion of patients with cardiac comorbidities limit the applicability of these results to the older population.

However, cardiac function has been carefully monitored in adjuvant trastuzumab trials, with discontinuation based on asymptomatic decline in left ventricular ejection fraction or development of congestive heart failure (CHF). Therefore, these trials can be informative regarding risk factors for trastuzumab-associated cardiac toxicity. This woman's case will be used to review the age distribution, cardiac eligibility criteria, and risk factors for cardiac side effects from randomized trials of adjuvant trastuzumab, and to illustrate the considerations involved in prescribing adjuvant trastuzumab for older adults.

The NSABP-B31 and North Central Cancer Treatment Group (NCCTG) 9831 trials evaluated the addition of trastuzumab to anthracycline and taxane adjuvant chemotherapy regimens. Only 16% of patients enrolled in NSABP-B31 and NCCTG 9831 were 60 years of age or older. Cardiac exclusion criteria included an abnormal left ventricular ejection fraction, clinically significant valvular heart disease, poorly controlled hypertension, left ventricular hypertrophy on echocardiogram (NSABP B-31 only), clinically significant pericardial effusion (NCCTG 9831 only), history of a myocardial infarction, CHF, cardiomyopathy, severe conduction abnormality, and angina pectoris or arrhythmia requiring medication.^b

In NSABP B-31, treatment consisted of doxorubicin and cyclophosphamide (AC) every 3 weeks for 4 cycles followed by paclitaxel every 3 weeks for 4 cycles, or weekly for 12 doses. Patients were randomized to receive (or not receive) 1 year of trastuzumab, beginning with the paclitaxel portion of therapy. The addition of trastuzumab to an anthracycline-based chemotherapy regimen increased the 3-year cumulative incidence of cardiac events (defined as New York Heart Association class III or IV CHF or possible/probable cardiac death) from 0.8% to 4.1% (absolute increase of 3.3%). Trastuzumab was discontinued in 4% of patients because of symptomatic CHF and in 14% because of asymptomatic decreases in left ventricular ejection fraction. Risk factors for CHF included age of 50 years or older and post-AC left ventricular ejection fraction of 50% to 54%. The combination of these risk factors was associated with a 20% 3-year incidence of CHF.^c

In the N9831 Intergroup trial, patients received AC every 3 weeks for 4 cycles, and were subsequently randomized to paclitaxel weekly for 12 weeks (arm A); paclitaxel weekly for 12 weeks, followed by trastuzumab weekly for 1 year (arm B); or the combination of paclitaxel and trastuzumab weekly for 12 weeks followed by trastuzumab weekly to complete 1 year of therapy (arm C). The 3-year cumulative incidence of cardiac toxicity (CHF or cardiac events) was 0.3%, 2.8%, and 3.3% for arms A, B, and C, respectively. Risk factors for a cardiac event among patients assigned to the trastuzumab-containing arm included age of 60 years or older, prior or current use of antihypertensive medication, and lower left ventricular ejection fraction (< 55% but above lower limit of normal) at registration for the study. Notably, 5% of patients experienced decreases in left ventricular ejection fraction after AC, ruling out the use of trastuzumab.^d

The median age of participants on the Herceptin Adjuvant (HERA) trial was 49 years; 16% of patients were 60 years of age or older.^e Patients underwent chemotherapy at the discretion of the treating physician, although the total dose of doxorubicin could not exceed 360 mg/m² and the total dose of epirubicin could not exceed 720 mg/m². After completion of chemotherapy, patients were randomized to either 1 or 2 years of trastuzumab, or observation. Cardiac eligibility included a postchemotherapy left ventricular ejection fraction (LVEF) of 55% or more and no history of CHF, coronary artery disease (transmural infarct on ECG or angina pectoris requiring antianginal medication), uncontrolled hypertension (defined as systolic blood pressure > 180 mm Hg or diastolic blood pressure > 100 mm Hg), clinically significant valvular heart disease, or high-risk arrhythmia.

At a median follow-up of 12 months, 4.3% of patients discontinued trastuzumab because of cardiac side effects. The incidence of severe CHF (0.60% vs. 0%), symptomatic CHF (2.15% vs. 0.12%), and confirmed decreases in LVEF (3.04% vs. 0.53%) was higher in the group treated with trastuzumab. Risk factors for cardiac dysfunction included higher cumulative doses of doxorubicin or epirubicin, lower screening LVEF, and higher body mass index. Risk factors associated with an increased incidence of cardiac side effects included hypertension, cigarette smoking, diabetes, hypothyroidism, and age of 60 years or older, although none of these reached statistical significance.^f

The standard duration of trastuzumab is 1 year; however, shorter courses have been studied. The FinHer study evaluated the usefulness of 9 weekly doses of trastuzumab in addition to chemotherapy, and found that even this short course

Case Study 3 Continued

of trastuzumab was associated with improved recurrence-free survival.⁹ The HERA trial evaluated a longer duration of adjuvant trastuzumab (1 vs. 2 years). Efficacy and toxicity results are pending. Other investigators have explored the usefulness of nonanthracycline, trastuzumab-containing combinations. The Breast Cancer International Research Group evaluated the use of a nonanthracycline regimen of docetaxel, carboplatin, and trastuzumab (TCH) and compared it with AC followed by docetaxel, and AC followed by docetaxel and 1 year of trastuzumab. The median age of patients on this trial was 49 years (range, 22–74 years). The second interim analysis, presented at the 2006 San Antonio Breast Cancer Symposium, shows a lower risk for grade 3 or 4 CHF ($P = .0015$) or more than 10% relative decline in LVEF ($P < .0001$) with receipt of the nonanthracycline/trastuzumab combination.^h

For the patient described in this case, adjuvant trastuzumab will certainly decrease the risk for relapse and mortality from HER2-positive breast cancer, but her age and hypertension place her at increased risk for a cardiac event. Therefore, careful monitoring of cardiac function during therapy is mandatory. Indeed, careful attention must be paid to cardiac status and treatment of cardiac risk factors in all older patients during cancer therapy. The standard duration of trastuzumab is 1 year, whereas the optimal duration (either shorter or longer) is currently being investigated. Studies are needed to determine the impact of long-term trastuzumab therapy on the cardiac function of all breast cancer survivors, with particular focus on older adults.

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The report showed that the percentage of patients aged 65 years and older enrolled in clinical trials evaluating hormonal therapy for breast cancer closely matched the percentage of breast cancer patients aged 65 years and older in the U.S. population. However, only 6% and 15% of the patients enrolled in trials of chemotherapy in the adjuvant and advanced disease settings, respectively, were 65 years of age and older, whereas 48% of the U.S. population with breast cancer was in that age group.

A pilot study evaluating potential barriers to enrolling older women with breast cancer in clinical trials found that patients aged 65 years and older with stage II disease were as likely as their younger counterparts to accept enrollment if a trial was offered, but physicians were less likely to offer this option to older patients.⁷² Another putative barrier to enrolling older patients in clinical trials is limited availability of information related to potential treatment toxicities in

this population.⁷² Nevertheless, a study evaluating the effectiveness of providing an educational intervention (involving an education seminar and distribution of educational materials) on enrollment of older patients in cooperative group clinical trials did not find an association between its implementation and increased accrual of older patients.¹⁴²

Task force members agreed that active participation of older women with breast cancer in randomized clinical trials should be encouraged, the determination of causal relationships between a treatment intervention and patient outcome can only be addressed by these trials, and treatment optimization for this group of patients can only be achieved through these studies. However, strict eligibility requirements for many clinical trials, possibly resulting in inclusion of older patients with few or no comorbidities, were mentioned as a potential barrier to the usefulness of extrapolating results from these studies to the

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overall population of older patients. In addition, the diversity of the older population regarding functional reserve and life expectancy adds another level of complexity to the design of clinical studies that include these patients.

The need to make treatment decisions for many older breast cancer patients not well represented by clinical study populations will exist for some time. Thus, several members of the task force suggested that, in the interim, well-designed high-quality population-based studies may be useful to address issues related to this group of patients.^{143,144} Although retrospective studies are limited with respect to the conclusions that can be drawn, they may be more suited to accommodating the population diversity and providing information in the short-term. Collaborative projects across clinical trials are other possibilities for evaluating the risks and benefits of a particular type of therapy in larger numbers of older breast cancer patients.¹³⁰ Table 5 lists

topics for potential future studies that were mentioned by task force participants.

Conclusions

Changes in functional reserve, decreased tolerance to certain cancer therapies, and an increase in competing causes of morbidity and death complicate the treatment decision-making process for older women with breast cancer. Although evidence-based guidance to help balance the benefits and risks of breast cancer treatment in older patients is limited, this population of women is large and will continue to increase for the next few decades. A great need exists to better facilitate individualized treatment based on geriatric assessment, tumor biology, clinical trial results, and the concerns and goals of the patient. Unfortunately, meaningful data to help health care providers and patients make important treatment decisions are scarce.

Table 5 Areas Requiring Future Study

Clinical studies to address pharmacokinetics/ pharmacodynamics of cancer therapies in older patients and effects of drug interactions
Clinical studies of older cancer patients with a coprimary objective of collecting/banking blood and tumor samples to allow for current/future evaluations of factors such as genomic profiles and inflammatory markers
Use of databases to evaluate frequency of women with breast cancer in certain age groups (i.e., < 50 years, 50–69 years, and ≥ 70 years) who undergo breast reconstruction, sentinel node biopsies, and/or radiation therapy
Use of databases to evaluate the frequency of HER2 and ER/PR positivity in breast cancer patients in certain age groups (i.e., < 50 years, 50–69 years, and ≥ 70 years)
Studies of attitudes of older women with breast cancer and their physicians concerning particular treatment options, such as chemotherapy and breast reconstruction
Long-term survivorship studies to evaluate functional and medical long-term effects of treatments, especially effects on bone marrow and heart
Studies on relationship of tumor-related biology and host-related biology as it impacts outcomes of patients with breast cancer (older vs. younger)
Population-based/retrospective studies to address issues in older woman with breast cancer who are precluded from evaluation in prospective clinical trials because of the heterogeneous nature of the population

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

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Post-test

Please circle the correct answer on the enclosed answer sheet.

1. Which statement is TRUE regarding breast cancer?
 - a. The median age of patients with breast cancer is 55 years.
 - b. Approximately 20% of breast cancer cases occur in women 75 years of age or older.
 - c. The U.S. population of women 65 years or older is expected to increase by 20% in the next 25 years.
 - d. Census Bureau projections indicate that 35 million individuals in the U.S. will be 65 years or older by 2030.
2. Which of the following areas related to breast cancer in the older women was NOT considered controversial by the task force?
 - a. The design of clinical trials involving older women with breast cancer
 - b. An understanding of the attitudes and biases of older women with breast cancer with respect to treatment choice
 - c. The need for randomized clinical trials involving older women with breast cancer
 - d. Defining the older breast cancer patient by a specific chronologic age cut-off value
3. Which of the following statements about physiologic reserve is FALSE?
 - a. Physiologic reserve progressively declines with age.
 - b. Limitations in physiologic reserve are most apparent during times of stress.
 - c. Age is a good predictor of the rate of decline of physiologic reserve.
 - d. Supportive care measures administered during cancer treatment can help minimize toxicity risks associated with limited physiologic reserve.
4. According to a National Vital Statistics Report, what is the average life expectancy for an 85- or 86-year-old woman in the United States?
 - a. 2 to 3 years
 - b. 4 to 5 years
 - c. 6 to 7 years
 - d. 9 to 10 years
5. Which of the following patients is LEAST likely to be a good candidate for chemotherapy with capecitabine?
 - a. A 66-year-old woman with renal insufficiency
 - b. A 72-year-old woman with hypertension and osteoporosis
 - c. A 67-year-old woman with congestive heart failure
 - d. A 75-year-old woman with a history of deep venous thrombosis and arthritis
6. Which statement regarding breast cancer in the older woman is TRUE?
 - a. Breast cancer tumors in women 65 years or older are less likely to be hormone receptor-positive and more likely to be HER2-negative compared with breast cancer tumors in younger women.
 - b. An older woman with breast cancer is more likely to be diagnosed with advanced disease compared with a younger woman with breast cancer.
 - c. An older woman with breast cancer is more likely to be treated with breast-conserving therapy compared with a younger woman with breast cancer.
 - d. In the United States, the incidence of breast cancer in women 65 years of age is higher than in women 75 years of age.
7. Which statement regarding the attitudes and preferences of older women with breast cancer and/or their physicians is FALSE?
 - a. "Expert advice" was identified by several studies as an important factor influencing the treatment choices of older women with breast cancer.
 - b. Results of several studies indicate that older women with breast cancer place a greater emphasis on the impact of treatment options on quality of life compared with younger women with breast cancer.
 - c. The attitudes and preferences of older women with breast cancer is an under-explored area.
 - d. The attitudes and biases of physicians with respect to treating older women with breast cancer are well understood.
8. Which of the following about the Comprehensive Geriatric Assessment (CGA) is FALSE?
 - a. It provides an accurate estimate of breast cancer-specific mortality risk for an individual patient.
 - b. It provides an assessment of "functional age" for an individual patient.
 - c. It leads to the identification of patient problems and the development of a plan for resolving those problems.
 - d. It includes evaluations of mental, nutritional, emotional, and functional status, as well as the presence of comorbidities and level of social support for an individual patient.
9. Which of the following statements regarding patients with early-stage estrogen receptor-negative breast cancer is TRUE?
 - a. It is more common in older compared with younger patients.
 - b. The benefits of chemotherapy with respect to risks of recurrence and mortality appear to depend on patient age.
 - c. There is evidence that the risk of recurrence is highest in the first 5 years after diagnosis.
 - d. Sequential single-agent chemotherapy is the treatment of choice for most older patients.
10. Which of these statements on the findings of clinical studies evaluating the toxicity of adjuvant chemotherapy in older women with breast cancer is FALSE?
 - a. The incidence of trastuzumab-related cardiotoxicity is higher in older versus younger women.

- b. Serum creatinine is a good measure of the ability of the older patient to tolerate chemotherapeutic agents eliminated by the kidneys.
- c. Risk of treatment-related death was found to be higher for older versus younger women receiving anthracycline-based regimens.
- d. Risk of acute myelogenous leukemia/myelodysplastic syndrome is higher for older versus younger women receiving certain types of adjuvant chemotherapy for breast cancer.
11. Which of these statements regarding use of endocrine therapy in older women with breast cancer is TRUE?
- a. Adjuvant endocrine therapy alone without surgery is an option for very frail older women with estrogen receptor-positive disease.
- b. The benefits of adjuvant endocrine therapy in patients with estrogen receptor-positive breast cancer are more pronounced in younger women.
- c. Common side effects of tamoxifen include arthralgias, altered lipid levels, and decreased bone density.
- d. The preferred initial approach for patients with estrogen receptor-positive metastatic disease is single-agent chemotherapy.
12. Which of these statements regarding use of radiation therapy in older women with breast cancer is FALSE?
- a. Women 70 years or older treated for stage 1 (tumor ≤ 2 cm) estrogen receptor-negative breast cancer with breast-conserving surgery and tamoxifen without radiation therapy have a low risk of disease recurrence.
- b. In older women with breast cancer undergoing breast-conserving surgery followed by radiation therapy, the incidence of local failure has been reduced when a “boost” of radiation is added.
- c. A retrospective analysis showed that overall local recurrence rates for women receiving post-mastectomy radiation therapy were similar across age groups.
- d. A retrospective analysis showed that older women with 4 or more positive lymph nodes after mastectomy may have a higher risk of local recurrence than younger women with the same disease characteristics.
13. Which of the following statements regarding enrollment of older women with breast cancer in randomized clinical trials is TRUE?
- a. The percentage of patients with breast cancer 65 years or older is higher in clinical trials involving adjuvant chemotherapy than in clinical trials involving endocrine therapy.
- b. Most patients 65 years or older participating in randomized clinical trials have lower-risk disease.
- c. Older women (≥ 65 years) with stage 2 breast cancer were found to be less likely than younger women to accept enrollment in a clinical trial, if offered.
- d. Most patients 65 years or older participating in randomized clinical trials had few comorbidities.

Post-Test Answer Sheet

Please circle one answer per question. A score of at least 70% on the post-test is required.

1.	a	b	c	d	6.	a	b	c	d	11.	a	b	c	d
2.	a	b	c	d	7.	a	b	c	d	12.	a	b	c	d
3.	a	b	c	d	8.	a	b	c	d	13.	a	b	c	d
4.	a	b	c	d	9.	a	b	c	d					
5.	a	b	c	d	10.	a	b	c	d					

The activity content helped me to achieve the following objectives:

(1 = Strongly disagree; 3 = Not sure; 5 = Strongly agree)

Identify data from clinical trials specifically addressing management of breast cancer in the older patient.

1 2 3 4 5

Estimate life expectancy of age cohorts in the older population.

1 2 3 4 5

Identify specific toxicity issues in older patients.

1 2 3 4 5

Recommend management options for primary, adjuvant, and metastatic disease in older patients.

1 2 3 4 5

Time spent completing this activity?

< 30 min 30 min 45 min 1 hr 1.5 hrs > 1.5 hrs

Please indicate the extent to which you agree or disagree with the following statements:

You were satisfied with the overall quality of this activity.

Strongly agree Agree Undecided Disagree Strongly disagree

Participation in this activity changed your knowledge/attitudes.

Strongly agree Agree Undecided Disagree Strongly disagree

You will make a change in your practice as a result of participation in this activity.

Strongly agree Agree Undecided Disagree Strongly disagree

The activity presented scientifically rigorous, unbiased, and balanced information.

Strongly agree Agree Undecided Disagree Strongly disagree

Individual presentations were free of commercial bias.

Strongly agree Agree Undecided Disagree Strongly disagree

**NCCN Task Force Report:
Breast Cancer in the Older Woman**

Release Date: July 11, 2008
Expiration Date: July 11, 2009

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Signature _____ Date _____

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