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Diagnosis and Treatment of Breast Cancer in the Elderly

Chris E. Holmes MD, PhD; Hyman B. Muss, MD

ABSTRACT As the population of the United States ages, women over the age of 65 have become a prominent cohort in the breast cancer population, with approximately 50% of all new breast cancers occurring in women aged 65 years and older. Early studies in breast cancer often excluded women based on age or comorbidity, leaving physicians and patients with a growing number of diagnostic and treatment options, each of which often carry short-term morbidity risks for potential long-term gain. We review the current data available for diagnosis and treatment of elderly women with breast cancer in both the adjuvant and metastatic disease setting. In addition, the role of screening and new concepts in prevention are discussed with emphasis on the older patient. (*CA Cancer J Clin* 2003;53:227-244.) © American Cancer Society, 2003.

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INTRODUCTION

Breast cancer remains the most common cancer in American women, with an estimated 211,300 new diagnoses in 2003.¹ Aging remains one of the single greatest risk factors for the development of new breast cancer, with the estimated risk of new breast cancer at 1 in 14 for women aged 60 to 79 compared with 1 in 24 women aged 40 to 59 and 1 in 228 women aged 39 and younger.¹ As a result, an estimated 35% of women are over the age of 70 at the time of invasive breast cancer diagnosis.² Almost 50% of women will be aged 65 or older at diagnosis.³ In addition, incidence rates continue to rise for women over the age of 50, a trend not seen in the cohort under 50 years of age.⁴ Currently, the median age of breast cancer diagnosis in the United States is 62.⁴

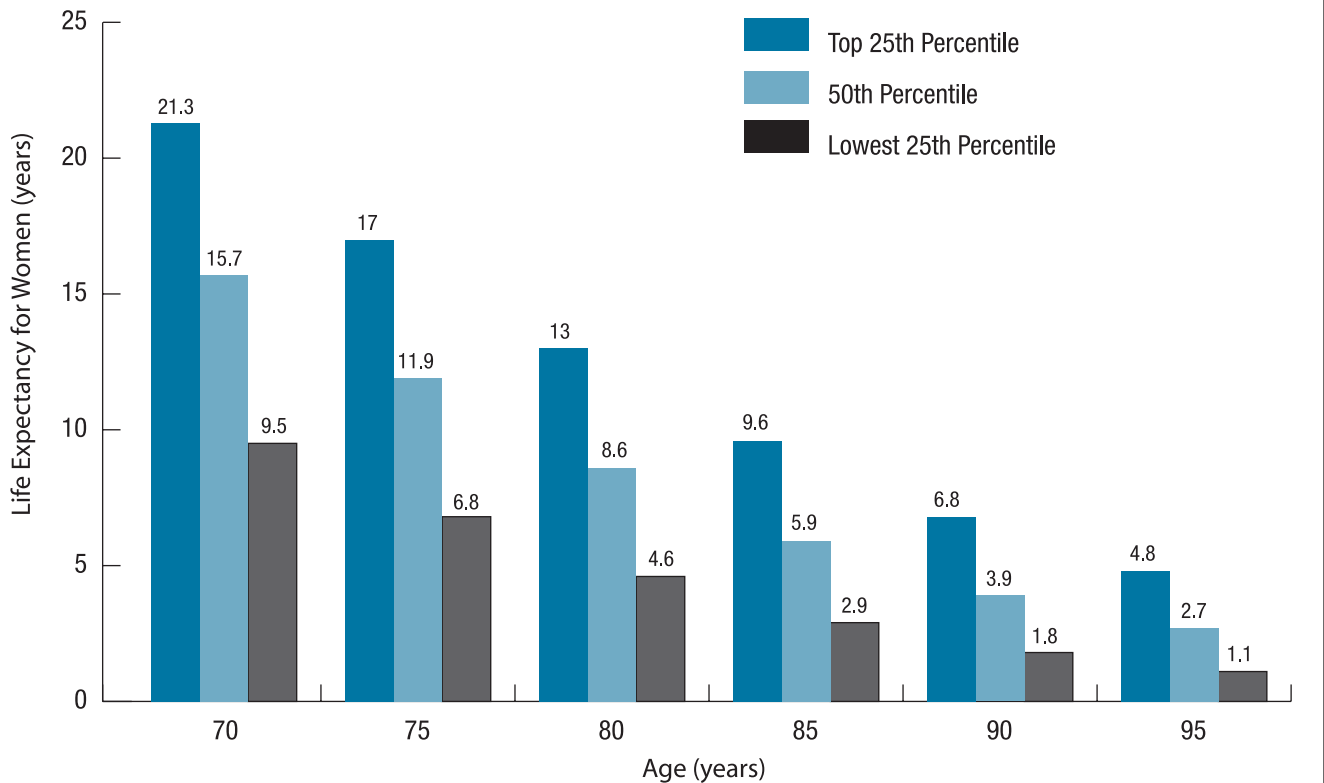
Concurrent with the increased risk of breast cancer throughout a woman's life are data outlining an increase in America's aged population. Although persons aged 65 and older represented 11.3% of the total population in 1980, this number is anticipated to rise to 20% by 2030.³ In addition, age shifts within the 65 and older population have resulted in a greater number of persons 75+ years of age; by 2030, this age group is estimated to account for just under 50% of the total cohort over the age of 65. In total, these staggering figures suggest that women over the age of 65 will become the most prevalent patient cohort in the breast cancer population.

A central concept in decision making in the elderly patient with breast cancer is that of life expectancy. Accurate predictions and knowledge of life expectancy are inherently important in decisions regarding screening older populations using mammography, treatment of the primary lesion, and use of systemic adjuvant therapy. Treatment options now available to the patient with breast cancer often carry short-term risks and toxicities in older women that are tempered by long-term survival gains. The estimated life expectancy for a 65-year-old woman in the United States is estimated at 17.5 years. Although 15 years older, an 80-year-old woman is anticipated on average to live an additional 8.6 years.⁵ An appreciation of this nonlinear relationship between age and life expectancy is crucial in clinical decision making, as the impact of natural disease history and risk/benefit analysis of therapeutic interventions must be made within this context. In addition, variability within an age cohort must be recognized by the clinician. This variability is reflected in Figure 1, which defines life expectancy for women based on the upper, middle, and lower quartiles for that age group. For example, 50% of all women aged 75 are estimated to live an additional 12 years, with 25% of them living over 17 years.⁵ The challenge remains for the physician to accurately estimate an older patient's position among these quartiles based on individual health status, including concomitant comorbidity.

The five-year relative (disease-specific) survival for women diagnosed with breast cancer increases with age until the age of 75. Currently, the projected five-year relative survival for women younger than 45 years of age is 83%, whereas women

FIGURE 1

Upper, Middle, and Lower Quartiles of Life Expectancy for US Women at Selected Ages



Reprinted with permission from Walter LC, Covinsky KE. Cancer screening in elderly patients: A framework for individualized decision making. *JAMA* 2001;285:2,750–756. Copyright© 2001, American Medical Association.

aged 65 to 74 have an expected five-year relative survival of 89%. Five-year relative survival rates also vary based on stage at diagnosis, with overall estimates of 96.8% five-year relative survival with localized disease and 78.4% with regional disease.⁴ Disappointingly, the five-year relative survival estimate of 22.5% for metastatic disease has not changed appreciably over the last two decades.^{4,6} Not unexpectedly, the probability of death due to causes other than breast cancer increases with increasing age.⁷

TUMOR BIOLOGY AND STAGE AT PRESENTATION

Infiltrating ductal carcinoma remains the most common histologic subtype of breast cancer diagnosed in older and younger patients. Older patients have been found to have a greater frequency of tumors with more indo-

lent histologies and an overall more favorable biologic tumor profile.^{6,8} This profile is characterized by a higher percentage of estrogen receptor-positive (ER+) tumors (83% ER+ in patients under 65, 87% to 91% ER+ tumors in patients 65 and older).⁹ The proportion of ER+ tumors continues to rise even within the over-65 cohort, with 87% of patients aged 65 to 74 years having ER+ tumors, compared with 91% of patients aged 85 and older. Reduced proliferation markers (such as S-phase fraction) and HER2/neu negativity are also features of breast tumors in the elderly.⁹

The majority of new patients with breast cancer present with Stage I or II disease: an observation that holds true for both young and old patients.¹⁰ In contrast, the most elderly cohort (age ≥ 85) are more likely to present with metastatic disease (approximately 9%) or an unknown stage at the time of study analysis.¹⁰ Based on recent

data from the National Cancer Institute's Surveillance, Epidemiology and End Results Program, approximately 48% of women with metastatic breast cancer at presentation will be 65 or older.⁴

SPECIAL CONSIDERATIONS IN CLINICAL DECISION MAKING IN THE ELDERLY

The gerontologic community has long recognized the heterogeneity within the elder patient group. The concept of chronological versus physiological age is difficult to quantify, yet is of inherent importance in clinical decision making. Aging affects multiple body systems and remains an individualized process that correlates poorly with chronologic age. The concept of "functional age" has thus emerged. Two surrogate markers of functional age, comorbidities and the gerontologic assessment, are currently used in cancer care decisions.

Current recommendations by the National Comprehensive Cancer Network (NCCN) include the use of a geriatric assessment tool in developing care plans for all cancer patients aged 70 and older.¹¹ No current assessment tool has emerged as the preferred choice. However, it has been suggested that performance status alone is not an adequate assessment of functional status.^{12,13} Basic components of the geriatric assessment can be found in Table 1. In contrast, performance status scales reflect fewer and less varied domains of functioning, such as self-care and ability to ambulate. Physicians are encouraged to become familiar with and use a form of geriatric assessment beyond performance status in decision analysis for older patients with breast cancer.

An assessment of comorbidity is included in all comprehensive geriatric assessments. Although patients of any age may have concomitant illness, the number of comorbidities significantly rises with increasing age.³ In fact, it should be anticipated that a patient with breast cancer between the ages of 70 and 80 will have an average of three to four comorbidities.¹⁰ Figure 2 provides a graphical representation of selected comorbidities and their prevalence in older patients with breast cancer. In addition to concomitant illness, comorbidities in the elderly patient with breast cancer may include

TABLE 1

Basic Components of the Geriatric Assessment Recommended for All Breast Cancer Patients Over the Age of 70	
Parameter	Key Elements of Assessment
Function	Independent performance of Activities of Daily Living (ADLs) Instrumental Activities of Daily Living (IADLs), including transportation, money management, medication management, meal preparation Performance status
Comorbidity	Number and severity of comorbid conditions
Socioeconomic	Social support, including caregivers Access to transportation
Geriatric syndromes	Screen for dementia/depression Vision, gait, balance, and hearing assessment Neglect and abuse
Polypharmacy	Number of medications and potential drug-drug interactions
Nutrition	Weight, nutritional assessment, weight loss

Adapted from Balducci L and Yates J.¹¹

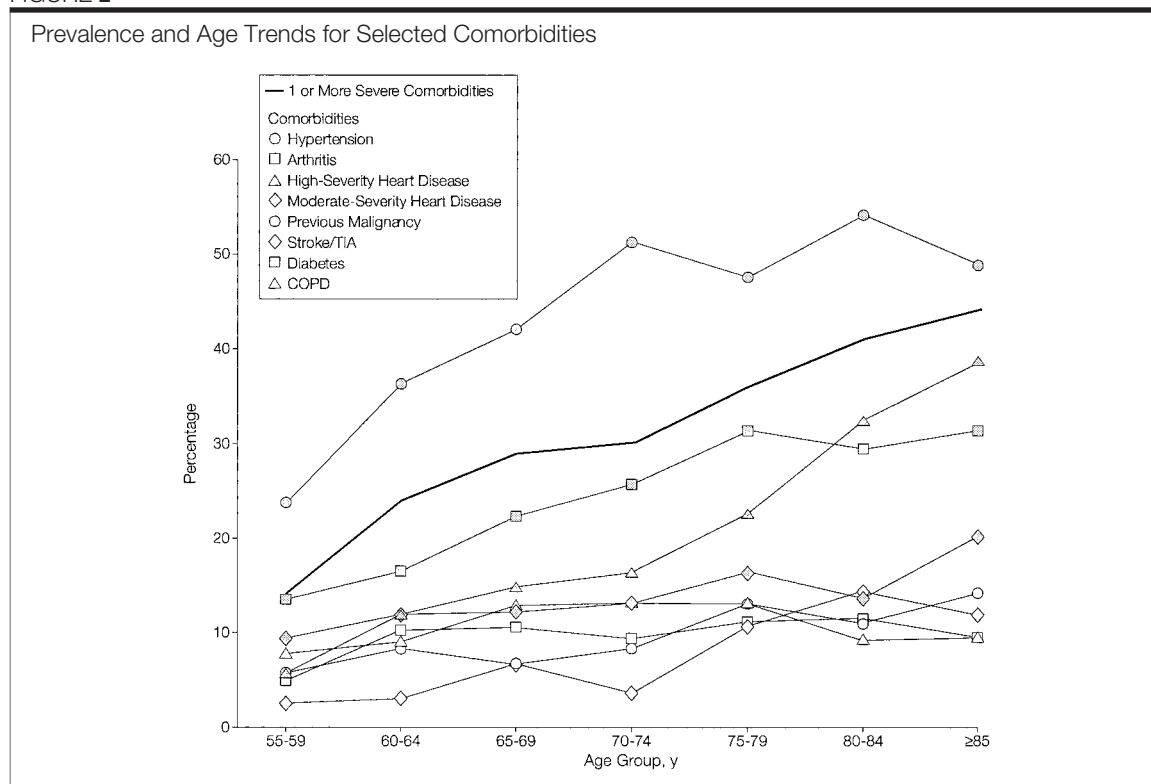
functional status limitations, nutritional impairment, and the presence of geriatric syndromes such as dementia, delirium, and fall risk.

Although the interplay between comorbidity and breast cancer treatment and breast cancer survival remains an underinvestigated area, the presence of three or more comorbid conditions has been associated with a fourfold higher rate of all cause mortality at three years (compared with women with primary breast cancer with no comorbid conditions).¹⁴ A 20-fold higher rate of mortality from causes other than breast cancer was seen in this same patient group. Work that models and estimates the effect of early breast cancer on expected survival has suggested that the benefit of adjuvant therapy decreases with increasing age and comorbidity.¹⁵

CANCER DETECTION AND SCREENING

Current American Cancer Society (ACS) screening guidelines for women aged 40 years

FIGURE 2



Reproduced with permission from Yancik R, Wesley MN, Ries LA, et al.¹⁰

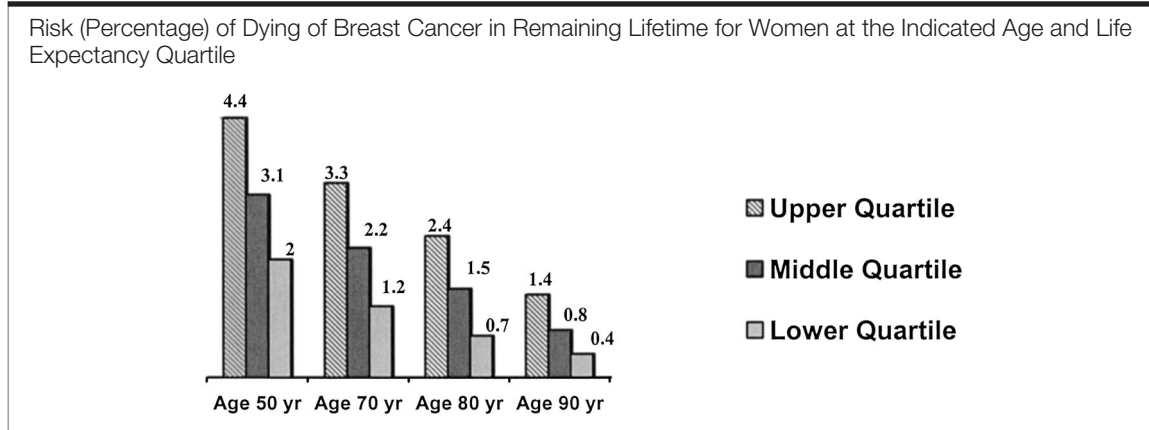
and older include annual mammography and a clinical breast examination as part of a periodic health examination, preferably annually. In addition, women should be told by their health care providers about the benefits and limitations of breast self-examination, and the importance of promptly reporting any new breast symptoms should be emphasized. The most recent ACS guidelines also include a recommendation that screening decisions in older women should consider their current health status and estimated life expectancy, and that a woman should continue to receive a screening mammography as long as she is in reasonably good health and would be a candidate for treatment. Thus, although no specific age currently represents a definitive “cut-off” for screening benefits, patients with comorbidities whose life expectancy is shorter than 5 years would not be anticipated to benefit from routine mammography.¹⁶

Surveillance figures from 2000 reveal that 65.3% of women over the age of 65 had mammography within the past year, a number

slightly higher than the 40- to 64-year cohort (62.5%).² This represents an encouraging trend in elderly breast cancer care, inasmuch as historically there has been a documentation of underuse of mammography in older women. Women over the age of 70 remain underrepresented in screening populations and represent a group in which considerable impact might still be made.¹⁷

Breast cancer presentation characteristics do not differ markedly in the older population. The painless mass represents the most common symptom of breast cancer. In older women, a new lump is likely to represent a malignancy. Breast pain, thickening, swelling, or nipple symptoms such as discharge or retraction should be vigorously pursued in older women. Breasts become less dense with aging, making the clinical examination easier in older women. These differences also translate into an improved positive predictive value of an abnormal mammogram in women over 65 years of age.¹⁸ Given the propensity for a new dominant lump

FIGURE 3



Quartiles are expressed as upper, middle, and lower quartiles. Data approximate those expected for patients who have not received regular cancer screening. Adapted from Walter LC, Covinsky KE.⁵

found on physical examination to represent malignancy and the positive predictive value of mammography in this population, the diagnostic algorithm for postmenopausal patients centers on promptly obtaining a tissue diagnosis by core biopsy or excisional biopsy. Once diagnosed, the TNM staging of breast cancer remains the same for both older and younger women.

A body of evidence suggests that annual mammography screening and clinical breast examination reduce breast cancer mortality in women between 50 and 65 years of age. Except for one Scandinavian trial, prospective, randomized data are not available to guide women or clinicians on the use of mammography screening in the older patients. A meta-analysis of available literature from 1966 to 1993 suggested that annual mammography in women 50 to 74 years of age was shown to reduce breast-cancer related mortality by approximately 26% within 7 to 9 years of screening initiation.¹⁹ The mortality benefits of screening mammography in women 40 to 74 years of age have also been supported by the US Preventive Services Task Force based on a recent analysis of the available literature.^{20,21} This task force concluded that the overall balance of potential benefits of screening mammography versus potential harms improves with increasing age.

Helpful in individualized decision making are estimates for risk of women dying of breast cancer in their remaining lifetimes at a partic-

ular age. As seen in Figure 3, a healthy 70 year old has a greater chance of dying from breast cancer than the average 50 year old (3.3% versus 3.1%, respectively).⁵ In contrast, competing comorbidities at any age over 70 result in a substantially decreased risk of breast cancer death. On a population basis, the number of patients one needs to screen with mammography to prevent one breast cancer-related death is estimated at 242 for the average 70-year-old woman and 533 for the average 80 year old.

PRIMARY PREVENTION OF BREAST CANCER

Prevention of breast cancer in older women has primarily focused on chemoprevention strategies. Traditional breast cancer risk factors including early menarche, family history of breast cancer, late age at birth of first child, late menopause, and a history of benign breast disease are factors that have been defined in the general population but that cannot be altered in the elderly patient. On the other hand, breast cancer risk is increased by approximately 35% among current long-term users of hormone replacement therapy, and the risk among former users returns to that of never-users within 5 years after cessation.²² Observational studies have found increased breast cancer incidence among women who gain weight after menopause and among those who consume

TABLE 2

A Role for Tamoxifen in Breast Cancer Prevention			
Average annual rate of invasive breast cancer and overall risk reduction in the incidence of invasive breast cancer by age for patients enrolled in NSABP-1*			
	Rate per 1000 Women		% Risk Reduction
	Placebo	Tamoxifen	
All women	6.76	3.43	49
Aged ≤ 49 years	6.70	3.77	44
Aged 50–59 years	6.28	3.10	51
Aged ≥ 60 years	7.33	3.33	55

Adapted from Fisher B, Costantino JP, Wickerham DL, et al.²⁵

*High-risk women were randomly assigned tamoxifen versus placebo. Reported median follow-up time = 54.6 months.

more than two alcoholic drinks daily. It seems likely that elderly obese women who lose weight and elderly heavy drinkers who cut back on alcohol consumption may have a lower risk of breast cancer, in addition to the other health benefits of these changes. The most current and commonly used model available to the physician and patient to estimate the older patient's risk of breast cancer is the Gail Model: a computerized algorithm using known risk factor combinations to estimate breast cancer risk over time.²³ Physician and patient access to this risk assessment tool designed to estimate an individual's risk of breast cancer is available at the National Cancer Institute's Web site (<http://bcra.nci.nih.gov/brc/>). For patients with a strong family history of breast or ovarian cancer, the Claus model may be preferable.²⁴

The selective estrogen receptor modulator (SERM), tamoxifen, represents the first agent available to elderly patients that has been shown to decrease the incidence of breast cancer. Data supporting tamoxifen use as a primary prevention was reported in the National Surgical Adjuvant Breast and Bowel Project Trial P-1 (NSABP P-1), which evaluated the efficacy of tamoxifen in reducing the incidence of invasive breast cancer in women at increased risk.²¹ Participants who had a five-year estimated risk of 1.66% or more of developing invasive breast cancer were randomized to receive oral tamoxifen (20 mg daily) or a placebo for 5 years. Of note, the average 60-year-old woman will have a Gail Model Risk of 1.66%. Thirty percent of participants were 60 years or older, with 6% over the age of 70 years. For

women over 60 years of age, tamoxifen reduced the risk of invasive breast cancer by 55%, an outcome comparable with that of other age cohorts (Table 2).

Although promising, these results are currently insufficient to recommend tamoxifen as a primary prevention tool for all women over the age of 60. Tempering the recommendations are the paucity of survival data for patients who received tamoxifen as part of NSABP P-1 and the increased rate of tamoxifen-related adverse events in older patients, including endometrial cancer and vascular events.²⁵ An excellent estimation of the risks versus benefits of tamoxifen in this setting can be obtained from a model that accounts for endometrial cancer and thromboembolic risk (Table 3).

Recent results from the International Breast Cancer Intervention Study—a double-blind, placebo-controlled randomized trial of tamoxifen (20 mg/day for 5 years) in women aged 35 to 70 who were at increased risk of breast cancer—have questioned further the overall

TABLE 3

Tamoxifen Prevention: Risk versus Benefit			
Minimal five-year risk of invasive breast cancer needed for tamoxifen benefit to exceed risk in the general population by age group.			
	Women (years)		
	50–59	60–69	70–79
Uterus	4.0%	>7.0%	>7.0%
No uterus	1.5%	3.5%	6.0%

Data adapted from Gail MH, Costantino JP, Bryant J, et al.²³

risk to benefit ratio of tamoxifen in the prevention setting.²⁶ Although citing a 32% reduction in risk of breast cancer that was not significantly impacted by age, this study found an overall increase in mortality among women using tamoxifen. Unfortunately, although a twofold increase in risk of endometrial cancer was reported in women predominately over the age of 50, overall, elderly women remained underrepresented in this trial (<10% women aged 65 years or greater). Additionally, The Royal Marsden Hospital Chemoprevention Trial (which assessed tamoxifen in the prevention of breast cancer in healthy women with a family history of breast cancer) and the Italian Tamoxifen Randomized Prevention Trial (which assessed tamoxifen in healthy women aged 35–70 who had undergone a total hysterectomy) showed no difference in the incidence of breast cancer in patients receiving tamoxifen.^{27,28} Notably, patients over the age of 70 were ineligible to participate in both of these trials, and women over 60 years of age were not adequately represented.

In 1999, The American Society of Clinical Oncology (ASCO) concluded that, for women with a defined five-year projected risk of breast cancer greater than or equal to 1.66%, “tamoxifen (at 20 mg/day for up to five years) may be offered to reduce their risk.”²⁹ Currently, the use of tamoxifen for cancer prevention in older women remains a complex decision, with the ideal patient being the older woman with a high risk of breast cancer who has no major comorbidities and a high predicted five-year survival. The use of the Gail model for estimating individual patient risk may aid in decision making by the patient and physician. A knowledgeable and experienced clinician should provide counseling regarding potential risks and benefits. Counseling may be aided by models that estimate risk versus benefits in distinct patient groups and accounts for known endometrial cancer and thromboembolic risk (Table 3). Should a patient decide to initiate tamoxifen therapy, it is recommended they receive annual Pap tests and pelvic examinations, as well as periodic eye examinations because of a modest increase in cataract risk.

The use of raloxifene, a SERM with estrogen agonist and antagonist effects distinct from tamoxifen, has been reported in the chemoprevention setting. The Multiple Outcomes of Raloxifene Evaluation trial was originally designed to establish a role for raloxifene in reducing bone fractures in women with postmenopausal osteoporosis. A secondary outcome reported at a median 40-month follow-up was a 76% reduction in the incidence of newly diagnosed invasive breast cancer in the raloxifene treated cohort.³⁰ Of note, the over-60 cohort represented greater than 80% of the patients studied in this trial with the mean age reported at 66. Raloxifene was found to reduce the risk of endometrial cancer in this trial but maintained a thromboembolic risk comparable with tamoxifen. Although the data are promising, raloxifene is currently not FDA approved for breast cancer chemoprevention, and long-term efficacy and safety remain to be established. Patients should be encouraged to enroll in the ongoing STAR prevention trial (Study of Tamoxifen and Raloxifene in breast cancer prevention) designed to assess further the role of tamoxifen and raloxifene in women at high risk for breast cancer. Details concerning eligibility criteria for this trial can be found at <http://www.nsabp.pitt.edu/STAR/Index.html>.

MANAGEMENT OF EARLY STAGE BREAST CANCER

After diagnosis and staging, informed treatment decisions revolve around several major issues, including the following: 1) surgical options, 2) role of radiation therapy, 3) role of adjuvant hormonal therapy, and 4) chemotherapeutic options.

Surgical Options and Considerations in the Elderly Patient

Surgical options and tolerability of surgery in the elderly population are important issues, given that misinformation and misconceptions may limit a woman's options and impact survival. A burgeoning literature suggests that surgery in healthy elderly women is safe and without additional risk compared with their younger counterparts.³¹ Breast-conserving therapy (lumpectomy,

axillary dissection, breast irradiation) has now been shown to be equal in efficacy to more extensive surgical options with no significant differences in overall 20-year survival.^{32,33} Data suggest that elderly women are less likely to be offered or receive breast conservation surgery, with 25% of women aged 80 or older receiving breast preservation compared with 42% of women under 50 years of age.³⁴ In a recent cost analysis, Warren, et al.³⁵ showed no substantial increase in cost for breast conserving surgery and breast radiation therapy compared with modified radical mastectomy in elderly women, thereby obviating cost as a factor in treatment decisions for this population.

Lymph node dissection as an adjuvant to primary tumor removal remains a major component of staging and local control. Currently, no randomized data are available to guide decision making in the cohort over 70 years of age. Given that adjuvant hormonal therapy is recommended in most ER+ patients regardless of nodal status, axillary dissection should be considered for those patients who would be considered for chemotherapy if node-positivity was documented. A second subset of patients in which data seem to favor no nodal dissection are those with ER+, T1 lesions that may be adequately managed with lumpectomy and tamoxifen.^{36,37} Such management is likely to result in a higher frequency of ipsilateral breast tumor recurrence, compared with women treated with lumpectomy, tamoxifen, and breast radiation, but is unlikely to have any significant impact on survival. The sentinel lymph node technique—an axillary node sampling technique using injection of a tracer material into the skin and breast mass and subsequent monitoring of uptake in a small number of axillary nodes—has recently been developed. This technique has undergone preliminary investigation in Stage I and II breast cancer with promising results and is being compared with standard axillary dissection in a large ongoing Phase III randomized trial (NSABP B-32).

The avoidance of surgery in elderly patients has been pursued via investigation of medical management with tamoxifen therapy alone. While a clear difference in survival has been difficult to demonstrate, about 60% to 70% of

patients receive a complete or partial response, with persistence up to five years in 90% of patients.³⁸ Local recurrence rates have been substantial, with consistent estimates of 25% to 30%.^{39–41} Given the significant local relapse rates, standard of practice has not favored primary tamoxifen treatment except in exceptionally frail patients or those with a significant reduction in life expectancy. More recently, aromatase inhibitors have been used in this setting and may prove superior to tamoxifen. However, surgery should still be considered the standard of care, except for very frail patients.

Radiation Therapy in the Elderly

Radiation therapy is generally recommended for all women who receive breast conservation surgery and in postmastectomy women with a high (20% or more) probability of local recurrence.⁴² Postmastectomy radiation in a patient with one to three involved axillary nodes is currently under investigation. An accurate estimate of risks associated with radiation therapy is difficult to ascertain for current patients because reported side effects often reflect treatment techniques that have now been improved and updated. In general, radiation therapy side effects are mild and well tolerated. Common short-term side effects may include skin hyperpigmentation or erythema and mild fatigue.⁴³ Studies using modern radiation therapy techniques have not demonstrated an increased risk of cardiac disease in women treated with radiation therapy alone or in combination with standard dose doxorubicin; however, follow-up on these trials is still limited.^{44,45} The contribution of radiation therapy to lymphedema incidence is confounded by the type of surgery and extent of axillary dissection.

The principal benefit of adjuvant radiotherapy is a significant reduction in isolated local recurrence rates. The 10-year probability of local recurrence is reported at 8.8% for women receiving radiotherapy and 27.2% for those who receive no radiotherapy.⁴⁶ This two-thirds reduction in local recurrence was maintained across all age groups. A substantial impact of radiotherapy on mortality has been

TABLE 4

Age (y)	Tamoxifen		Polychemotherapy	
	Reduction in Recurrence (%)	Reduction in Mortality (All Causes)	Reduction in Recurrence	Reduction in Mortality (All Causes)
<50	45 (8)*	32% (10)	34% (5)	27% (8)
50-59	37 (6)	11% (8)	22% (4)	14% (4)
60-69	54 (5)	33% (6)	18% (4)	8% (4)
70+	47 (3)	34 (13)	—	—
ER+	50 (4)	28% (5)	18% (4)	9% (5)
ER neg	6 (11)	-3% (11)	30% (5)	17% (6)

Data with regards to ER/PR status reflect all patient age subpopulations treated with tamoxifen. Only data reflecting patients 50 to 69 years of age are reported in the polychemotherapy-treated population with regards to ER/PR status. Recurrence and mortality rates are reported based on five years of tamoxifen therapy as reported by the Early Breast Cancer Trialists' Collaborative Group.

*Numbers in parentheses represent standard deviations.

more difficult to elucidate in the elderly population. Meta-analysis suggests an absolute mortality benefit at 20 years of 0.8 to 2.3% based on recurrence risk for women aged 60 to 69 years who receive radiation therapy.⁴⁶ Tempering these results are radiotherapy-related increases in nonbreast cancer-related causes of death, including vascular causes. These hazards increased with advancing age.

Because the standard of care for most early-stage hormone receptor-positive patients now involves the adjuvant use of tamoxifen therapy, we await mature results of several ongoing trials to guide elderly patients in treatment decisions. A recent trial aimed at this question is the National Surgical Adjuvant Breast and Bowel Project B-21 study: a trial designed to enroll patients of all ages to compare local recurrence rates in women with small (<1 cm) tumors treated postoperatively with either breast irradiation and tamoxifen, irradiation alone or tamoxifen alone.⁴⁷ While no difference in survival was noted between the groups, there was a significant reduction in ipsilateral breast recurrence for patients treated with both tamoxifen and irradiation versus either modality alone (2.8% radiation therapy and tamoxifen versus 9.3% radiation therapy alone or 16.5% tamoxifen alone).

Adjuvant Hormonal Therapy in the Elderly

Current recommendations by the National Institutes of Health in a 2000 consensus state-

ment suggest that "adjuvant hormonal therapy should be recommended to women whose breast tumors contain hormone receptor protein, regardless of age, menopausal status, involvement of axillary lymph nodes, or tumor size."⁴⁸ This conclusion is mirrored in recent recommendations from the St. Gallen International Consensus Panel 2001, which now define endocrine-responsive disease as tumors containing as few as 1% of cells staining positive for hormone receptor protein.⁴² Currently, tamoxifen is the most commonly used hormonal therapy, with data supporting a five-year course of therapy. Adjuvant hormonal therapy is not currently recommended for ER negative breast tumors.

Supporting these recommendations are results from the Early Breast Cancer Trialists' Collaborative Group, which demonstrate that five years of adjuvant tamoxifen therapy in known ER+ women results in a 50% proportional reduction in recurrence risk and a 28% decrease in mortality at 10 years.³⁸ An absolute improvement in 10-year survival of 10.9% was observed after five years of tamoxifen therapy in ER+, node positive women. A significant, albeit smaller, improvement in survival of 5.6% was seen in ER+, node negative women as well. As indicated in Table 4, the reduction in risk for both recurrence and death was maintained in women over the age of 70 years. Tamoxifen therapy has additional effects in all women, including bone protective effects, as

well as increased endometrial cancer and thromboembolic risks. In general, all older women with ER+ or PR+ tumors should be considered candidates for hormonal adjuvant therapy. Older women with a history of recurrent venous thrombosis, venous thrombosis on tamoxifen or estrogen therapy, or gynecologic malignancy with a maintained uterus should be considered for aromatase inhibitor therapy in lieu of tamoxifen. A second SERM, toremifene, has recently shown comparable efficacy, benefit, and toxicity profiles to tamoxifen.⁴⁹

Translating annual odds of relapse and death into meaningful individualized care plans remains a challenge for the patient and physicians. Physicians may aid women in better understanding their individual long-term benefits of adjuvant therapy by using easy to understand analysis tables generated by Loprinzi and Thome.⁵⁰ Online programs to predict the benefits of tamoxifen and chemotherapy in the adjuvant setting on both relapse-free and overall survival are available. “Adjuvant!” was developed by Ravdin, et al.⁵¹ [<http://www.adjuvantonline.com>] and the “Numeracy” program was developed by Loprinzi and Thome⁵⁰ [<http://mhs.mayo.edu/adjuvant>]. Both use 1998 overview data.

Recent publication of the ATAC trial (Arimidex,TM tamoxifen alone or in combination) suggests that use of the aromatase inhibitor, anastrozole (ArimidexTM) in the adjuvant setting may confer additional disease-free survival for postmenopausal, hormone receptor positive women (89.4% three-year disease-free survival versus 87.4% three-year disease-free survival for tamoxifen, $P < .05$).⁵² In this study, 9,366 patients were treated with tamoxifen or anastrozole alone or in combination with a median follow-up of 33.3 months. All women were postmenopausal, with about 45% over the age of 65 years at the time of enrollment. Conflicting side-effect profiles were reported in the study, including a reduction in venous thromboses in the anastrozole group but an increase in bone fractures in this group compared with tamoxifen treated patients. Although the elderly patient cohort is well represented in this trial, the conflicting early side-effect data and the relatively early follow-up for

initial data assessment (30 months) suggest that treatment with tamoxifen should continue to be the endocrine therapy of choice. A similar recommendation has been made by an American Society of Clinical Oncology task force.⁵³ The choice of tamoxifen versus anastrozole in the elderly patient initiating adjuvant hormonal therapy today is difficult and should be discussed on an individual patient basis in light of the new ATAC data. Anastrozole has recently been approved by the United States Food and Drug Administration for use in the adjuvant setting in postmenopausal women with ER+ early breast cancer.

Chemotherapeutic Options in the Adjuvant Setting

Cytotoxic chemotherapy represents the second systemic therapy available to women in the adjuvant setting. The most common adjuvant chemotherapy choices include cyclophosphamide, methotrexate, and fluorouracil (CMF), and doxorubicin and cyclophosphamide (AC). Individual tumor characteristics (such as HER2/neu status) are currently under study in determining their influence on adjuvant chemotherapy choice. In addition, the use of agents such as taxanes and trastuzumab (a monoclonal antibody that targets HER2) in the adjuvant setting is currently under intensive investigation given the success of these agents in the advanced breast cancer treatment setting.

While there is a paucity of data for women over the age of 70, a 1998 meta-analysis by the Early Breast Cancer Trialists' Collaborative Group clearly delineates the benefits of chemotherapy for women up to the age of 69 years (see also Table 4).⁵⁴ In this study, ER+ patients in the age group of 60 to 69 years who received chemotherapy demonstrated a proportional risk reduction of 18% ($\pm 4\%$) in recurrence and 8% ($\pm 4\%$) in mortality. This proportional reduction was about half as great as that seen in women under the age of 50, with patients in this latter age group demonstrating a 34% ($\pm 5\%$) and 27% ($\pm 5\%$) reduction in recurrence and mortality, respectively. For women aged 50 to 69 years, these benefits translate into an absolute gain in 10-year sur-

TABLE 5

Recommendations for Adjuvant Therapy for Postmenopausal Women With Operable Breast Cancer		
Risk Group	Tumor Characteristics	Treatment
Node-negative		
Low risk	ER and/or PR-positive \leq 2 cm, Grade 1	Tamoxifen or none
Average/high risk	ER and/or PR-positive with either size > 2 cm or Grade 2-3	Tamoxifen + chemotherapy or tamoxifen*
Node-positive	ER/PR-negative	Chemotherapy
	ER/PR-positive	Chemotherapy + tamoxifen or tamoxifen*
	ER/PR-negative	Chemotherapy

Adapted from Goldhirsch, Glick, Gelber, et al.⁴²

*Based on available evidence, chemotherapy is considered an acceptable option in this patient population. Individual risk profiling and patient preference may justify the use of tamoxifen alone.

vival of 2% for node negative disease and 3% for node positive disease. Interestingly, the absolute benefit on recurrence was the same regardless of nodal status. Because only 609 of 18,718 (~3%) women randomized to chemotherapy or no chemotherapy and included in the meta-analysis were aged 70 years or older, no meaningful conclusions could be drawn for women in this age group. An NCI-supported randomized trial comparing standard adjuvant chemotherapy (CMF or AC) with the oral agent, capecitabine, is currently underway for women aged 65 years and older with high-risk node-negative and node-positive breast cancer: this trial will also assess quality of life, compliance, and tumor biology issues in these patients (Cancer and Leukemia Group B trial 49907; details available at: <http://www.cancer.gov>).

Although meta-analysis data support a decrease in mortality for all subsets of postmenopausal women given chemotherapy, the administration of chemotherapy to all postmenopausal and elderly women remains controversial. It is clear that postmenopausal women with ER+ tumors derive greater benefit from adjuvant tamoxifen therapy compared with chemotherapy alone. For women over 50 years of age, a proportional risk reduction in death of about 25% is estimated with adjuvant tamoxifen alone, compared with about 10% for adjuvant chemotherapy alone (AC).⁵⁰

The benefit of combined adjuvant chemoendocrine therapy in women over the age of 65 years is difficult to assess due to a paucity of randomized trials that incorporate this age group. The addition of anthracycline-containing regimens to tamoxifen in women 50 years

or older has been reported to increase three-year survival (93% ACT [doxorubicin, cyclophosphamide, tamoxifen] versus 85% for tamoxifen alone, $P = .04$).⁵⁵ However, the proportion of women older than 65 years of age is not specified in this study. Additionally, significant differences in five-year disease-free survival are seen with the addition of CMF-based regimens in ER+ women under the age of 65 years receiving tamoxifen (63% for CMF+T versus 55% T alone, HR 0.71).⁵⁶ In contrast, women with ER+ tumors over the age of 65 in this study demonstrated no appreciable benefit in five-year disease-free survival from the addition of CMF. The true benefit of combined chemoendocrine therapy utilizing standard CMF and AC regimens for our more elderly patients remains to be elucidated in well-conducted clinical trials. Recently, the French Adjuvant study group has reported five-year follow-up results comparing tamoxifen alone versus tamoxifen plus epirubicin in the adjuvant setting for 338 patients over the age of 65 with node positive, operable breast cancer. In this study, the relative risk of relapse was 1.85 with tamoxifen alone versus epirubicin plus tamoxifen ($P = .02$) without significant increases in toxicity noted.⁵⁷

While the data are incomplete for all women in the adjuvant setting, the elderly subgroups remain underrepresented in the current clinical trials available for decision analysis. International consensus panel recommendations for adjuvant therapy in postmenopausal women are outlined in Table 5.⁴² While consensus panel guidelines in 1998 contained separate

recommendations for elderly women (> 70 years of age), the 2001 guidelines did not. Of note, the current guidelines remain appreciably the same as those recommended for the elderly cohort in 1998.⁵⁸

Given that a modest survival benefit is seen in most groups of patients receiving adjuvant chemotherapy, a renewed interest in tolerability, risks, and side effects in elderly patients has now come to the forefront for both physicians and patients. Several potential short-term toxicities of adjuvant chemotherapy exist, including nausea, emesis, mucositis, alopecia, and neutropenia. Nausea and emesis have been substantially decreased with the use of 5HT3 receptor antagonists. Alopecia occurs in nearly 100% of patients receiving anthracyclines, whereas alopecia (either complete or incomplete) is seen in approximately 50% to 70% of women receiving CMF. For some older patients, these short-term toxicities continue to play a major role in decision making. The impact of chemotherapy on older persons' long- and short-term cognitive function remains underinvestigated in the literature; any impairment in cognitive function noted while the patient is undergoing chemotherapy should precipitate withholding of further therapy until an evaluation by a cognitive specialist is complete.

Historically, concerns regarding chemotherapy-related cardiac toxicity and general tolerability have played a major role in the limited use of chemotherapy in the elderly population. Anthracycline-containing regimens such as AC are favored in younger patients due to improved disease-free and overall survival, compared with non-anthracycline-containing regimens.⁵⁴ Concerns regarding substantially increased cardiotoxicity in older patients for these regimens have not been borne out in several small retrospective series. A comparable incidence of side effects including myelosuppression, cardiotoxicity, and a decrease in quality of life in relatively healthy women over 65 has recently been reported by Dees, et al. using the common adjuvant regimen, doxorubicin and cyclophosphamide.⁵⁹ Crivellari, et al.⁵⁶ have evaluated the toxicity of a standard adjuvant therapy regimen, CMF (cyclophosphamide, methotrexate and fluorouracil), in older patients. Important side effects of CMF includ-

ing Grade 2 and 3 mucosal toxicity (diarrhea, gastritis, and mucositis) and hematologic toxicity were increased in patients older than 65 years. Underappreciated is an increased risk of thromboembolic disease in patients receiving chemotherapy with or without tamoxifen.⁶⁰

The delineation of both the physical and psychological tolerability of chemotherapy needs urgent investigation to guide physicians and elderly patients appropriately. To aid the physician and patient in decision making, Extermann, et al.¹⁵ offer a series of graphs and tables for estimating the potential benefit of adjuvant treatment on mortality for patients with different levels of comorbidity aged 65 to 85 years. Currently, treatment decisions must be individualized with attention to potential toxicities as well as life expectancies, significant comorbidities, and patient preference. Interest in chemotherapeutic regimens with potential reduced toxicity has burgeoned; however, no current data support their use over standard regimens in the elderly population.

MANAGEMENT OF LOCALLY ADVANCED BREAST CANCER

Preoperative (neoadjuvant) chemotherapy and endocrine therapy for women with locally advanced disease have gained renewed interest. Unfortunately, studies have not targeted the elderly population, and the benefit of this strategy in this cohort is difficult to delineate. Beneficial downstaging has been demonstrated in the National Surgical Adjuvant Breast and Bowel Project B-18 trial, which involved more than 1,500 women with T1 to 3, N0 to 1, M0 breast cancer who were randomly assigned preoperative versus postoperative chemotherapy (AC). This study had a substantially younger population with slightly greater than 50% of patients under the age of 50 years. Preoperative chemotherapy resulted in increased tumor shrinkage and rate of breast conservation therapy versus postoperative therapy. Importantly, an improved survival benefit has not been demonstrated for those patients receiving preoperative chemotherapy.⁶¹ Preliminary data only are available from ongoing trials using

taxane therapy in the neoadjuvant setting; definitive recommendations regarding the role of neoadjuvant chemotherapy await mature data. For elderly patients with large initial lesions who wish to pursue breast-conserving surgery, the decision to proceed with neoadjuvant therapy remains an individualized decision neither supported nor refuted for patients in their age cohort.

Endocrine therapies including tamoxifen and aromatase inhibitors show potential in the neoadjuvant setting as well. Recent results of a trial comparing letrozole with tamoxifen in the preoperative setting demonstrated a significantly higher tumor response rate for letrozole (60% versus 48%).⁶² Although long-term results are awaited on survival benefits, endocrine therapy can be effective in downstaging patients with ER+ tumors and may be considered in elderly patients, particularly given the ease of administration and favorable toxicity profile. As indicated earlier, the initial use of tamoxifen therapy alone has been associated with a significant response in 60% to 70% of patients; however, local recurrence rates largely preclude use of this single modality outside the neoadjuvant setting.

RECOMMENDATIONS FOR FOLLOW-UP CARE

Given the improved survival and advances in patient care, women of all age groups and their physicians now face the question of appropriate follow-up care. Although this question is not addressed completely by primary investigations in both younger and older women, ASCO currently recommends patient education regarding symptoms of breast cancer recurrence as well as a monthly breast self-examination.⁶³ These recommendations may be obtained online through the ASCO Web site (<http://www.asco.org>). Annual mammography and pelvic examination also remain a part of follow-up care. The need for annual pelvic examination is emphasized further in the woman on tamoxifen therapy. ASCO guidelines also suggest physician office visits every 3 to 6 months (to include history and physical exam) for 3 years, followed by visits every 6 to

12 months for 2 years, and then annually. The latter recommendations are predicated on the majority of breast cancer recurrences occurring within five years of primary treatment. Currently not recommended are routine chemistries and blood counts, additional radiological evaluation including chest roentgenography, or tumor markers.

MANAGEMENT OF METASTATIC BREAST CANCER

All treatment of metastatic breast cancer is palliative. Treatment of the older woman with metastatic breast cancer requires an establishment of realistic goals, physician and patient selection among a growing number of palliative treatment options, and an emphasis on patient quality of life. Overall average survival for patients with metastatic breast cancer is estimated at two to three years. However, it should be recognized that, in up to 10% of patients, breast cancer may behave as a chronic disease with patients living 10 years or longer. Quality of life and symptom palliation remain the cornerstones of decision making for women of all age groups with metastatic breast cancer.

The overall treatment strategy for older women with metastatic breast cancer is essentially the same as that for younger women and has recently been comprehensively reviewed.⁶⁴ The use of endocrine therapy for postmenopausal women with ER+ and/or PR+ tumors without rapidly progressive and immediately life threatening disease is the initial treatment of choice. Tamoxifen or an aromatase inhibitor is favored as first line therapy in all women. For those women who relapse at least 1 year after completing adjuvant tamoxifen therapy, tamoxifen may still be effective. Recent studies suggest that antiestrogen naïve patients or those without exposure for greater than one year may derive a similar and perhaps modestly superior benefit from aromatase inhibitors compared with tamoxifen.⁶⁵ The NCCN guidelines for 2002 currently suggest that either tamoxifen or an aromatase inhibitor may be an appropriate choice in these patients; these practice guidelines are available to all physicians and patients at <http://www.nccn.org>.

The anticipated duration of initial response to hormonal therapy is approximately one year. Hormonal therapy should persist until disease progression. Recent (2002) NCCN Practice Guidelines continue to recommend nonsteroidal aromatase inhibitors such as anastrozole or letrozole as the preferred second-line agent in postmenopausal women with prior antiestrogen therapy or those who are within one year of antiestrogen therapy.

The selective estrogen receptor down-regulator, fulvestrant, has been shown to be similar in efficacy to the aromatase inhibitor anastrozole and has been approved recently for use in patients who have disease progression on antiestrogens.⁶⁶ For patients who respond to therapy or who have long periods of disease stability (more than 24 weeks), third-line therapy with progestins or antiestrogens should be considered. Other strategies include retrying previous effective agents or changing from one aromatase inhibitor class to another (trying exemestane after progression on anastrozole or letrozole).

The use of chemotherapy for metastatic breast cancer in the elderly should be considered in endocrine refractory patients with evidence of disease progression or new/increasing symptoms attributable to metastatic disease. ER and PR negative patients without life-threatening metastases should be considered for one course of endocrine treatment: responses may be seen in 10% to 20% of these patients.⁶⁷ Christman, et al.⁶⁸ have found that elderly women in overall good health are able to tolerate chemotherapy as well as their younger counterparts. These same women also derive benefit from combination chemotherapy with similar response rates and overall survival as their younger counterparts. In general, the severity and duration of myelosuppression is more pronounced in older patients, an observation that has not translated into increased mortality.⁶⁸

Choice of chemotherapeutic regimens and agents is dependent on individual patient characteristics and potential interacting comorbidities. Historically, anthracycline-based regimens commonly have been used in combination with other agents. A review of the literature

supports the use of sequential single agent therapy for women with metastatic breast cancer.⁶⁴ Table 6 outlines the major chemotherapeutic options and special considerations needed in treating an older population.

An emerging area in metastatic breast treatment is based on molecularly guided agents such as trastuzumab, a humanized monoclonal antibody that binds the transmembrane glycoprotein receptor encoded by the HER2 gene. HER2 testing is now recommended in all metastatic breast cancer patients. Trastuzumab has been associated with low toxicity and response rates of about 20% when given as a single agent and has shown response rates of 30% to 70% when given in combination with taxanes or vinorelbine with moderate toxicity.^{69–71} A recent randomized trial demonstrated that the addition of trastuzumab to both anthracycline-based and paclitaxel chemotherapeutic regimens in HER2 overexpressing patients resulted in improved disease-free progression, longer duration of response, and improved median survival.⁷⁰ Of note, the median age in this trial was fewer than 55 years, although the trial included women over the age of 70. Unfortunately, investigators identified increasing age as a significant risk factor for cardiac dysfunction in 27% of the patients receiving anthracycline, cyclophosphamide, and trastuzumab. The United States Food and Drug Administration has now approved the use of trastuzumab and paclitaxel as first-line therapy in patients with HER-2 overexpressing metastatic breast cancer.

Supportive Care for Elderly Patients Receiving Chemotherapy

Bone metastases are a major complication of metastatic breast disease and may be present in up to 80% of patients. Common complications and sources of morbidity associated with bone metastases are pain, pathologic fractures, spinal cord compression, and hypercalcemia. Bisphosphonates act by inhibiting osteoclastic bone resorption and have been studied in the prevention and treatment of metastatic lytic bone lesions for over a decade. Randomized trials have now demonstrated that pamidronate reduces overall skeletal morbidity including pain and skeletal complica-

TABLE 6

Agent	Special Considerations
Anthracyclines (epirubicin and doxorubicin)	Limited cardiotoxicity in older patients. Avoid use of doxorubicin in patients with an EF <50%. Significant alopecia, myelosuppression, nausea, and emesis potential. New liposomal doxorubicin preparation demonstrates improved side-effect profile. Epirubicin in metastatic breast cancer associated with reduced cardiotoxicity, nausea, and myelosuppression than doxorubicin.
Cyclophosphamide Methotrexate	Elimination decreased in patients with impaired renal function. Excretion dependent on renal function, which decreases with age. Dose adjustments based on renal function in older women showed reduced toxicity. Patients with pleural effusions and ascites at risk for prolonged drug elimination and toxicity.
Fluorouracil	No increased GI toxicity noted in breast cancer patients (as compared with colorectal cancer patients). Fluorouracil-induced cardiac toxicity does not appear to increase with age.
Capecitabine (Xeloda)	Oral 5-fluorouracil allows for home-based therapy. No trials in older patients. Minimal myelosuppression. Hand-foot syndrome is frequently dose limiting, and diarrhea is possible. Age does not significantly affect pharmacology. Dose reduction for renal impairment. Monitor carefully for neuropathy.
Vinca alkaloids (vincristine/vinblastine) Vinorelbine	Pharmacokinetics comparable in older and younger women. Favorable toxicity profile in elderly patients.
Taxanes (paclitaxel/docetaxel)	Limited data in older patients. Hepatic impairment increases toxicity. Sensory and motor neuropathy and fluid retention (docetaxel) side effects. May cause mild to moderate myalgias and arthralgias.
Gemcitabine*	Age-related differences in pharmacokinetics. Favorable toxicity profile with mild myelosuppression as a single agent.
Herceptin (trastuzumab)	Humanized monoclonal antibody approved for use in patients with HER-2/neu overexpressing tumors. Early reports of cardiotoxicity may limit use in older women.

*Not FDA approved for use in breast cancer.

tions when added to either standard hormonal⁷² or chemotherapeutic regimens⁷³ for metastatic breast cancer patients with at least one lytic bone lesion. Notably, these trials specifically did not address the older age cohort. While neither trial demonstrated a significant survival advantage in groups receiving pamidronate, the reduction in morbidity and a paucity of substantial pamidronate-related side effects suggest the older patient with metastatic breast cancer and evidence of lytic bone destruction should be offered monthly bisphosphonates therapy. Zoledronic acid (Zoledronate), a newer bisphosphonates, has been shown to be as effective as pamidronate in a limited number of patients and offers the advantage of a shorter infusion time.⁷⁴

Aggressive supportive strategies are often recommended in older patients receiving chemotherapy. The Senior Adult Care Task Force Report suggests the maintenance of hemoglobin levels greater than or equal to 12 g/dL with

erythropoietin compounds in older patients receiving cytotoxic chemotherapy.¹¹ The relief of fatigue, promotion of functional independence, and a reduction in neutropenia in the elderly underpin this recommendation. ASCO guidelines from 2000 suggest high-risk patients may benefit from secondary and primary prophylactic use of colony-stimulating factor (G-CSF, GM-CSF).⁷⁵ No recommended age guidelines are identified in these recommendations. Notably, the guidelines principally identify those patients at high risk based on the anticipated incidence of febrile neutropenia associated with a particular chemotherapy regimen. Special circumstances, including poor performance status and comorbidity, are noted in these guidelines as situations in which colony stimulating factors might be used without definitive supporting data. Given the large financial burden that may be incurred by the patient, as well as the small but real side-effect

profile (including bone pain), the use of growth factor support should be individualized based on therapy risk and patient physiologic status. Limited data suggest that older patients derive the same hematologic responses to growth factors as younger patients.⁷⁶

ELDERS AND CLINICAL TRIAL
PARTICIPATION/RESEARCH: BARRIERS AND
OPPORTUNITIES

As the US population continues to age, the need for increased enrollment in clinical trials of elderly women with breast cancer is imperative. The discrepancy between trial eligibility and trial enrollment in patients over the age of 65 is substantial, with one study reporting only 35% of women over the age of 65 years offered participation, compared with 51% of women fewer than 65 years of age.^{77,78} Interestingly, when older patients are offered an opportunity to participate in a clinical trial, their acceptance rate was approximately the same as younger patients.⁷⁷ Barriers to enrollment of elderly patients in clinical trials have included prior exclusion based on age alone, as well as strict enrollment criteria that excluded patients with even mild abnormalities in renal, hepatic, or cardiovascular functions. The latter significantly impacts those older patients with comorbidities. Limited physician and patient expectation regarding outcome and potential treatment, lack of financial support, educational opportunities, and social support have also been identified as barriers to trial participation by the elderly.⁷⁹ Coexisting concerns in the literature concerning the care of the elderly patient with breast cancer are an imperative to “first do no harm” and to avoid unfavorable and age-biased recommendations and treat-

ment practices without sufficient data. This observation underscores the need to pursue rigorous clinical trials in order for the physician community to appropriately guide patients with regard to therapeutic options that contain both significant risks and benefits. The National Institutes of Health and National Institute of Aging offer major grant opportunities for research related to cancer in aging (refer to <http://www.nia.nih.gov/funding>).

CONCLUSIONS

Several pivotal concepts that guide clinical decision making and choice of treatment options in the elderly patient with breast cancer include 1) the average life expectancy of the patient at a given age, 2) comorbidities and their impact on diagnostic and therapeutic options as well as life expectancy, and 3) potential treatment benefits (including survival versus quality of life benefits) versus risks of a proposed treatment strategy. An understanding of the physiologic, physical, and psychological barriers to breast cancer diagnosis and treatment—as well as the recognition of the delicate interplay between patients’ and physicians’ expectations—remains pivotal in providing appropriate breast cancer care to the older patient. Despite the magnitude of the problem of breast cancer in the elderly, many issues surrounding diagnosis and treatment of the elder patient with breast cancer are complicated by inadequate representation of this group in clinical trials. As we await additional evidence to support clinical practice, physicians should encourage participation of the elderly patients with breast cancer in clinical trials and emphasize shared decision making in breast cancer care.

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