Published in final edited form as:
*Clin Geriatr Med*. 2012 February ; 28(1): . doi:10.1016/j.cger.2011.10.002.

# Early breast cancer in the older woman

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## SYNOPSIS

Breast cancer is a disease associated with aging; there is a rise in both breast cancer incidence and mortality with increasing age. With the aging of the US population, the number of older adults diagnosed with breast cancer and the number of breast cancer survivors is on the rise. The majority of cases of breast cancer are diagnosed with early stage (non-metastatic) potentially curable disease. This article will review the treatment of early stage breast cancer in older adults including a focus on the risks and benefits of surgery, radiation therapy, endocrine therapy, chemotherapy, and trastuzumab. Although the majority of studies to date demonstrate that older adults experience similar benefits from most multimodality treatments for breast cancer as compared to younger adults, these studies have primarily been performed in healthy and fit older adults. There are limited data at the extremes of age or in those patients with significant comorbidity or functional decline. A primary question facing the doctor and patient is whether the breast cancer is likely to impact the patient's life expectancy or quality of life. If so, then the risks and benefits of treatment must be considered with a final decision regarding therapy made in the context of the patient's preferences. This article will review the toxicities (both short- and long-term) from common cancer therapies in early breast cancer. Finally, the decision as to type of secondary screening and prevention of future breast cancers must also be weighed against the life expectancy of the older adult.

## INTRODUCTION

Breast cancer, like many common cancers, is primarily a disease of older adults. In the United States, the median age at the diagnosis of breast cancer is 61 years, and 41% of breast cancers are diagnosed in women age 65 or older.[1] The median age at death from breast cancer is 68 years, and 57% of deaths from breast cancer occur in those > age 65.[1] Early stage breast cancer in the older adult, as in the younger adult, is a curable disease in the overwhelming majority of patients. Almost 1.5 million women over age 65 in the United States are breast cancer survivors, and over 820,000 of these women are age 75 or older.[1]



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Disclosures

Dr. VanderWalde is a full-time employee of Amgen and owns stock in Amgen

Breast cancer incidence and mortality increases with age (see Table 1). Older adults are both more likely to develop breast cancer than younger adults, and are significantly more likely to die of breast cancer. For example, the oldest women (age 85+) have approximately 3 times the incidence of breast cancer as compared to the youngest population (age 40–44),and they have 13 times the mortality rate.[2] In this manuscript, we review the data regarding breast cancer in the older adult including a discussion of tumor biology, treatment modalities, and the short- and long-term risks and benefits of therapy in the older adult.

## BREAST CANCER BIOLOGY IN THE OLDER WOMAN

There are conflicting data regarding whether there are true differences in breast cancer biology with increasing age. Some evidence suggests that the biology of breast cancer in older adults is less aggressive.[3–6] A review of SEER and San Antonio databases demonstrated that older women are more likely to have hormone receptor positive and HER2 negative disease, which generally carries a more favorable prognosis.[7] On the other hand, there is also evidence to support the hypothesis that breast cancer is more aggressive in older adults. For example, one study showed up to 19% of older women to have luminal B tumors, which are more likely to present with higher grade, larger size, and increased propensity to spread to lymph nodes, despite being hormone receptor positive.[8]

Despite the conflicting data regarding breast cancer biology and aging, there are sound data suggesting that the specific characteristics of the tumor should be utilized to guide the risk of relapse and the need for therapy. For example, Oncotype DX (Genomic Health) is a 21 gene assay which yields a score that predicts both breast cancer recurrence and chemotherapy efficacy. Among 668 patients with node-negative breast cancer treated with tamoxifen, Oncotype DX accurately predicted whether there was a low, intermediate, or high risk of distant recurrence and was also predictive of overall survival. The gene signature's predictive effect was ultimately independent of age.[9]

## TREATMENT PATTERNS IN OLDER ADULTS WITH BREAST CANCER

There are ample data suggesting a difference in treatment patterns between older and younger adults with breast cancer. There are several possible reasons for these differences including other comorbidities (outweighing the risk of cancer or influencing treatment tolerance), poorer perceived or actual treatment tolerance,[10] poorer access to care, and/or patient or physician preference.[10–16] The challenge that faces older adults and their physicians is that there is less evidence based data to guide these decisions in older adults secondary to the under enrollment of older adults on clinical trials.[17–22] For example, a review of Southwest Oncology Group therapeutic trials revealed that in studies of breast cancer, only 9% of women enrolled were age 65 or older, despite the fact that 49% of the population of women with breast cancer were in this age group.[17] Patients over 70 made up only 20% of subjects enrolled in US Food and Drug Administration registration trials from 1995 to 1999, though they made up fully 46% of the US cancer population in that period.[18] The under-enrollment of older patients with breast cancer contributes to a poorer understanding of the risks and benefits associated with cancer treatment and might be a contributing factor for the difference in treatment patterns in this population. However, recent studies focusing specifically on older patients have successfully reached their target accrual, demonstrating the feasibility of studying this population of patients and successfully accruing to clinical trials which guide key clinical questions.[23–24]

## TREATMENT

Treatment for breast cancer is multimodality in nature. Patients with early breast cancer are generally treated with surgery with or without radiation therapy for local control of the

disease. Treatment options for the control of systemic disease include chemotherapy, endocrine therapy (for hormone receptor positive disease) and trastuzumab (for Her2 positive disease). Each of these modalities of therapy have specific risks and benefits as they relate to the older patient, and each will be discussed in turn.

## Surgery

Surgical treatment options for breast cancer generally include mastectomy or breast conserving surgery (BCS, also known as lumpectomy), with sentinel lymph node sampling and axillary lymph node dissection if the sentinel node reveals tumor. However, it is unclear whether older women receive surgery as often as younger adults, and whether they receive similar modalities of surgery. One study demonstrated that older women are less likely to receive BCS (as compared to mastectomy or no surgical treatment), with only 21% of adults age 80 or older receiving this modality.[25] Single-institution studies suggest that older women have comparable rates of receiving definitive surgery to younger adults.[26–27] One institution reported that 95% of women age 70 or older received primary surgery, and 89% received axillary lymph node dissection as appropriate.[27]

It is recognized that age alone is not the most important factor in the determination of surgical risk.[28–29] The Preoperative Assessment of Cancer in the Elderly (PACE)[29–33] incorporates elements of the comprehensive geriatric assessment, a brief fatigue inventory, performance status measures, and the American Society of Anesthesiologists grade.[31] In a prospective international study, 460 consecutive older adults with cancer underwent PACE prior to surgery. Poor performance status, dependence in instrumental activities of daily living (IADLs), and moderate to severe fatigue were found to be independently associated with an extended hospital stay in the post-operative period.[32] Another recent trial demonstrated that measures of frailty, disability, and comorbidity are good predictors of 6-month post-operative mortality or institutionalization after major surgery in older adults.[34] However, even at the extremes of age, breast cancer surgery carries a low risk of morbidity and mortality and can be done under local anesthesia with sedation if the risk of general anesthesia is too great.[35]

Other investigators have evaluated whether we need to perform surgery for breast cancer in older adults, particularly if there is an alternative treatment option, such as an anti-estrogen. The data from individual studies are conflicting. A Cochrane Review was reported on seven trials of women age 70 or older that randomized women to surgery with or without tamoxifen as compared to tamoxifen alone (without surgery). The women were all considered to be fit for general anesthesia and surgery. Nevertheless, despite improved progression-free survival among women treated with surgery as compared to those treated with tamoxifen alone, there was no benefit seen in overall survival.[36] The impact of cancer progression on overall quality of life remains a consideration.

The role of axillary lymph node dissection is an area of active study. A randomized study of 473 women with hormone-receptor positive early breast cancer compared surgery with axillary dissection versus surgery alone in women over age 60 with clinically node negative disease. The median age was 74 years and all women received tamoxifen following surgery. At a median follow-up of 6.6 years, both disease free survival and overall survival were similar in the two groups. (Hazard ratio [HR] for disease free survival- 1.06; 95% CI, 0.79 to 1.42; P = .69; HR for overall survival- 1.05; 95% CI, 0.76 to 1.46; P = 0.77). The authors concluded that it is possible to avoid axillary dissection in women age 60 or older with hormone receptor positive early breast cancer and clinically node negative disease, provided that the patients receive endocrine therapy following surgery.[37]

An interesting dilemma exists for prevention of future cancer specifically among those older patients who would like to reduce their risk of developing future breast cancer by prophylactic removal of the breasts. In older women with a personal history of breast cancer, the benefit of prophylactic surgery is uncertain. In a large retrospective cohort study of women diagnosed with unilateral breast cancer between 1979 to 1999, it was found that of 1072 women who had a prophylactic contralateral mastectomy following their first cancer, only 0.5% developed a contralateral breast cancer, as compared to 2.7% of those who underwent surveillance alone. (HR 0.03, 95%CI 0.006–0.13).[38] While the risk of developing contralateral breast cancer increased with age, this difference was not statistically significant (HR age >70 vs age <39 5.3, 95% CI 0.4–73). As such, making a conclusion about the relative efficacy of contralateral prophylactic mastectomy in older adults as compared to younger adults is difficult.[38] Additionally, any overall survival benefit achieved by prophylactic surgery for breast cancer has been shown to be minimal to non-existent.[38–39] A recent analysis found that the relative cost-effectiveness of prophylactic mastectomy decreases with increasing age, to the point that the authors conclude that it is not cost-effective to perform prophylactic mastectomies in patients with a first diagnosis at age >70 as fewer quality adjusted life years are gained by prophylactic surgery in the older cohort than in the younger.[40] Even in women with a genetic mutation that predispose to development of future breast and ovarian cancers (such as BRCA-1 and 2), prophylactic mastectomy and oopherectomy may not be of significant benefit in older women. A decision analysis by Schrag et al revealed that in women with a first breast cancer diagnosis at age 60 or older, the gains in life-expectancy from contralateral mastectomy and bilateral oopherectomy are modest at best, and range from 2 weeks in low penetrance mutations to 1.1 years in high-penetrance mutations.[41]

## Radiation Therapy

In the general population of women with early breast cancer radiation treatment to the preserved breast is standard practice following breast conserving surgery (BCS).[42] When combined with whole-breast radiation, BCS has equivalent survival as compared to mastectomy alone. Additionally, it is standard to administer radiation to the chest wall following mastectomy if the tumor size is greater than 5cm or if there are 4 or more positive lymph nodes.[43] Radiation is used as an adjunct to surgery, and decreases the risk of both local recurrence and subsequent metastatic spread.

In older women, studies have shown that whole-breast radiation given per guidelines following surgery decreases in-breast recurrences and some studies suggest that it lengthens disease-specific and overall survival as well. Use of radiation, however, decreases with increasing age. Truong et al reported on 4,836 patients aged 50–89 with early stage breast cancer who were treated with BCS, of whom 773 were older than 74 years. After a median follow-up of 7.5 years, radiation omission was associated with significantly increased relapse rates as well as poorer disease-specific and all-cause survival. As many as 26% of women age >74 did not receive radiation, as compared to only 7% of those age 50–64.[44] In women age >50 with small, node-negative breast cancer, radiation when added to tamoxifen following BCS has been shown to significantly decrease the risk of breast or axillary recurrence as compared to tamoxifen alone.[45] A randomized trial evaluated the benefits of radiation following breast conserving therapy in women age 70 and older with stage I hormone receptor positive breast cancer who received systemic therapy with tamoxifen. After a median of 5 years of follow-up, receipt of radiation decreased the rate of local or regional recurrence from 4% to 1%; however, there was no difference in overall survival and the majority of patients who died succumbed to comorbid diseases other than breast cancer.[46] A recent update of these data appear to confirm a lack of survival benefit of radiation even after 10.5 years follow-up, though the risk of local recurrence remained

higher in the tamoxifen-only group (9% in tamoxifen only arm vs. 2% in tamoxifen plus radiation, p=0.0001).[47] A retrospective analysis of the SEER-Medicare database evaluated the efficacy of radiation in women age 70 or older in the treatment of small node-negative cancer. A 4% absolute lower risk of second ipsilateral breast cancer (in-breast recurrence) was seen in the cohort who received radiation. Women age 70–79 with few comorbidities benefited most, while women age 80 or older or those with significant comorbidities were less likely to benefit.[48]

On the other hand, patients with high risk breast cancer, even after mastectomy, seem to clearly benefit from radiation. Using a SEER database review, Smith et al identified 11,594 women age 70 or older who received mastectomy for breast cancer, and classified them as either low, intermediate, or high risk based on tumor size and lymph node involvement. The authors then looked to see whether receipt of post-mastectomy radiation therapy improved survival in women with high-risk disease (defined as tumor over 5cm and/or 4 or more positive lymph nodes). After a median follow-up of 6.2 years, radiation therapy was associated with a significant improvement in overall survival (HR 0.85, p=0.02). There was no corresponding improvement seen among low or intermediate risk patients.[49]

Radiation therapy seems to be relatively well tolerated in older adults,[47, 50] though unique issues that might identify those older women as less likely to tolerate radiation include poor functional status, preexisting pulmonary or cardiac disease, and decreased cognition.[51] Additionally, shorter courses of radiation, such as single-dose intraoperative radiotherapy, are under study and show promise in preventing in-breast recurrences in a subset of patients with early breast cancer with possibly fewer long-term side effects.[52]

## Systemic Therapy

Various types of systemic therapy are utilized in early breast cancer, including endocrine therapy, cytotoxic chemotherapy, targeted therapy with trastuzumab, or various combinations of these. A list of agents commonly used in the adjuvant setting in early breast cancer is provided in Table 2.

**Endocrine therapy—**Women with hormone receptor-positive breast cancer benefit from adjuvant endocrine therapy following surgery and/or radiation for early breast cancer, both in improved relapse-free and overall survival. The two classes of endocrine therapy available in the post-surgical setting for post-menopausal women are the selective estrogen receptor modulator (tamoxifen) and the aromatase inhibitors (AIs).

Both tamoxifen and AIs have been shown across age groups of postmenopausal women with hormone receptor positive disease to lower the risk of relapse and increase overall survival.[53] Five years of tamoxifen has been shown to decrease the annual rate of breast cancer recurrence by 51% and this benefit is preserved regardless of patient age.[53] Therapy with an aromatase inhibitor is only beneficial in postmenopausal women. Randomized studies in the adjuvant setting of aromatase inhibitors verses tamoxifen demonstrate that aromatase inhibitors are associated with an improvement in disease free survival; however there is no difference in overall survival.[54–55] As such, it is generally recommended that older adults with hormone-receptor positive disease (the overwhelming majority of cases) be treated with aromatase inhibitors; however, the optimal strategy of employing AIs (ie. whether to use AIs alone or in sequence following tamoxifen) remains unclear and the risks and benefits of each drug need to be considered for the individual patient.[56] Treatment with tamoxifen is associated with an increased risk of endometrial cancer and thromboembolism. On the other hand, tamoxifen has a beneficial effect on bone health in older women and improves the lipid profile. Aromatase inhibitors do not increase the risk of endometrial cancer; however, they do carry a risk of thromboembolism (although this risk is lower in

comparison to tamoxifen). In addition, treatment with aromatase inhibitors is associated with a loss in bone mineral density.[57–60] Attention to maximizing bone health is important in all older adults; however, it is particularly important in women receiving therapy with an aromatase inhibitor.

While tamoxifen and AIs are both generally well tolerated in the older adult, their efficacy may be hindered by non-adherence or discontinuation of endocrine therapy.[61] One study reported the observation that adults over age 65 are 28% less likely to be adherent to endocrine therapy than younger adults.[62] However, studies are conflicting, and while some suggest age is a risk factor,[61–62] others do not.[63–64] Regardless, rates of discontinuation of endocrine therapy are higher than might be expected in survivors of early breast cancer,[64–65] and as such, it remains important to determine which older adults are likely to benefit from and which are more likely to develop intolerable side effects of therapy with endocrine therapy. During therapy, asking about medication usage is essential, and if adverse effects prevent adherence, consideration should be given to switching agents. Because endocrine therapy is oral it is also important to ensure that the patient is able to manage her own medications, or has someone to help manage them on her behalf.

**Chemotherapy—**The decision of when and whether to offer adjuvant chemotherapy to a woman with early breast is one of the more difficult clinical decisions in the field, regardless of the age of the patient. Chemotherapy in early breast cancer may be given prior to surgery (neoadjuvant) or after surgery (adjuvant). The purpose of neoadjuvant or adjuvant chemotherapy is to decrease the risk of relapse and mortality from breast cancer by treating micrometastatic disease. A randomized study demonstrated equivalent efficacy in terms of relapse-free and overall survival whether the chemotherapy is given in a neoadjuvant or adjuvant fashion.[66] Neoadjuvant therapy may also serve to decrease tumor size in order to enable the option of breast conservation.

The decision of whether or not to administer chemotherapy is based on weighing the tumor characteristics (risk of relapse and mortality), the patient characteristics (such as their functional status, comorbidity, social support, risk of toxicities), and the patient's preferences. Tools such as Oncotype DX, a 21-gene panel assay, can be utilized among patients with node negative hormone receptor positive disease to predict the risk of relapse as well as the efficacy of adjuvant chemotherapy.[9]

Data from the Early Breast Cancer Trialists' Collaborative Group suggests a decreasing benefit from adjuvant chemotherapy with increasing age; however, the authors acknowledge that too few women over the age of 70 were included in randomized clinical trials to reliably inform these data.[67] In contrast, a meta-analysis of patients enrolled in randomized clinical trials for node positive disease demonstrated that older women appear to derive similar benefit from the experimental chemotherapy arm as younger individuals.[68]

Prospective randomized clinical trials have demonstrated a benefit to standard adjuvant chemotherapy in an older adult. The Cancer and Leukemia Group B Study 49907 randomized women age 65 or older with early breast cancer to receive either standard chemotherapy (doxorubicin and cyclophosphamide [AC] or cyclophosphamide, methotrexate, and 5 fluorouracil [CMF]] or capecitabine, an oral chemotherapeutic agent not routinely given as a single agent for the adjuvant treatment of breast cancer. Treatment with capecitabine was associated with a significantly worse relapse-free survival, with women receiving capecitabine more than twice as likely to relapse as those receiving standard chemotherapy. Additionally, a statistically significant overall survival benefit was seen with standard chemotherapy (HR 1.85, 95% CI 1.11–3.08). Rates of clinically significant adverse events were similar across study arms, with a slight increase in the rate of febrile

neutropenia in the standard chemotherapy arm as compared to capecitabine (8–9% vs 1%).[69] Rates of adherence to capecitabine (an oral agent) were 75% and were not related to age.[70] Another prospective randomized controlled trial has been reported that randomized women older than age 65 with early breast cancer to either tamoxifen alone or tamoxifen combined with six cycles of chemotherapy.[71] The authors found that a statistically significant decreased risk of relapse after 6 years of follow up with the chemotherapy group (HR of relapse in tamoxifen alone arm 1.93, 95% CI 1.70–2.17). Older adults also did not appear to exhibit unacceptable levels of toxicity with the chemotherapy regimen given.

Other studies have been geared towards developing therapeutic strategies to avoid exposure to anthracyclines which are associated with a risk of cardiac toxicity. A randomized clinical trial in the general population of early breast cancer demonstrated that a taxane containing regimen (docetaxel + cyclophosphamide for 4 cycles [TC]), was superior to a standard anthracycline based regimen (doxorubicin + cyclophosphamide for 4 cycles [AC]) in both disease-free and overall survival, even among the older adults on the study.[72] Toxicity was similar across age groups, though older women had more febrile neutropenia with TC and more anemia with AC.

In summary, adjuvant chemotherapy when indicated should not be withheld from older women with early breast cancer due to age alone, and that chemotherapeutic agent choice can be similar to that which would be used in the younger adult.[73] However, the clinician must be particularly attuned to potential toxicities and should develop an individualized plan with the patient to determine the likelihood of benefit given other risk factors.

**Toxicity Considerations with Chemotherapy in the Older Woman with Breast Cancer—**Supportive care given together with chemotherapy is of primary import among older adults, who have increased risk of both bone marrow suppression and GI toxicity from cytotoxic agents. Older adults with breast cancer are at a higher risk of neutropenia with chemotherapy. In a study of adults age 65 and older with lung, breast, or ovarian carcinoma, or non-Hodgkin lymphoma, patients were randomized to receive prophylactic pegfilgrastim (Neulasta; Amgen) before every cycle of various chemotherapeutic regimens, or secondary pegfilgrastim administered only at the discretion of the treating physician. Median age was 72 years. Of the 686 patients with solid tumors analyzed, the rate of grade 4 neutropenia was 54% (95% CI 53%–64%) in those who received growth factor by physician discretion, and only 22% (95% CI 18%–27%) in those who received growth factor after every cycle. The prevalence of febrile neutropenia was 10% in the physician discretion arm, but only 4% in the every-cycle arm (p=0.001). Patients who received pegfilgrastim after every cycle were significantly less likely to experience dose delays, dose reductions, or receive antibiotics. The authors conclude that growth factors should be used proactively in all older adults to support the optimal delivery of chemotherapy.[74]

Because of the risk of neutropenic infections among older adults, multiple consensus panels including the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), the European Organization for Research and Treatment of Cancer (EORTC), and the International Society of Geriatric Oncology (SIOG), have recommended up-front prophylactic granulocyte-colony stimulating factor (G-CSF) in any older adult treated with chemotherapy regimens with febrile neutropenia rates comparable to those seen with the CHOP regimen (cyclophosphamide, vincristine, doxorubicin, and prednisone) given for non-Hodgkin lymphoma.[75]

Though it has been thought that older patients experience less chemotherapy-induced nausea and vomiting than younger patients, this remains a potentially serious complication. Older adults tend to have decreased nutritional reserve and fluid stores, and thus periods of

prolonged nausea or vomiting can quickly lead to dehydration, electrolyte imbalances, and malnutrition. The combination of doxorubicin and cyclophosphamide, commonly used in adjuvant therapy, is in particular highly emetogenic, while the agents are at least moderately emetogenic when given alone.[76] Therefore, it is important to anticipate moderate to severe nausea and vomiting in older adults receiving adjuvant chemotherapy for breast cancer,[77] to deliver adequate prophylactic anti-nausea medication,[78] and to have a low threshold to initiate further treatment for symptoms.[75] Additionally, older adults are more likely to develop diarrhea, dehydration, and mucositis with chemotherapy than younger adults,[79] and are less likely to tolerate these complications than younger adults.[75] Therefore early treatment of the symptoms, including intravenous fluid, should be delivered to older adults with a low threshold for hospitalization if needed.[75]

**Predicting Chemotherapy Toxicity in Older Adults with Cancer—**Investigators have sought to determine whether items in a comprehensive geriatric assessment (CGA), in combination with those captured in daily clinical practice, can identify patients at risk for chemotherapy toxicity. A multi-institutional prospective study of 500 patients with cancer identified the following factors predictive of chemotherapy toxicity: 1) age > 73, 2) cancer type (GI or GU), 3) receipt of poly-chemotherapy, 4) receipt of standard dosing of chemotherapy, 5) creatinine clearance <34 ml/min (Jelliffe formula using ideal weight), 6) hemoglobin (male: <11 g/dL, female: <10 g/dL), 7) the need for assistance with taking medications, 8) >1 fall in the last 6 months, 9) hearing impairment, 10) limited in walking one block, and 11) decreased social activities due to physical or emotional health.[80] The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) study evaluated 562 patients with cancer and found that albumin, need for assistance with instrumental activities of daily living, lactate dehydrogenase, and diastolic blood pressure were predictive of hematologic toxicity, and hemoglobin, creatinine clearance, albumin, self-rated health, comorbidity, ECOG performance status, mini-mental status exam, and mini-nutritional assessment were predictive of non-hematologic toxicity.[81]

**Trastuzumab—**Approximately 25% of breast cancers overexpress the HER-2 receptor on the surface of tumor cells, making those cancers potentially susceptible to HER2 directed therapy.[82] While many anti-HER2 agents are being studied in early breast cancer, the only agent currently widely approved or used in this setting is trastuzumab (Herceptin; Roche), a monoclonal antibody that prevents dimerization of HER2 and has been shown to increase disease free and overall survival in early breast cancer when given in combination with chemotherapy.[83–84] Older age has been shown to correlate with increased likelihood of developing therapy-related cardiotoxicity, however, and this risk is compounded when trastuzumab is given with an anthracycline containing regimen.[85–86] Additionally, baseline cardiac comorbidities, such as diabetes or preexisting coronary artery disease may predispose to higher rates of trastuzumab-related cardiotoxicity in older adults.[87]

Single-agent trastuzumab has a relatively favorable side effect profile, however, trastuzumab given in combination with chemotherapy is associated with increased toxicities in older adults. An ongoing trial known as RESPECT is randomizing women age 70–80 with HER 2-positive early breast cancer to therapy with either trastuzumab alone or trastuzumab with standard chemotherapy.[88] This trial may guide clinicians in the future to determine whether older women with early stage HER2- positive breast cancer who receive trastuzumab can safely forgo adjuvant chemotherapy and the associated toxicities.

# FOLLOW-UP OF THE OLDER WOMAN WITH BREAST CANCER

## Long-Term Side Effects in the Older Adult

**Constitutional Side Effects—**Fatigue is one of the most pervasive side-effects of breast cancer treatment, may occur in up to 80–90% of patients treated,[89] and is the most commonly described side effect in women who undergo chemotherapy for breast cancer.[90] However, being a subjective symptom, it is notoriously difficult to measure and as such may be often neglected.[91] Cancer-related fatigue differs from normal fatigue in that it is more insidious in onset, more pervasive, and more severe.[92] Breast cancer survivors often continue to experience fatigue well after the completion of treatment. This appears to be the case regardless of the modality of treatment used, though the percentage may be somewhat higher in those who received both radiation and chemotherapy than in either group alone.[93] Because of the effect on functioning, fatigue can be quite debilitating in older adults, who may have limited mobility, energy, or functioning at baseline. Fatigue could potentially be the difference between an active, functioning older adult, and a bed-bound dependent one. Broekel et al surveyed 61 women with a history of breast cancer who had completed adjuvant chemotherapy an average of 18 months previously and compared their self-reports of fatigue to 59 women with no history of cancer. The authors found that women with a history of cancer reported an average level of fatigue 50% greater than the controls, were more likely to report that fatigue interfered with their overall quality of life, their ability to work, and their concentration.[94] While it has been postulated that older patients with cancer may have more severe fatigue than younger patients with cancer, definitive evidence for this is lacking.[91] While there are few studies comparing rates of fatigue in older adults to younger adults, one study demonstrated that age-related factors tend to play a larger role than cancer-related factors in older long-term survivors of cancer.[95] Yoga, nutritional therapy, and sleep therapy have been shown to decrease fatigue in survivors.[91,96] Various exercise programs have been associated with decreased fatigue and improved quality of life in patients with breast cancer.[91,97] Evaluation and treatment of comorbid conditions including depression and anemia may help to decrease contributing factors associated with fatigue. It is particularly important to evaluate for and treat depression in older adults as it is commonly missed in routine evaluation.

The term “chemobrain” has been utilized to describe the subjective cognitive effects of chemotherapy. However, this entity is complex, is likely multifactorial, and impacts a subset of the population who receive therapy.[98] It has been noted that patient report of neurocognitive impairment often does not correlate with neurocognitive impairment on performance tests.[98–100] Older adults may also be vulnerable to neurocognitive changes associated with cancer therapy. One study among older adults who received chemotherapy for breast cancer showed a significant decline in cognitive function at least in the short term, though the differences in degree of cognitive decline was not compared to the non-geriatric adult population.[98] A more recent study found that age and baseline cognitive reserve appear to be associated with rates of cognitive changes with chemotherapy, though these changes begin to improve over time, and it is not clear what the impact of these changes are on functioning.[101] Further research is needed to identify the magnitude of the problem, the risk factors for cognitive decline, and interventions to help minimize this risk.

**Cardiac Side Effects—**Anthracyclines (doxorubicin, daunorubicin, epirubicin) can be associated with a dose-dependent progressive decrease in systolic left ventricular ejection fraction, indistinguishable from CHF due to other causes. The cardiomyopathy can also present as symptomatic or asymptomatic diastolic dysfunction.[102] Age at the time of treatment is also a risk factor. One study showed that adults over the age of 65 who received anthracycline-containing chemotherapy for breast cancer had a hazard ratio for developing

cardiomyopathy of 2.48 (95% CI, 2.10 to 2.93) compared with the non-chemotherapy group. Likewise, the hazard ratio was 1.38 (95% CI, 1.25 to 1.52) for overt congestive heart failure.[103] Using the SEER database, Pinder et al. found that women between the ages of 66–70 treated with anthracyclines for breast cancer had a hazard ratio of 1.26 (95% CI, 1.12 to 1.42) for developing cardiomyopathy compared to those who hadn't received anthracyclines. However, the relationship was not linear. In women aged 71–80, there was no association between chemotherapy type and cardiomyopathy.[104]

Trastuzumab is also associated with cardiomyopathy, especially when given in conjunction with an anthracycline. In NSABP B-31, cardiac events were measured among patients receiving AC (doxorubicin and cyclophosphamide) followed in sequence by trastuzumab and paclitaxel. The cumulative incidence of symptomatic heart failure at 3 years was 4.1% in the trastuzumab group, compared with 0.8% in the non-trastuzumab group. No cardiac deaths were reported in the trastuzumab group. Increasing age and decreasing EF after AC and before starting trastuzumab were independent risk factors for developing CHF.[85]

**Skeletal Side Effects—**Older adults with bone loss are more likely to have increased risks of falling, fracture, disability, and even mortality. Aromatase inhibitors are potent inhibitors of estradiol production and hence markedly decrease circulating levels of estrogen.[105] The depletion of estrogen has a negative effect on bone density.[105–107] A number of Phase III clinical trials reporting on the adjuvant use of aromatase inhibitors have reported increased risk of bone loss and osteoporotic fracture in patients taking aromatase inhibitors as compared to those taking either tamoxifen or not on therapy.[57–60, 108–115]

Calcium, Vitamin D, and weight-bearing exercise strengthen bones and decrease the risk of development of osteoporosis. Effective screening strategies and treatment should be employed in older adults at risk for treatment related bone loss.. The American Society of Clinical Oncology has recommended for all women with breast cancer over the age of 65 to have annual DEXA scans of the spine and hip and to take calcium and Vitamin D supplements. If the osteoporosis threshold (T-score of $< -2.5$) is reached, addition of a bisphosphonate is recommended.[116] For patients with osteopenia, the decision to utilize bisphosphonates should be individualized.

## INTEGRATING GERIATRIC PRINCIPLES INTO ONCOLOGY TREATMENT DECISIONS

An integral part of the cancer treatment decision is to determine whether the patient will die *of* cancer, or simply *with* cancer. Furthermore, one needs to weigh whether the cancer is likely to cause significant disability for the patient in his/her lifetime.[117] While younger patients with breast cancer can usually anticipate that having a diagnosis of cancer will shorten their life expectancy without treatment, the same may not be true for older adults. The prevalence of comorbid conditions increases with age.[118–119] Competing comorbidities increase the risk that the older adult with cancer may die of another cause.,[120] In this setting an indolent cancer may not influence the lifespan or quality of life of the patient.

However, estimating life expectancy is a complex process that extends beyond chronological age. Tools and prognostic indices developed and reported in the geriatric literature can help assist oncologists in estimating life expectancy. Walter and Covinsky, using US life-table data, described life expectancy by upper, middle, and lower quartiles. For example, while the median additional life expectancy for a 70 year old woman is 15.7 years, 25% of 70 year-old women can expect to live an additional *2*1.3 y*e*ars or more, while 25% of these women can only expect an additional 9.5 years or less.[121] Carey et al developed a functional morbidity index that takes into account age, gender, and self-reported

functional status to stratify adults age 70 or older into varying risk groups for 2-year mortality.[122] Lee et al developed a similar tool for clinicians to determine 4-year mortality. This tool takes into account comorbid conditions as well as age, gender, and functional status.[123] Estimation of life-expectancy may have significant intra-observer variability and these tools could help to more precisely fine tune our estimates.

A Comprehensive Geriatric Assessment (CGA) has been used in the general geriatric population to assist in an evaluation of life expectancy, to identify vulnerable older adults, and to guide interventions to optimize care in this population.[124–126] The domains evaluated in a CGA include functional status, comorbidity, cognitive function, psychological state, social support, nutritional status, and a review of concurrent medications. Consensus guidelines recommend the routine use of the CGA for older adults with cancer; however the exact means of integrating a CGA into oncology practice is an area of active research.[127–128] It has been postulated that the CGA might be used to guide treatment strategies in older adults with cancer,[126129–130] and various cancer-specific geriatric assessments have been proposed.[130–131] In addition, researchers are utilizing the CGA to identify factors predictive of chemotherapy toxicity risk[80– 81] as well as nomograms for overall survival.[132] The majority of this research has been performed among patients with all cancer types; however, specific studies focusing on the treatment of older adults with breast cancer is underway.

## CONCLUSION

Care of the older woman with early breast cancer is of particular import to both the oncologist and geriatrician due both to the prevalence of the disease in this population as well as the subtleties necessary in individualizing treatment decisions. In general, older women are able to tolerate many of the same modalities of treatment for early breast cancer as younger women, but special consideration must be given to future life-expectancy, co-morbidities, and other elements that might be identified using a comprehensive geriatric assessment. Both short and long-term side effects of cancer therapies can be clinically important in the older woman, and appropriate screening and support for these toxicities are necessary.

## Acknowledgments

Dr Hurria’s research has been supported by NIH research grants K23 AG026749 and U13 AG038151.

She has received additional research funding from Celgene and GlaxoSmithKline, and has also served as a consultant to Amgen and Genentech

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**Table 1**

Incidence and mortality of female breast cancer by age in the United States 1995–2007 (Altekruse et al 2010)

| Age | Incidence (per 100,000 person-years) | Mortality (per 100,000 person years) |
|---|---|---|
| 40–44 | 121 | 14 |
| 45–49 | 186 | 23 |
| 50–54 | 226 | 35 |
| 55–59 | 280 | 49 |
| 60–64 | 349 | 62 |
| 65–69 | 394 | 73 |
| 70–74 | 410 | 87 |
| 75–79 | 434 | 108 |
| 80–84 | 422 | 134 |
| 85+ | 339 | 177 |

**Table 2**

Systemic therapies commonly used in early breast cancer

| **Chemotherapy:** | **Cyclophosphamide** |
|---|---|
| | Doxorubicin |
| | Epirubicin |
| | Paclitaxel |
| | Docetaxel |
| | Fluorouracil (5-FU) |
| | Methotrexate |
| | Carboplatin |
| Endocrine Therapy | Tamoxifen |
| | Letrozole |
| | Anastrazole |
| | Exemestane |
| Targeted therapy | Trastuzumab |