Adjuvant Therapy of Breast Cancer in Women 70 Years of Age and Older: Tough Decisions, High Stakes

In this review we will discuss how to evaluate older breast cancer patients, including estimating survival, defining functional limitations, and providing guidelines for optimal adjuvant therapies.

Introduction

We had a 78-year-old patient tell us recently, “I am too old to get breast cancer,” but sadly, she was wrong. A woman born today has an average life expectancy of 80 years. Less appreciated is that for women 70, 75, and 80 years of age, the average remaining life expectancy is 16, 12.5, and 10 years, respectively.[1] Breast cancer in the US remains the most common cancer in women, with an incidence and mortality rate that rise dramatically with increasing age. Women below the age of 65 years have a breast cancer incidence of 82 per 100,000 women, while those 65 years and older have a rate that jumps to 404 per 100,000.[2] Women 70 years of age and older comprise 30% to 40% of all breast cancer patients, and while the average age at diagnosis of breast cancer is now 61 years, the majority of deaths occur in women 65 years and older. Despite major advances in treatment, breast cancer remains only behind lung cancer as the leading cause of cancer death in women.

Advances in screening and adjuvant therapy have led to major reductions in breast cancer mortality rates,[3] but these benefits have been less in older women.[4] For example, data from National Vital Statistics Reports and the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute showed that the rate of breast cancer death in the general population relative to 1990 decreased 2.5% per year for patients aged 20 to 49 years, 2.1% annually for those aged 50 to 64 years, and 2% per year for those aged 65 to 74, but it decreased by only 1.1% per year for those 75 and older. In addition, death due to breast cancer in women newly diagnosed between 1980 and 1997 decreased by 3.6% per year in women less than 75 years old but only 1.3% per year in those 75 years and older (P < .01), with the absolute 10-year risk of breast cancer death decreasing 15.3% in women aged 50 to 64 years, but only 7.5% for those aged 75 and older.[4] Why are there disparate rates for older women? Some of this difference may be due to less use of screening mammography as women age, but the role of screening mammography in older women remains controversial, especially for those aged 75 and older.[5] Probably the most important reason for this disparity in breast cancer–specific survival (which accounts for dying from other causes) is the less frequent use of potentially life-saving adjuvant therapies in these older patients, including post-operative radiation; endocrine therapy; chemotherapy; and, for patients with human epidermal growth factor receptor 2 (HER2)-positive (HER2+) tumors, trastuzumab (Herceptin). Sometimes not offering state-of-the-art therapy to older patients represents “good clinical judgment,” but for many patients such “low-balling” of treatment is inappropriate and results in poorer survival.[6] In this review, we discuss how to evaluate older patients, including assessment of functional status and estimating life expectancy, as well defining the role of post-operative radiation and systemic adjuvant therapy. (See the Table for a list of useful websites; excellent recent reviews of this topic are also available.[7,8])

| TABLE |
Useful Online Resources for Management of Older Patients With Breast Cancer

FIGURE 1

Comparison of Two Hypothetical 75-Year-Old Patients

**Approach to the Older Patient**

When discussing treatment options with older breast cancer patients, it is critical to determine whether breast cancer is the patient's major illness. Although the patient and family members will be concerned about the breast cancer, they may be less aware of the importance of other comorbidities and how they impact breast cancer management and life expectancy. For instance, many patients 70 years and older have substantial comorbidities that shorten life expectancy, such as hypertension, diabetes, and dementia. In one study of postmenopausal breast cancer patients, those 70 to 74 years of age had, on average, three comorbidities, and those 75 to 84 years old had four.[9] This is important in that, among patients 70 years and older, about 85% of those with node-negative and 65% of those with node-positive breast cancer die of non-breast-cancer-related causes.[10] Functional loss is also important and has a major impact on life expectancy.[11] Identifying comorbid illness and functional loss and managing them appropriately are essential if one is to offer the most beneficial treatment options. For example, two 75-year-old women, patient A and patient B (see Figure 1), have various clinical and functional factors that must be considered before treatment options are presented. Although these patients are the same age, they are markedly different. In a model that uses these data to compute 5- and 9-year mortality, patient A and B have 5-year estimated mortality risks of 6% and 16%, and 9-year mortality risks of 15% and 75%, respectively.[11](also see www.eprognosis.org).

The use of a comprehensive geriatric assessment (CGA) is the best way to estimate functionality in an older adult. The CGA is an interdisciplinary approach that evaluates key domains including physical function, psychosocial function and support, cognitive function, medication use (“polypharmacy”), and nutritional status.[12] What is important for oncologists to know about CGA is that identifying problems can lead to interventions that can improve quality of life as well as survival.[13] Realistically, it is not possible to refer all older patients for geriatric assessment—a 2- to 3-hour evaluation—nor are there enough geriatricians available to see the tsunami of older cancer...
patients in a timely manner. To circumvent this obstacle, new assessment tools have been
developed that utilize a small amount of professional time for assessment of cognitive function, an
“up and go test,” and assessment of performance status. Assessment of function includes evaluating
the patient's ability to perform activities of daily living that are essential for patients to care for
themselves at home (eg, bathing, dressing, toileting, walking), as well as instrumental activities of
daily living that are essential for allowing independence in the community (eg, preparing meals,
using the telephone, housework, taking medicines, managing finances), and documenting the
number of falls within 6 months of cancer diagnosis. Depression, social support, and nutritional
status are also self-evaluated using validated instruments. The abbreviated CGAs have been shown
to be feasible in the cooperative group setting and should be performable in a busy office or clinic
with only modest use of staff time. Patients identified as having major issues with physical or
cognitive function, falls, depression, or psychosocial support can be referred to a geriatrician so that
these issues can be addressed before treatment is selected. Another option is to use screening tools,
such as the Vulnerable Elders Survey-13 (VES-13), to identify patients with functional impairment
and poor self-reported health and then refer them for a more detailed geriatric assessment.[14]

Information obtained from the CGA will lead to a better plan of care that will shape the clinical
decision for the patient and ultimately impact her quality of life. Often providers focus on the number
of comorbidities, and less attention is focused on the type, severity, and duration of the
comorbidity.[15] When considering adjuvant therapy, patients with limited survival will almost never
be candidates for chemotherapy.[16]

Management of the Primary Lesion in Frail Patients or Those With
Advanced Locoregional Disease

For patients with life expectancies of 5 years or more and resectable lesions, surgery remains the
key to successful control of the primary tumor. A Cochrane analysis has shown that for older
patients, primary endocrine therapy with tamoxifen was associated with survival outcomes similar to
those of women treated with surgery, with or without endocrine therapy. However, the majority of
women given tamoxifen alone had breast tumor progression by 5 years.[17] Although aromatase
inhibitors (AIs) might prove superior to tamoxifen in this setting, they are not likely to change these
results greatly, and we recommend surgery for patients with life expectancies of more than 5 years.
For older women with hormone receptor–positive (HR+) locally advanced breast cancer who are not
candidates for tumor resection or who wish to increase their odds of breast preservation,
neoadjuvant endocrine therapy can be of major benefit and makes many older patients candidates
for breast-preserving surgery.[18]

Adjuvant Radiation Therapy

There are randomized data on the use of tamoxifen (20 mg daily) with or without breast radiation
(RT) for older women with early-stage breast cancer. One series[19] enrolled 769 patients, (age ≥ 50
years) with pathologic T1 or T2 invasive cancers, negative margins, and pathologically negative
axillary lymph nodes (except in patients 65 years and older who were eligible if pathologically or
clinically node-negative). Whole-breast RT was given in a hypofractionated regimen of 40 Gy (16
fractions) followed by a boost of 12.5 Gy (5 fractions) to the lumpectomy site. The 5-year local
relapse rate was 0.6% in the RT plus tamoxifen group and 7.7 % for those receiving tamoxifen alone
(P < .05). This significant benefit for RT was noted in the more favorable T1 receptor–positive
subgroup. There were no differences in distant relapse or overall survival, but such differences might
not be expected in the relatively short follow-up of this favorable subgroup. A second randomized
trial (Cancer and Leukemia Group B [CALGB] 9343) included 636 women 70 years and older with
lumpectomy-treated T1, HR+, clinically or pathologically node-negative tumors. All patients received
tamoxifen and were randomized to radiation or no radiation.[20] After a median follow-up of 10.5
years, the incidence of locoregional recurrence was 2% in the tamoxifen and RT group compared
with 9% in the tamoxifen-alone group.[21] Breast cancer–specific survival was 98% for the
tamoxifen-alone group and 96% for the tamoxifen/RT group, and while all-cause mortality was 43%,
the vast majority of deaths were due to non-breast cancer causes.
Absolute Reduction in the 10-Year Risk of Any Locoregional or Distant First Recurrence With the Addition of Radiation

The Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) meta-analysis compared nearly 11,000 patients with early-stage breast cancer who received postoperative radiation or not in randomized clinical trials.[22] The RT-treated group had an overall 16% absolute decrease (19% vs 35%) in the risk of breast cancer recurrence and a 4% absolute decrease (21% vs 25%) in the risk of dying from breast cancer—clearly showing that good local control correlates with improved survival. This analysis stratified women by age, and while the benefit was less in the older cohort (women 70 years and older), there was still an absolute overall reduction in the 10-year risk of a locoregional or distant recurrence of 8.9% (95% confidence interval [CI], 4.0–13.8). There were 1340 patients in the 70-and-older subset (see Table 3a in the web appendix of Ref. 22) and the benefits of radiation and tamoxifen in reducing locoregional and distant recurrence in these patients are presented in Figure 2A through 2C. Based on these absolute risk reductions, our recommendations for use of breast radiation are summarized in Figure 2D. Unlike the CALGB 9343 trial, which did not include information on grade, data from the EBCTCG suggests that patients with high-grade T1 tumors treated with adjuvant tamoxifen or an AI alone should be considered for adjuvant RT.

Endocrine Therapy and Chemotherapy

General principles

The challenge in making treatment decisions in older vs younger patients is how to estimate the benefits of treatment after factoring in life expectancy, functional status, and potential side effects. The majority of breast cancers in women 70 years and older are HR+ and HER2-negative (HER2−).[23] The major issue in these patients, most of whom are candidates for endocrine therapy, is the potential added value of chemotherapy. HR+, HER2− breast cancers have significantly different clinical outcomes compared with triple-negative (estrogen receptor [ER]-negative, progesterone receptor [PR]-negative, and HER2-negative) breast cancer (TNBC) and with HR−, HER2+ cancers. For HR+, HER2− tumors, the majority of relapses for patients given adjuvant endocrine therapy are seen 5 years after diagnosis, with a continued hazard for relapse of 1% to 2% per year after 5 years; the majority of deaths in this group are seen after 5 years as well.[24] Conversely, the majority of patients with TNBC or HR−, HER2+ breast cancers relapse within 5 years. This difference in natural history based on HR phenotype has profound treatment implications for older patients with short estimated survival times. Endocrine therapy is usually well tolerated by older patients with only modest risks for toxicity. Older patients with a life expectancy less than 10 years who have HR+, node-negative disease, or only one to three positive nodes, are excellent candidates for endocrine therapy. Few will benefit from chemotherapy. Furthermore, chemotherapy can cause substantial toxicity, leading to loss of function and diminished quality of life.

TNBC and HER2+ breast cancers are each seen in about 15% of older patients. For TNBC, chemotherapy is the only systemic therapy of benefit and should be considered for most patients. HER2+ cancers that are HR− are the worst breast phenotype when untreated, and consideration of chemotherapy and trastuzumab is appropriate for most of these patients. Those with small HR+, HER2+ tumors (triple positive) have a better short-term prognosis, and the decision regarding chemotherapy/trastuzumab is more complex[25]; those with larger tumors with this phenotype should be considered for chemotherapy and trastuzumab.

There is no question that the addition of chemotherapy to endocrine therapy improves survival in women with HR+ early-stage breast cancer.[26] However, data are sparse for patients 70 years and older; moreover, it is likely that the benefits of chemotherapy vary greatly depending on the biologic characteristics of the tumor.[27] For patients 70 years and older with T1 and T2 node-negative, HR+
tumors (and probably for those with one to three positive lymph nodes [28]) who are recommended for adjuvant endocrine therapy, the added value of chemotherapy can be estimated by the Oncotype DX assay (Genomic Health, Redwood City, California).[29] Current data from this assay suggest that the major benefit of chemotherapy in this patient group is in those with high recurrence scores, and that chemotherapy is of no added value among patients with low recurrence scores. The value of chemotherapy in those with an intermediate score is uncertain and is being addressed in a randomized clinical trial, TAILORx (Trial Assigning Individualized Options for Treatment [Rx]; clinicaltrials.gov identifier NCT00310180); this trial is closed to accrual, and results are expected in 2015. At present we suggest that patients with intermediate recurrence scores also be evaluated using Adjuvant! Online (www.adjuvantonline.com[30]; also see Table) to estimate the added value of chemotherapy in lowering breast cancer mortality. The potential value of chemotherapy using the estimates from both Oncotype DX and Adjuvant! Online can help in making the decision of whether or not to recommend chemotherapy. Adjuvant! Online also integrates patient age into its survival calculations and can be adjusted to account for comorbidity—extremely helpful information when discussing the risks and benefits of treatment with older patients.

**Selection and pitfalls of endocrine therapy**

Randomized trials have clearly shown that tamoxifen in women 70 years and older dramatically lowers the annual risk of recurrence of breast cancer by 51% and the annual odds of dying of breast cancer by 37%.[26] These risk reductions are similar for node-negative and node-positive patients; however, the absolute value benefits can vary greatly and be quite small for patients with cancers that have a low risk of recurrence. Conversely, these results may represent a “worst-case scenario,” as many older patients are noncompliant with tamoxifen[31] (and Als). Tamoxifen is generally well tolerated in older patients and is extremely low in cost and readily available. There is a small risk of endometrial cancer, about 1%, associated with 5 years of use, and a similar small risk of venous thrombosis. In postmenopausal women, tamoxifen can also maintain or improve bone density and lower cholesterol levels. In older patients who have not had a hysterectomy, the requirement for a pelvic examination and Papanicolaou (Pap) smear yearly can be an obstacle to use but is essential for appropriate management.

Numerous randomized trials involving thousands of patients have now compared tamoxifen to Als, and updated American Society of Clinical Oncology (ASCO) guidelines for use of endocrine therapy are available.[32] In almost all of these trials, a small improvement in relapse-free survival of a few percentage points has been shown for use of Als, but without any convincing improvement in overall survival. A strategy of initiating endocrine therapy with tamoxifen and then changing to an Al 2 to 3 years later has been shown to improve survival and may represent the best strategy.[32] Until now, Als have been extremely expensive, but since coming off patent, costs have dropped dramatically. ASCO guidelines have recommended that Als be considered for use in all postmenopausal patients at some time during their endocrine treatment. Unlike tamoxifen, Als are not associated with an increased risk of endometrial cancer or thromboembolism, but even in older patients they can be associated with severe arthralgia and myalgia that can impede function. The symptoms, when severe, are hard to ameliorate. Changing to another Al can be helpful in some patients. If symptoms persist after changing Als, switching to tamoxifen is probably the best strategy. The other major toxicity associated with Al use is accelerated bone loss and an increased risk of fracture. Many older patients already have osteopenia or osteoporosis when breast cancer is diagnosed. Older patients on Als should be encouraged to exercise and use recommended doses of vitamin D and calcium. For those with severe osteopenia (T-score less than −2.0) or osteoporosis, either bisphosphonates or other bone-protecting agents such as denosumab (Prolia) should be considered. These agents, although generally safe, can add to the costs of treatment. The World Health Organization fracture risk assessment tool, “FRAX,” can be used to estimate fracture risk from clinical and bone densitometry data (www.shef.ac.uk/FRAX).

Older adults are more susceptible to medication nonadherence for a variety of reasons, but common associations with adherence problems include cognitive, visual, and physical impairments that impact the treatment plan. Polypharmacy is common among older adults because of their prescribed medications for treatment of comorbidities.[33] Because of the large number of medications taken by older patients, drug interactions and side effects are more common than in younger age groups, and patients must be closely monitored. In one study, 49% of patients over 65 years of age discontinued adjuvant tamoxifen before 5 years; being 75 to 80 years old, having increased comorbidity, having increased cardiopulmonary comorbidity, and having received breast-conserving therapy without breast radiation were all related to nonadherence.[31] Poor adherence to Als has
also been found in older women.[34] The best way to improve adherence is uncertain, but educating older patients and their families about the value of treatment and possible side effects of treatment is certainly important as family members and other caregivers play a key role in having patients take their medications as prescribed.[35] In addition, providers should query patients on each visit concerning compliance with treatment and should encourage adherence to therapy.

**Selecting chemotherapy**

The decision to recommend chemotherapy to an older patient is a complicated one and includes consideration of the effect of chemotherapy on improving survival, the potential for toxicity and resulting functional loss, and both the social (logistics and increased need for family support), and financial costs of treatment. Like endocrine therapy, chemotherapy regimens result in similar proportional reductions in recurrence and survival for both node-negative and node-positive patients. The major decision for the medical oncologist is which chemotherapy regimen to recommend. Historically, cyclophosphamide, methotrexate, and fluorouracil (CMF); and doxorubicin and cyclophosphamide (AC) were among the most frequently used regimens. These regimens resulted in significant improvements in breast cancer survival, but newer regimens have substantially enhanced these results.[36] In addition, recent data suggest that 4 cycles of docetaxel and cyclophosphamide (TC) are superior to 4 cycles of AC, even in older women.[37] Our bias is to select chemotherapy regimens based on their absolute reduction in breast cancer mortality (which is related to risk of recurrence), potential toxicity, and the patient's life-expectancy. Adjuvant! Online is a useful tool to use when making these decisions; it compares survival outcomes of first-generation chemotherapy regimens (such as CMF or 4 cycles of AC) with second-generation regimens (such as TC or 6 cycles of an anthracycline-containing regimen) and with third-generation regimens (such as dose-dense AC and paclitaxel; and docetaxel, doxorubicin, and cyclophosphamide [TAC]). For fit patients at high risk of recurrence, survival is improved by a few percentage points with more aggressive third-generation regimens compared with first- or second-generation regimens. For other patients, we suggest consideration of second-generation regimens such as TC, as they avoid the potential higher risks of cardiac damage and leukemia associated with anthracyclines. Unlike the more aggressive and more toxic third-generation regimens, which have not been extensively studied in older patients, the TC regimen has been well tolerated in older patients in the adjuvant setting, with minimal effect on functional status,[38] but is associated with a 20% to 30% risk of neutropenic fever unless prophylactic growth factors are used. An example of the potential benefits of first-, second-, and third-generation regimens in improving survival in older patients is shown in Figure 3. A large retrospective study of node-positive patients in randomized trials comparing less-intense vs more-intense chemotherapy showed that the more-intensive regimens were associated with a similar proportion of benefits in terms of improvement in relapse and survival rates for older vs younger patients.[39] It should be noted, however, that the effectiveness of second- and third-generation chemotherapy regimens in older patients, as estimated by Adjuvant! Online, has not been validated in clinical trials, and it is possible that the value of such regimens is overestimated in this patient group. FIGURE 3

![Figure 3](image_url)

**Added Value of Endocrine Therapy (Endo, "E") With Either Tamoxifen or an Aromatase Inhibitor and/or First- (1st), Second- (2nd), or Third (3rd)-Generation Chemotherapy**

Chemotherapy toxicity is a major concern in older patients, and there is a paucity of clinical trial data on how such toxicity affects function in older women. In one recent trial focused on elderly patients with breast cancer, both CMF and AC were found superior to capecitabine (Xeloda) in improving survival.[40] Surprisingly, AC was better tolerated than CMF, with 92% of patients completing the 4 planned cycles of AC but only 62% completing the 6 planned cycles of CMF. Third-generation regimens such as “dose-dense” AC and paclitaxel, AC followed by docetaxel, and TAC are all associated with substantial toxicity. Such regimens should be reserved for patients who are at very high risk of recurrence and highly functional, without major organ dysfunction. The recent EBCTCG study comparing long-term outcomes of combination chemotherapy (polychemotherapy) regimens showed that longer durations of chemotherapy, such as 6 cycles of an anthracycline-containing regimen, also provide similar improvements in survival.
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Regimen (with either doxorubicin or epirubicin), were superior to 4 cycles of AC or CMF. Concerns about toxicity should not preclude providing adequate dosing, and doses should be those shown to be effective in published trials. Arbitrary dose modifications of trial-defined dosage can be associated with poorer outcomes[41] and should be avoided; when necessary, granulocyte-stimulating growth factors should be used for initial and subsequent dosing, following published guidelines.[42,43] Patients with HER2+ tumors derive the best survival improvements from the combination of chemotherapy and trastuzumab. Trastuzumab, like anthracyclines, is associated with a higher risk of cardiac toxicity in older adults. The regimen of docetaxel, carboplatin, and trastuzumab is similar in efficacy to trastuzumab-and-anthracycline-containing chemotherapy and is associated with less cardiac toxicity[44]; it should be considered for older patients with HER2+ high-risk tumors. Other potentially less toxic chemotherapy regimens such as TC can also be given with trastuzumab. Although not tested in the clinical setting, trastuzumab alone might be considered for older, more frail patients with high-risk HER2+ tumors. At present, calculating the added value of including trastuzumab with chemotherapy in patients with HER2+ tumors cannot be done directly using Adjuvant! Online, but it can probably be fairly estimated by multiplying the chemotherapy percentage in the “Adjuvant Therapy Effectiveness” box by 1.5 (based on a hazard ratio of about 0.5 for chemotherapy plus trastuzumab compared with chemotherapy alone).

FIGURE 4

General Approach to the Patient Using Geriatric Assessment

Summary

Caring for women 70 years of age and older with early-stage breast cancer is challenging. A general approach to caring for such patients is presented in Figure 4. In addition to the challenges posed by multiple comorbidities and loss of function for many of these patients at the time of diagnosis, there are scant data from clinical trials that can be used to guide treatment decisions. More widespread use of CGA can certainly help to determine the suitability of treatment,[13] and using CGA as part of clinical trials to determine therapy has been shown to be of benefit and should be more widely used.[45] In addition, addressing the barriers to clinical trial participation by elders, developing methods to ensure that adequate numbers of elders participate in major trials, and increasing funding for research in geriatric oncology are all essential if we are to increase our knowledge and provide optimal care for this ever-expanding group of patients.

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