Section A-Research paper

Breast Cancer Management among Elder Patients

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Abstract

Background: Breast cancer is a disease associated with aging, with almost one-half of all new breast cancer cases diagnosed annually in the United States occurring in women age 65 and older. Recent data suggest that although breast cancer outcomes in younger women have shown substantial improvement as a result of advances in treatment and screening, the benefits in older women have been less pronounced. Although older adults have been under-represented on cancer clinical trials there is an emerging body of literature to help guide treatment decisions. For early stage breast cancer, the discussion regarding treatment options involves balancing the reduction in risk of recurrence gained by specific therapies with the potential for increased treatment-related toxicity potentially exacerbated by physiological decline or comorbidities that often co-exist in the older population. A key component of care of the older adult is the recognition that chronologic age alone cannot guide the management of an older individual with breast cancer; rather, treatment decisions must also take into account an individual's functional status, estimated life expectancy, the risks and benefits of the therapy, potential barriers to treatment, and patient preference. This article reviews the available evidence for therapeutic management of early-stage breast cancer in older adults, and highlights data from geriatric oncology literature that provides a basis on which to facilitate evidence-based treatment..

Keywords: breast cancer, older patient,

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Introduction

Breast cancer is largely a disease of older women, with almost half of all new breast cancer cases diagnosed annually in the United States occurring in women age 65 and older.[1] While there have been improvements in breast cancer survival for the population as a whole, these improvements are much smaller in older adults than in younger adults. Treatment decisions for early stage breast cancer in an older adult must consider the reduction in recurrence risk that would be gained by specific therapies and balance that risk with the potential for treatment-related toxicity. Older adults have been underrepresented on prospective clinical trials, so there are therefore less data to guide treatment decisions, particularly at the extremes of age; however, evidence regarding treatment of older adults with breast cancer has increased over the past decade, and we review that evidence here.

Tumor Characteristics versus Outcomes

When compared with cancer in younger women, breast cancers in older women are less likely to exhibit aggressive tumor characteristics. For example, the percentage of breast cancers that are estrogen receptor (ER)-positive increases with age[2], from < 60% in women aged 30–34 years to as high as 85% in women age 80–84 years.[3] Older women are also more likely to have tumors with lower proliferative indices and are less likely to have overexpression of HER2.[4] Despite the fact that older patients with breast cancer are more likely to have favorable tumor characteristics, outcomes in older women do not reflect this apparent advantage. Instead, a recent report found that the 5-year relative survival of patients ≥ 70 years was lower than that of

patients aged 15–70. [5] Older women are also significantly less likely to be treated according to guidelines, potentially increasing their risk of disease recurrence and mortality.[6] Recent data suggest that although breast cancer outcomes in younger women have shown substantial improvement as a result of advances in treatment and screening, the improvements in outcomes of older women (particularly the oldest 20% of patients with breast cancer) have been much more modest.[7]

Treatment of Early Stage Breast Cancer

Surgery

The gold standard treatment for patients of any age with early stage breast cancer is surgery. The surgical mortality rate in older women with breast cancer in reasonable health is negligible (<1%).[8–10] The main factor influencing surgical morbidity and mortality is not age but the presence of significant comorbidity.[11] In the frail or debilitated patient who cannot tolerate surgery, treatment should be individualized, and a primary endocrine approach (without planned surgery) could be considered in patients with hormone receptor positive disease. It should be noted, however, that a Cochrane meta-analysis reported that primary endocrine treatment with tamoxifen is inferior to surgery (with or without hormonal treatment) in terms of local control and progression-free survival in medically fit women age ≥70. However, a significant difference in overall survival was not demonstrated. Because the average response to tamoxifen occurs between 18 and 24 months, those women who do progress will have to consider additional endocrine treatment or choose surgery or radiotherapy at a greater age. Therefore, based on the results of the meta-analysis, this approach is only recommended for those who refuse surgery or who are otherwise unfit for it.[12] Current recommendations from the International Society of Geriatric Oncology (SIOG) strongly recommend the involvement of a geriatrician to optimize management of the patient's comorbidities and to aid with the assessment of life expectancy if primary endocrine treatment is being considered without surgery.[13]

Because most older women tolerate breast-conserving surgery (BCS) and mastectomy just as well as younger patients, they should be offered the same surgical options.[14] If given a choice, women age ≥ 70 are more likely to choose breast conservation over mastectomy.[15] Importantly, older women treated with BCS (partial mastectomy and radiation) in comparison to total or modified mastectomy are less likely to report functional limitations following treatment.[16] However, despite these data, older women are more likely to be treated with mastectomy than younger women[17] and less likely to be offered or to undergo breast reconstruction.[18] As body image remains important for many older women, and older women treated with BCS report a better body image than those treated with mastectomy, BCS should be offered if the patient meets clinical criteria.[19]

Axillary Lymph Node Dissection

Proper management of the axilla in all patients with breast cancer has been an evolving area of active investigation. An axillary lymph node dissection (ALND) is no longer a routine part of the surgical management of breast cancer when the axilla is clinically negative, having been replaced with the less morbid sentinel node biopsy (SLNB). SLNB is feasible and well tolerated in older women, and is associated with lower rates of arm disabilities than ALND.[20,21] However, studies conducted in women aged 65 and over with early stage breast cancer showed underutilization of SLNB among women who were eligible for the procedure.[22,23] Although ALND remains standard for women with ≥ 3 positive sentinel nodes, in patients of all ages the need for ALND has been questioned for those with T1 disease and 1 or 2 positive sentinel nodes (clinically node negative) based on the results of the ACSOG Z0011 trial.[24,25]

Some authors suggest that older women do not need axillary lymph node assessment if the information gained will not influence treatment or outcome. This is particularly true for those individuals who have comorbid conditions that preclude adjuvant chemotherapy. This approach has been investigated in trials of older women with ER-positive breast cancer and a clinically negative axilla. The International Breast Cancer Study Group 10–93 randomly assigned 473 women age ≥ 60 to primary surgery and tamoxifen with or without ALND. Although the endpoint of the study was quality of life (QOL), at a median follow-up of 6.6 years, the rates of disease-free (67% vs 66%) and overall survival (75% vs 73%) were similar.[26] Additional studies have reported comparable results.[27,28] It is reasonable to discuss these data in older women with small (≤ 2 cm) ER-positive tumors with a clinically negative axilla who will receive adjuvant endocrine therapy, if the

finding of LN positive disease would not influence adjuvant treatment decisions. However, the standard of care is to apply the usual surgical approaches including SLNB for fit older women with breast cancer.

Adjuvant Radiotherapy

For healthy older women, as with younger patients, breast irradiation is considered a standard component of breast-conserving surgery. Breast irradiation is generally well tolerated, with good to excellent cosmesis in older women, and chronologic age alone should not be a limiting factor in its inclusion.[29,30] However, the rate of ipsilateral breast cancer recurrence decreases with age, and although radiotherapy after BCS is associated with similar proportional reductions in local recurrence across age groups, the absolute benefits of treatment are lower in older women since their risk of local recurrence is less.[31] This has prompted the reevaluation of the role of radiotherapy (RT) for selected older patients with breast cancer. One large randomized trial specifically examined the role of adjuvant radiotherapy following BCS in women age ≥70. In this study from the Cancer and Leukemia Group B (CALGB 9343), older women with ER-positive tumors ≤ 2 cm treated with tamoxifen were randomized to treatment with or without RT.[27] The most recent update (at a median follow-up of 10.5 years) reported a significant difference in the rate of local recurrence in the women treated without RT (9% vs 2%; *P*=.0125). However, there were no significant differences in breast- cancer-specific survival or overall survival.[32] The majority of deaths to date have been due to reasons other than breast cancer. Thus, adjuvant RT may reasonably be omitted in a select group of women age ≥70 treated with endocrine therapy for small (<2 cm) ER-positive, clinically node-negative breast cancers. Few data exist that reliably predict whether or not RT can be omitted in older patients who do not fit these highly selective criteria, and determining the specific indications for RT in older patients is an issue that will continue to grow in significance with the aging of the population. [33]

Despite the compelling data from CALGB 9343, a recent article by Soulos et al. examinined the effect of the CALGB 9343 trial on the Medicare population and determined that the reporting of the trial had minimal impact on the use of RT in the studied population, with the use of RT remaining high in clinical practice. Additionally, they found no evidence of differential uptake among patients with limited life expectancy or among the oldest women, with the use of RT among patients with the shortest life expectancy still exceeding 40% after publication of their article, suggesting that increased dissemination of these results are needed.[34]

Postmastectomy Radiation (PMRT)

Clinical trials indicate that postmastectomy radiotherapy (PMRT) is associated with improved survival and decreased local regional recurrence for women with high-risk breast cancer.[31] Women age >70 were underrepresented in these clinical trials, yet PMRT decisions in these individuals is extrapolated from the trials conducted in primarily younger women. Evidence from population-based cohort studies supports the assertion that older women with high-risk cancer may also benefit from PMRT. In one study of 939 women aged ≥70 treated with mastectomy without PMRT, only patients with tumor size ≥ 5 cm and/or ≥4 positive nodes experienced a risk of local regional recurrence similar to the control arms of the PMRT clinical trials, suggesting that the intervention might only show a survival benefit in high-risk patients.[35] One large population-based cohort study of women aged ≥70 treated with mastectomy for newly diagnosed breast cancer reported that PMRT was associated with a survival benefit for high-risk (T3/T4 primary tumor and/or N2/N3 nodal involvement) but not for low-risk (T1/T2, N0) or intermediate-risk T1/T2, N1) patients. However, only 38% of the high-risk patients in this cohort (treated between 1992–1999) actually received PMRT.[36] For women with high-risk disease, PMRT should be offered. Further clinical trials in this age group are needed to clarify treatment for women with lower-risk disease (ie, 1–3 positive axillary nodes).

Adjuvant Endocrine Therapy

In general, because of its favorable toxicity profile and confirmed effectiveness in improving relapse-free and overall survival, adjuvant endocrine therapy is recommended for older women with ER-positive breast cancer. For most postmenopausal women, aromatase inhibitors (AIs) are the preferred agent, with improvements in disease-free survival (DFS) as well as lower rates of thrombosis and endometrial cancer compared with tamoxifen.[37] The benefits of endocrine therapy are preserved across age groups. In the BIG I-98 trial comparing 5 years of letrozole versus tamoxifen, there was an age-independent DFS benefit reported for letrozole, including women age ≥75.[37] In the MA.17 trial (5 years of letrozole vs placebo following 5

years of tamoxifen), a subgroup analysis of older women revealed a statistically significant benefit in DFS from letrozole only in women <60 years of age.[38] However, there was no interaction between age and treatment, indicating a similar effect of letrozole among all age groups. Additionally, there was no difference in toxicity or QOL at 24 months in the group of patients ≥70 years who were treated with letrozole or placebo, making extended letrozole an option for fit older women.

Despite the benefits of aromatase inhibitor therapy in older women, side effects such as musculoskeletal discomfort, accelerated bone loss, and fracture risk are important to monitor in older women, who have higher rates of osteopenia and osteoporosis than younger counterparts. Although the studies were not designed to determine fracture rates as the primary outcome, in a meta-analysis of 7 trials comparing AIs to tamoxifen in postmenopausal women with early stage breast cancer, AIs significantly increased the risk of bone fractures.[39] Monitoring bone density and instituting appropriate antiresorptive therapies as indicated is especially important in this population. Furthermore, studies have reported a potential association between aromatase inhibition and cardiovascular risk; however, further research is needed to clarify these findings.

A Danish Breast Cancer Cooperative Group study identified a subgroup of patients with such a favorable prognosis that omission of adjuvant endocrine therapy could be considered. They reported that in the absence of systemic therapy, women aged 60–74 years with small (≤1 cm), node negative, ER+, grade 1 ductal carcinoma or grade 1 or 2 lobular carcinoma had the same mortality as age-matched women in the general population, suggesting there may be a population in which no endocrine therapy could be considered.[40]

Adjuvant Chemotherapy

Older adults have been under-represented on adjuvant chemotherapy trials to date; however, a landmark randomized trial specifically focused on older adults has recently been reported. In this prospective randomized study, women age ≥65 were randomized to standard polychemotherapy (cyclophosphamide, methotrexate, and fluorouracil [CMF] or doxorubicin and cyclophosphamide [AC]) or capecitabine alone. At a median follow-up of 2.4 years, patients treated with capecitabine were twice as likely to suffer a relapse and almost twice as likely to die as patients randomly assigned to standard chemotherapy. The benefit was greatest in the subgroup of women with hormone-receptor-negative cancer (HR 2.62, *P*=.001). These data suggest that standard adjuvant chemotherapy has a role in the treatment of fit older women.[41] Treatment guidelines from the National Comprehensive Cancer Network do not set an upper age limit for the utilization of chemotherapy, acknowledging that both life expectancy and comorbidity must be taken into account.[42] Two large international randomized trials (CASA and ACTION), comparing adjuvant chemotherapy with no chemotherapy in older women, closed prematurely because of insufficient accrual; highlighting the challenges of conducting randomized trials with a no chemotherapy arm in this population.[13]

Data from cooperative group studies enrolling women across all ages demonstrates that older women in good general health derive similar benefits from systemic chemotherapy as younger adults; however, they are at increased risk of treatment toxicity. A retrospective analysis of 4 CALGB trials for node-positive breast cancer reported that older patients derived similar benefits in comparison to younger patients from the experimental arm (which gave more aggressive chemotherapy), with improved relapse-free and overall survival.[43] However, women age ≥65 experienced greater treatment-related mortality and hematologic toxicity.[44]

An EBCTCG meta-analysis of randomized trials begun in 1995 showed statistically significant reductions in recurrence and breast cancer-specific mortality with polychemotherapy in both older and younger women, with a larger absolute magnitude of benefit in younger women.[45] The trials examined in this overview involved too few women age ≥70 to achieve statistical significance, although a 13% reduction in all-cause mortality was reported in women treated with adjuvant chemotherapy. The exact reason for these findings is unclear; however potential etiologies include the increasing risk of death from competing causes in older women, differences in tumor biology (an increased percentage of ER-positive cancers), or an age- related increased risk of treatment toxicity precluding the ability to deliver adequate dose intensity of adjuvant chemotherapy in older women.

Go to:

Weighing the Risk of Chemotherapy Toxicity in Older Adults: Integrating Geriatrics and Oncology

Similar principles guide the use of adjuvant chemotherapy in older as well as younger women, with judicious weighing of available tumor prognostic and predictive factors. However, with older women, a more comprehensive evaluation of patient characteristics (captured in a geriatric assessment) can assist in weighing the potential risks of therapy. A comprehensive geriatric assessment (CGA) includes an evaluation of functional status, comorbidities, polypharmacy, nutritional status, cognitive function, social support, psychological state, and geriatric syndromes (dementia, delirium, depression) (Table 1). Components of the CGA have been associated with cancer-specific survival in older patients with cancer.[46–49] When used to evaluate the older patient with cancer, the value of the CGA is twofold. First, components of the CGA can be predictive of morbidity and mortality for older patients. Secondly, the CGA can identify deficits that may be addressed prior to initiating cancer-directed therapies, thereby potentially minimizing morbidity.

Table 1

Domains and Applicability of the Comprehensive Geriatric Assessment (CGA)

Domain	Relevant Clinical Questions
Functional Status	*"Can my patient care for him or herself now and while receiving therapy?"*
Comorbidities	*"How will my patient's other medical problems impact the ability to tolerate cancer treatments and affect life expectancy?"*
Polypharmacy	*"Is my patient taking any medications which are flagged as being potentially "inappropriate" because of the risk of side effects in older adults? Are any medications duplicative or not needed? Will there be drug interactions between the current medications and the cancer-directed therapy?"*
Nutritional Status	*"Is my patient able to meet nutritional needs while undergoing therapy?"*
Cognitive Function	*"Can my patient make treatment-related decisions, follow a treatment plan, and know what to do if needing help?"*
Social Support	*"Does my patient have someone to provide care during therapy?"*
Geriatric Syndromes	*"Does my patient have age-associated medical conditions that can be optimized prior to treatment?"*

Predictive models for the risk of chemotherapy toxicity in older adults (incorporating geriatric assessment variables) have been developed. The Chemotherapy Risk Assessment Scale for High-Age patients (CRASH) score utilizes an individual's clinical, laboratory, and functional variables, with chemotherapy-regimen-specific toxicity criteria in order to develop risk categories for grade 3/4 nonhematologic or grade 4 hematologic toxicity.[50] The Cancer and Aging Research Group developed a predictive model and scoring algorithm for the risk of grade 3–5 chemotherapy toxicity in patients age ≥ 65, consisting of tumor and treatment variables, laboratory data, and geriatric assessment questions.[51] Both of these studies included patients across tumor types. A study specifically evaluating the clinical and biological risk factors for adjuvant chemotherapy toxicity is underway (R01 AG037037-01A1, ClinicalTrials.gov ID: NCT01472094).

To compensate for the resource and time restraints imposed by a typical oncologic consultation, a brief but comprehensive geriatric assessment for older patients with cancer that is mostly patient-administered and evaluates multiple domains of the standard CGA has been developed. Prospective studies have found that most older adults can complete this questionnaire without assistance, and that it identifies deficits that have been shown to affect the risk of chemotherapy toxicity in older adults.[52,54]

Conclusion

The number of breast cancer cases is rising because of the aging of the US population, rises in life expectancy and the association of cancer with aging. There is emerging data regarding the benefits and risks of breast cancer treatment in older adults; however, even more research is needed to inform evidence care, particularly at the extremes of age. Chronologic age alone provides inadequate information when it comes to formulating treatment decisions for an older individual with breast cancer. Melding the fields of geriatrics and oncology research and practice is essential to inform both research and clinical care.
This work followed the study done by O'Connor[55]

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