**Review Article** | Palliative Medicine and Palliative Care for Incurable Cancer

# A narrative review of the challenges and impact of breast cancer treatment in older adults beyond cancer diagnosis

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**Background and Objective:** Breast cancer is the most prevalent cancer among women worldwide, with 45% of them over 65 years old. Older breast cancer patients tend to be underrepresented and understudied in major clinical trials. This narrative review provides a comprehensive overview of the current evidence regarding treatment decision-making, treatment toxicities, and proposed survivorship management recommendations for geriatric cancer patients.

**Methods:** A literature search was conducted on PubMed and Google Scholar. The search strategy included a combination of keywords related to clinical management and treatment toxicities of older cancer breast cancer patients. English articles published between May 1990 to May 2024 were included.

**Key Content and Findings:** Older breast cancer patients represent a heterogeneous group with specific needs and treatment considerations. Treatment decisions for geriatric cancer patients should be based on a comprehensive geriatric assessment (CGA), which considers the patient's functional status, comorbidities, and preferences, rather than relying solely on chronological age. Breast cancer surgery is generally well tolerated in older patients, with a low rate of systemic complications and 30-day post-surgery mortality. In selected elderly patients, axillary surgery may be omitted to minimize side effects. The choice of endocrine therapy should take into account the side effect profile, patient's comorbidities, concomitant medications, and preferences. While aromatase inhibitors provide better efficacy, musculoskeletal side effects and osteoporosis may be a concern for older patients. CDK4/6 inhibitors have a similar efficacy in elderly patients as younger patients, but the incidence of neutropenia and dose modifications or interruptions are more frequent. Reported radiotherapy side effects are similar across age groups, although the occurrence of radiation-induced pulmonary toxicities was found to be associated with old age. Chemotherapy is reserved for triple-negative and HER2-positive disease in elderly patients due to known side effects. such as neutropenia, cardiotoxicity, and cognitive impairment. Data on the efficacy and safety of immunotherapy use in older patients are limited.

**Conclusions:** Physicians should make additional efforts to evaluate age-specific treatment efficacy and treatment-induced toxicities. Further efforts to enhance the representation of older patients in breast cancer trials are warranted.

**Keywords:** Systemic therapy survivorship; radiotherapy; hormonal therapy; target therapy; older adult population

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## Introduction

Breast cancer is the most prevalent cancer among women worldwide, with an estimated 2.3 million new cancer cases (1 in 4 new cancer cases) in the year 2020 (1). The median age of breast cancer diagnosis is 61 years, with 45% of breast cancer patients being over 65 years old and 10% are 80 years or older at diagnosis (2). With an aging population, the number of geriatric breast cancer patients is expected to increase. Yet, data on the management of older cancer patients are scarce as most clinical trials have excluded or underrepresented older patients (3). Age-related variability in patterns of care is high and older patients frequently receive less aggressive treatment compared to their younger counterparts (2). Treatment decisions making should not be made based on chronological age alone, instead, they should involve comprehensive geriatric assessments (CGAs) and consideration of functional age, estimated life expectancy, and patient preferences.

A previous review published in 2022 summarized the available data on treatment options, age-related factors, and toxicities pertinent to the management of older patients with breast cancer (4). In this narrative review, we aim to provide a comprehensive overview of the current guideline recommendations for geriatric cancer patients in treatment decision-making, acute and long-term toxicities associated with various breast cancer therapies, and propose survivorship management plans. We present this article in accordance with the Narrative Review reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-24-90/rc).

## Methods

A literature search was conducted on PubMed and Google Scholar from Jan to May 2024. The keywords used were elderly patients, breast cancer, clinical management, treatment toxicities, geriatric assessment, patients' preferences, surgery, radiotherapy, endocrine therapy, chemotherapy, immunotherapy and target therapy. Articles were chosen in the time frame of May 1990 to May 2024. Articles were included if they were retrievable and in the English language. Duplicates or irrelevant references were omitted. The search strategy was summarised in *Table 1*. Research articles were grouped according to geriatric assessment, surgery, radiotherapy, endocrine therapy, chemotherapy, immunotherapy and anti-HER2 target therapy.

## Geriatric assessment

Conducting a geriatric assessment at baseline and at regular intervals is important in the care of elderly cancer patients (5,6). International geriatric oncology guidelines suggest that CGA should include the evaluation of the patient's comorbidities, medications, physical, cognitive, psychological, and social functioning, frailty, falls, and nutritional status (5,6).

In treating elderly patients with cancer, oncologists should incorporate the results of the CGA to develop an integrated and individualized plan. This involves estimating the risks for adverse outcomes, identifying and addressing non-oncologic problems including cognitive, psychological and physical issues to ensure ability to comprehend and tolerate treatment, and providing information to patients and caregivers to guide shared decision-making for treatment (6). The CGA should form the core of clinical decision-making, as it best identifies the older adults who are resilient enough to receive intensive cancer treatments and those who are frail and vulnerable (7).

A randomized controlled trial in Australia demonstrated the benefits of an integrated oncogeriatric approach for elderly cancer patients aged 70 years and older planned for systemic anticancer therapy. Patients receiving the integrated oncogeriatric care reported better health-related quality of life (QoL), measured by the Elderly Functional Index score, over 24 weeks compared to those receiving usual care (8). Additionally, the integrated oncogeriatric care group had significantly fewer unplanned hospital admissions with a rate ratio of 0.6 [95% confidence interval (CI): 0.42–0.87; P=0.0066]. The integrated oncogeriatric care consisted of CGA and coordinated care between oncologists, geriatricians and multidisciplinary teams.

## Patients' preferences

While it is always important to understand patients'

**Table 1** The search strategy summary

| Items | Specification |
|---|---|
| Date of search | 3 January to 30 May 2024 |
| Databases and other sources searched | PubMed and Google Scholar |
| Search terms used | Elderly patients, breast cancer, clinical management, treatment toxicities, geriatric assessment, patients' preferences, surgery, radiotherapy, endocrine therapy, chemotherapy, immunotherapy and target therapy |
| Timeframe | May 1990 to May 2024 |
| Inclusion and exclusion criteria | Inclusion criteria: studies related to breast cancer treatment and treatment-related toxicities for elderly patients were included |
| | Exclusion criteria: articles not written in English were excluded. Preclinical studies, case reports, editorials and commentaries were excluded |
| Selection process | All authors |

preferences and priorities before making treatment decisions, this is especially significant in geriatric cancer care. Research has shown that compared to younger patients, elderly patients tend to place a higher priority on QoL and are less willing to tolerate the risks and burdens of intensive therapies to preserve life expectancy (7). A systematic review summarizing patient preferences among cancer patients aged 70 or older found that in the palliative setting, QoL was the most important outcome cited by 75% of patients. Conversely, in the curative setting, progression- and disease-free survival (67%) and treatment response (67%) were given the highest priorities (9). A trial was conducted among patients 65 years and older who were starting chemotherapy to assess their preferences of care (survival, independence, symptoms). It was found that survival was top priority in 60.7% of patients and maintaining independence was top priority in 31.5% (10). A study interviewing 73 elderly colorectal cancer patients and their physicians found an overall concordance rate of only 41% between the physicians' perceptions and patients' actual treatment preferences, highlighting the critical need to elicit and incorporate patients' preferences when making treatment decisions (11).

## Surgery

Breast cancer surgery is generally well tolerated in older patients. A prospective multi-center study in the UK of 2,816 women aged 70 years and above who underwent mastectomy or breast-conserving surgery found that the overall rate of systemic complications including cardiorespiratory problems, stroke, deep vein thrombosis and pulmonary embolism was low (2.1%). The rate of local wound complications including hematoma, infections, and wound dehiscence was 18.4%. There were no deaths reported within 30 days of surgery or attributable to surgery (12).

Choice of breast and axillary surgery is often affected by the patient's age, frailty and comorbidities. In the UK study, age, frailty, comorbidities, as well as the presence of dementia were significant predictors of mastectomy and omission of axillary surgery (12).

The omission of axillary surgery can be considered in older patients. The SENOMAC trial, in which 40% of the participants were 65 years old and above, demonstrated non-inferiority of sentinel-node biopsy only versus completion axillary-lymph-node dissection in patients with clinically node-negative, cT1 to T3 disease with one to two sentinel lymph node macrometastases (13).

Long-term side effects such as lymphedema and upper limb neuropathy may be managed by primary care physicians by offering lifestyle advice such as physical exercise, referring patients to a physical therapist or occupational therapist, prescribing analgesics for pain, or referring to appropriate specialists (14).

## Radiotherapy

Radiotherapy improves locoregional control in breast cancer. Recent clinical trials have better informed our understanding of the trade-off between local recurrence and reduction of treatment toxicity. Omission of radiation or shortening of fractionation should be discussed with thorough discussion

 

of the nuances of the treatment. In elderly patients with low-risk disease, the PRIME II trial demonstrated a significant difference in ipsilateral breast recurrence rates but similar 10-year distant recurrence incidence and overall survival in patients who did not received irradiation (15). The FAST-Forward trial, in which more than 50% of the patients were aged 60 years or older, showed that an abbreviated course of radiotherapy to the breast or chest wall (26 Gy in 5 fractions over one week) was non-inferior to the standard conventional fractionation (40 Gy in 15 fractions over 3 weeks) in terms of local control and toxicity profiles (16). The FAST trial, comparing 28.5 Gy in one-weekly 5-fraction schedule with 50 Gy in 25 fractions, showed that there were no significant differences in normal tissue effects at 10 years of follow-up (17). The accelerated radiotherapy regimen offers a more palatable alternative for elderly patients, as it reduces the treatment burden in terms of the time and financial commitment required for longer courses of radiotherapy.

Late radiotherapy side effects include skin and subcutaneous toxicities, lymphedema, pulmonary and cardiac toxicities. A literature review on acute and late radiotherapy-related toxicity in older breast cancer patients indicated that they tolerate radiotherapy as well as younger patients (18). Overall acute grade 3+ toxicity (0.0–10.5%) and late grade 3+ toxicity (0.0–13.0%) remained low. Frequent late toxicities were ≤ grade 2, including subcutaneous fibrosis, breast deformity, and telangiectasia. Grade 3 skin and subcutaneous toxicities were less than 5%. Grade 3 arm lymphedema was 0.1% and ≤ grade 2 pulmonary toxicity rates were 0.4% and 0.1%, respectively (18). Importantly, none of the studies that compared different age subgroups found significant age-related differences in toxicity rates.

Pulmonary toxicities include radiation pneumonitis and fibrosis. A prospective cohort of 250 breast cancer patients who received postoperative radiotherapy demonstrated that lung function parameters declined at 3 months after radiotherapy and remained low after a follow-up of 12 years (19). Old age was significantly associated with worse lung function parameters and higher rates of radiation fibrosis and dyspnea. However, it was reassuring that most patient reported mild dyspnea of grade 1 severity.

Left-sided radiotherapy in breast cancer leads to higher long-term cardiovascular risks such as developing coronary heart disease and cardiac death compared to right-sided radiotherapy (20). A population-based study of 29,102 Medicare patients showed that patients with left-sided breast cancer had a higher risk of percutaneous coronary intervention than those with right-sided breast cancer, with a cumulative incidence of 5.5% and 4.5%, respectively (20). This increase in risk was limited to patients diagnosed with myocardial infarction, coronary artery disease, congestive heart failure, or electrical abnormalities within one year before breast cancer diagnosis. The probability of an ischemic heart event is correlated with the mean heart dose (MHD) by a dose-effect relationship (20).

## Endocrine therapy

The majority of breast cancers in elderly patients are hormone positive and HER2 negative (2). Tamoxifen and aromatase inhibitors (AIs) are the backbone of endocrine treatment and are offered in the adjuvant, neoadjuvant, and metastatic settings. Newer agents such as cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, everolimus, PIK3CA inhibitors, and selective estrogen receptor degraders (SERDs) are increasingly used in the metastatic setting as well.

Selection of the appropriate hormonal treatment should take into account the elderly patient's comorbidities, concomitant medications, and personal preferences. AIs are generally preferred over tamoxifen in postmenopausal women as they provide better efficacy (21). However, in the elderly, particular side effects of AIs such as arthralgia, osteoporosis, and increased risk of fractures may impair physical functioning and affect their ability to maintain independence. One prospective study found that the 1-year mortality rate among 758 hip fracture patients aged 60 years and older was as high as 21.1% with usual care (22). On the other hand, tamoxifen is associated with increased risk of stroke, endometrial cancer, and blood clots. Both tamoxifen and AIs are also shown to be associated with lipid disorders (23) and cognitive impairment (24).

Multidisciplinary care involving geriatricians and primary care providers is critical to closely monitor and manage cardiovascular risks, cognitive impairment, and bone health in elderly breast cancer patients. For those receiving AIs, regular monitoring for musculoskeletal symptoms, dualenergy X-ray absorptiometry (DEXA) screening, treatment with vitamin D and bisphosphonates, and lifestyle interventions such as weight management and physical activity are warranted (14).

Adherence to endocrine therapies can be a problem in older patients. The non-adherence rate was observed to be as high as 41% among a cohort of 5,150 Medicare patients with a mean age of 76.4 years. Poorer adherence was observed in patients receiving AIs whereas patients receiving tamoxifen was observed to have the best adherence (25).

 

Physicians should provide adequate counselling of the importance of drug adherence together with close monitoring and prompt treatment of endocrine therapy related side effects (14).

CDK4/6 inhibitors in combination with hormonal therapy is the standard-of-care treatment in the metastatic setting. A systematic review and meta-analysis comparing the efficacy and toxicity profiles of different CDK4/6 inhibitors between older and younger breast cancer patients found that the magnitude of improvement in OS and PFS were similar across age groups, with a reduction in mortality risk by 21% in older patients [hazard ratio (HR) =0.79, 95% CI: 0.69–0.91, P<0.01] and 20% in younger patients (HR =0.80, 95% CI: 0.72–0.9, P<0.01) (26). Grade 1 to 4 neutropenia was significantly higher among the elderly [relative risk (RR) =12.2]. However, grade 3 to 4 neutropenia and diarrhea and other grade 1 to 4 toxicities were similar in elderly and younger patients.

Another systematic review on palbociclib found similar treatment efficacy regardless of age. Notably, global QoL was maintained in both older and younger patients. Despite higher rates of dose modifications, treatment interruptions and discontinuations in older patients compared to their younger counterparts, the PFS and OS outcomes were not adversely impacted (27).

## Chemotherapy

Chemotherapy improves survival in the neoadjuvant, adjuvant, and metastatic settings, and is considered in elderly patients especially for triple negative and HER2-positive disease (28). Common chemotherapeutic agents used in breast cancer include taxanes, anthracyclines, capecitabine, eribulin, and vinorelbine (21). The most common acute toxicities of chemotherapy include neutropenia, nausea and alopecia. Long-term side effects include fatigue, peripheral neuropathy, cardiac toxicity, and cognitive impairment.

A population-based survey of breast cancer survivors aged 65 years and above assessed the long-term patient-reported symptoms with and without prior chemotherapy (29). Compared to those who did not receive chemotherapy, patients who underwent chemotherapy were more likely to report symptoms such as fatigue, aching joints and muscles, numbness or tingling, problems with memory and concentration, hair loss, and arm or leg swelling. Furthermore, the chemotherapy-treated group was also more likely to experience moderate to severe symptoms and interference with daily activities. The most debilitating symptoms affecting daily functioning were numbness or tingling (44.1% *vs.* 22.9% in non-chemotherapy group, P<0.0001), aching muscles (57.8% *vs.* 44.1%, P<0.0001), and problems with memory (47.5% *vs.* 31.7%, P<0.0001) (29).

Chemotherapy is known to induce acute bone marrow suppression. Compared to younger patients, older patients are more likely to suffer from grade 4 hematologic toxicity and death from chemotherapy. Patients aged 65 years or older were 66% more likely than those aged 50 years or below to experience grade 4 hematologic toxicity (P<0.0001) (30). Therefore, careful patient selection with proper CGA and individualized estimates of chemotherapy toxicity risk are crucial when treating elderly patients.

Anthracyclines are associated with a significant risk of cardiac toxicity and should be reserved for high-risk disease in medically fit elderly patients with normal cardiac function. A retrospective cohort of 31,748 older breast cancer survivors showed that patients who received doxorubicin, compared with patients who did not, had higher rates of cardiomyopathy [odds ratio (OR) =2.48, 95% CI: 2.10–2.93], congestive heart failure (OR =1.38, 95% CI: 1.25–1.52), and heart disease (OR =1.35, 95% CI: 1.26–1.44) (31). The RR of cardiotoxicity remained elevated five years after diagnosis. Besides baseline cardiac assessment, primary care clinicians should monitor cardiovascular health and lipid levels and educate patients on healthy lifestyle modifications (14).

Chemotherapy-induced cognitive impairment may lead to poorer QoL and loss of independence in elderly patients. A systematic review and meta-analysis of 52 studies showed that the prevalence of cognitive impairment following chemotherapy for breast cancer were 21–34% assessed by neuropsychological tests, 44% by self-report, and 16% by short cognitive screening tools (32). Primary care physicians should inquire breast cancer survivors about cognitive difficulties, assess for and address reversible factors, and refer patients for neurocognitive assessment and rehabilitation as appropriate (14).

## Immunotherapy

Immunotherapy is used in combination with chemotherapy in triple-negative breast cancer in the neoadjuvant and metastatic settings (21). Common immunotherapy-related adverse events (irAEs) include dermatitis, colitis, thyroid dysfunction, pneumonitis, and deranged liver function.

Compared with trials reporting on cytotoxic, hormonal and targeted agents, immunotherapy had a

disproportionately lower representation of older adults (20% *vs.* 44% for cytotoxic and 54% for hormonal/targeted agents) (3). For example, in the KEYNOTE-522 trial, which assessed the use of neoadjuvant pembrolizumab in combination with chemotherapy in early triple-negative breast cancer, only 11% of the participants were 65 years old or above (33). Similarly, in the KEYNOTE-355 trial, which evaluated the palliative use of Pembrolizumab plus chemotherapy, only 20% of the participants were 65 years old or above (34). Both trials did not include age-specific differences in treatment-related side effects.

Combination immunotherapy-chemotherapy regimens are associated with high rates of grade 3 or higher adverse events. In the KEYNOTE-355 trial, the incidence of these severe adverse events was 68.1% in the immunotherapy-chemotherapy group and 66.9% in the placebo-chemotherapy group. The most common toxicities were anemia, neutropenia, and nausea, which are typically chemotherapy-related. Grade 3 or higher irAEs occurred in only 5.3% of patients in the immunotherapy-chemotherapy group (34).

A multicenter, international retrospective study of 928 cancer patients aged 80 years or above treated with single agent immunotherapy found that the incidence of grade 3 to 4 irAEs remained low (12.2%). Although 22.2% of patients who experienced an irAE required hospitalization, there were no irAE-related deaths (35). There were no significant differences in the rate of irAEs among patients aged younger than 85, 85 to 89, and 90 years or older. Notably, patients aged 90 years or older were more likely to discontinue treatment owing to irAEs than patients younger than 90 years (30.9% *vs.* 15.1%, P=0.008).

The limited data on the efficacy and safety of immunotherapy-chemotherapy combinations in elderly breast cancer patients underscore the need to include this population in clinical trials and report age-specific outcomes.

## Anti-HER2 targeted therapy

Anti-HER2 targeted therapies, such as trastuzumab and pertuzumab, are the cornerstone of treatment for HER2-positive breast cancers (21). A systematic review that evaluated the efficacy and cardiac safety of adjuvant trastuzumab in patients older than 60 years showed that adjuvant trastuzumab resulted in a 47% RR reduction (HR =0.53, 95% CI: 0.36–0.77) and a relatively low risk of cardiac events of 5% (95% CI: 4–7%) (36). Cardiotoxicity, including decline in left ventricular ejection fraction and congestive heart failure, are mostly reversible with appropriate medical management (37). Cumulative doses of anthracycline chemotherapy, underlying cardiovascular disease, prior radiation to the heart, and old age have been found to be significant risk factors of anti-HER2 targeted therapy induced cardiotoxicity (38). Minimizing the risk of cardiotoxicity is particularly critical in the elderly patient population, who often have higher baseline cardiovascular risks and comorbidities. Regular cardiac monitoring, optimization of cardiovascular health, and early intervention are paramount in older patients on anti-HER2 targeted therapy.

## Discussion

The purpose of this study was to provide an overview of the current landscape of treatment-related considerations and toxicities in elderly breast cancer patients. This overview aimed to identify gaps in the decision-making processes and treatment outcomes specific to this demographic and provide treatment recommendations that address the unique needs and challenges faced by elderly breast cancer patients.

The benefits of incorporating CGA in clinical decision-making in elderly breast cancer patients were demonstrated in the Australia randomised controlled trial with improvements in QoL and reduced unplanned hospital admissions (8). However, the incorporation of CGA in routine clinical management is still far from ideal. The American Society of Clinical Oncology (ASCO) Geriatric Oncology task force surveyed 1,277 cancer providers on their practice patterns and barriers to geriatric assessment in year 2021 (39). Approximately half of the participants were unaware of the ASCO Geriatric Oncology guidelines. Common barriers identified were lack of time and manpower, inadequate training and lack of awareness. This highlights the need of raising awareness and enhancing training programmes for cancer providers. The efficiency of CGA may be improved by utilizing validated online tools such as those provided by the Cancer & Aging Research Group (40) and ePrognosis (41).

This review has shown that breast cancer surgeries, radiotherapy, hormonal therapy, CDK4/6 inhibitors and anti-HER2 target therapy are generally well-tolerated in older patients with careful patient selection and prompt treatment of treatment-related toxicities. Careful balancing of treatment benefit and treatment-related toxicities are paramount in chemotherapy patient selection

 

in particular. The low 30-day mortality rates and low systemic complications of breast cancer surgery as shown by Morgan *et al*. (12) provide evidence that breast cancer surgeries, especially radical surgeries, should be offered and adequately explained to elderly patients.

This study is unique in its comprehensive review of cancer care processes for elderly breast cancer patients, encompassing decision-making facilitated by geriatric assessments and survivorship recommendations. However, as this is not a systematic review and no meta-analyses was performed, one significant limitation is the potential for selection or publication bias. Additionally, the studies reviewed varied widely in their objectives and methodologies, making it impossible to conduct quantitative analyses or quality scoring on the gathered data.

## Conclusions

Older patients with breast cancer are a unique group of patients with specific needs and treatment considerations. The diversity of functional health, comorbidities, treatment priorities and preferences among older patients necessitates use of CGA to assist physicians in tailoring treatment plans to meet each individual needs. It is important for physicians to carefully consider age-specific treatment efficacy and potential treatment-induced toxicities when making treatment decisions. Breast cancer surgeries were generally well tolerated. No significant age-specific differences were observed in radiotherapy-induced toxicities. It should be noted that older patients were more likely to suffer from grade 4 hematological toxicity when treated with CDK4/6 inhibitors or chemotherapy. Older patients remain significantly underrepresented and understudied in many major clinical trials. Further efforts to enhance the representation of older patients in breast cancer trials are warranted.

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