Controversial issues in the management of older adults with early breast cancer (EBC)

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Abstract

It is well recognized that the incidence of breast cancer increases significantly with age. Despite this, older people remain under-represented in many clinical trials and their management relies on extrapolation of data from younger patients. Providing an aggressive intervention can be challenging, particularly in less fit older patients where a conservative approach is commonly perceived to be more appropriate. The optimal management of this population is unknown and treatment decision should be personalized. This review article will discuss several controversial issues in managing older adults with early breast cancer in a multidisciplinary setting, including the role of surgical treatment of the axilla in clinically node negative disease, radiotherapy after breast conservation surgery in low-risk tumors, personalizing adjuvant systemic therapy, and geriatric assessments in breast cancer treatment decisions.

Keywords

Older adults, early breast cancer, surgery, radiotherapy, chemotherapy, geriatric assessment

Disclosures

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Introduction

The risk of breast cancer (BC) increases with age. It is estimated that 21% of all incident cases and 13% of BC mortality occur in patients aged ≥70 years in developed countries [1]. While older cancer patients often have distinctive clinical features, aging occurs heterogeneously and treatment approaches cannot be generalized. Moreover, their under-representation from the majority of clinical trials has made their management even more challenging. With advancing strategies and increasing interest in geriatric oncology, several controversies have emerged on how to manage this complex patient group appropriately. This review aims to discuss several current management controversies in older adults with EBC.

I. Management of the axilla in clinically node negative disease

During the last decade, the scope of axillary surgery has dramatically changed mainly due to our better understanding of the role of tumour biology and to major advances in systemic therapy. Prognosis and treatment decisions, originally partially based on axillary lymph node status, are now mainly based on disease burden, biological tumor subtype and multi-gene assays.

Current international guidelines [2-4], recommend sentinel lymph node biopsy (SLNB) as the "standard of care" in clinically node negative (cN0) disease and no further treatment of the axilla is advised in cases of a negative SLN, or when it contains isolated tumour cells or a micro-metastasis as there is no benefit in terms of disease free survival (DFS) or overall survival (OS) [5].

When the SLN is positive for malignancy, axillary lymph node dissection (ALND) is still the "gold standard". However, those patients with only one or two positive SLNs who fulfil the "Z011" trial {a randomised controlled trial between ALND and no ALND following positive SLN(s) for hormone sensitive invasive carcinoma treated by breast conserving surgery (BCS) and whole breast radiotherapy (WBRT)} criteria and who will receive WBRT and systemic adjuvant treatment following BCS, can now be spared further axillary treatment [6] according to major international and national guidelines [7-9]. Furthermore, radiotherapy (RT) to the axilla has also been shown to be an excellent alternative to ALND in the AMAROS trial [10], associated with a significantly lower incidence of morbidity (lymphedema).

Hence, axillary surgery is even less important in older women because of their high mortality from competing comorbidities and with adjuvant hormonal therapy usually achieving long-term DFS. Patients ≥80 years have been found to have on average five medical conditions affecting their OS, as compared to only one or two in patients in their 50s [11]. Relative to their younger counterparts, older patients have shorter life expectancy due to co-morbidities or competing causes of death [12]. Furthermore, they tend to have BC with more favorable phenotypes, i.e. HER2-negative and oestrogen receptor (ER)-positive (and also very ER-rich) [13].

Two randomized trials studied the possibility to omit ALND in older women with cN0 EBC. Rudenstam *et al*. (n=473, 60-91 years) reported similar DFS and OS for surgery + axillary clearance and surgery alone, at a median follow-up of 6.6 years [14]. Martelli *et al.* (n=219, 65-80 years) found just a 2% axillary metastatic involvement at 5-years follow-up; a further analysis at 15-years showed no differences in OS between patients who underwent ALND and those who did not [15]. The CALGB 9343 trial randomized 636 women aged ≥70 years with T1 N0 ER-positive EBC to tamoxifen ± WBRT [16].

Results showed a very low axillary recurrence rate at a median follow-up of 12.6 years – none in those who underwent ALND and in those who did not undergo ALND but received tamoxifen plus WBRT, but 3% in those on tamoxifen alone [17].

Therefore, it is reasonable that combined geriatric and tumor biology assessment should impact on making decisions related to managing this age group. In general, despite chronological age, axillary treatment should be consistent with general guidelines in otherwise fit women. While in most biologically frail or very old and frail patients, omission of axillary staging (SLNB) and/or ALND may be appropriate and may limit any functional detrimental impact on the upper limb that is often already affected by arthrosis.

II. Role of Radiotherapy (RT) after Breast Conservative Surgery in Low-risk Disease

The evidence-base for WBRT, specifically in low-risk older patients after BCS for EBC is limited. The loco-regional recurrence rate in CALGB 9343 trial was 1% in irradiated (RT+) and 4% in non-irradiated patients (RT-) at 5 years, p=0.001 [16] and the difference had increased (2% RT+, 9% RT-) at a median follow-up of 10.5 years [17]. The 5-year results of the trial changed practice, albeit modestly [18] and the National Comprehensive Cancer Network guidelines [19] allow BCS±WBRT in women ≥70 years with clinical stage 1 hormone receptor positive EBC. The PRIME 2 trial [20] randomized 1326 women ≥65 years with T1, T2 (≤3cm), pN0 tumours to 5-year adjuvant endocrine therapy (ET) ±WBRT. There was a modest but statistically significant reduction in local recurrence at 5 years from RT (4.1% vs. 1.3%, p=0.0002), and as in the CALGB 9343 trial, there was no compromise in OS. The authors suggested that RT omission was a reasonable option for these selected older women and the accompanying editorial [21] agreed, though we have yet to see the impact of

the results of PRIME 2 trial on the treatment guidelines. Resistance to RT omission persists even in selected cases [22] due to the risk of local recurrence and the availability of alternative forms of RT (e.g. hypofractionated or intraoperative RT) [23]. While some guidelines [24, 25] do not recommend RT omission after BCS, recent survey of treatment recommendations in older women with BC found that 26% of clinicians choose to omit RT on the basis of chronological age [23]. There is no international consensus on how small a difference in 5-year local recurrence rates for RT+ and RT- patients would have to be for RT to be omitted. If the RT effects are extrapolated from the EBCTCG overview of the breast conserving therapy, the current estimated 5-year rate in the absence of RT is 3% [26]. While clinicians still have concerns for local recurrence even in low risk patients [27], the impact can be minimized with the possibility of further salvage BCS.

New trials are assessing biomarkers to refine the selection of "low-risk" patients for RT omission. In the UK PRIME TIME study, women ≥60 years with ER+ and progesterone receptor (PgR) positive, T1 tumors for whom residual risk of local relapse is <1% per year are screened by a biomarker panel (IHC4+C) [28]. Patients with <5% or > 5% risk of recurrence at 10-years are treated with ET alone or with WBRT and ET, respectively. A local recurrence rate of <1% per year at 10 years would seem a reasonable threshold for RT omission. The PRECISION trial is using genomic profiling by Prosigma assay to select "low-risk" women (50-75 years) with ER+, PgR+, HER2-negative, grade 1-2 tumors to ET without RT in a single-arm study [29].

For older irradiated patients, hypofractionation (e.g. 40 Gy in 15 or 42.5 Gy in 16 fractions) is recommended as in younger patients [30]. Though tumor bed boost after WBRT resulted to a 3.5% statistically significant gain in local control after 10.8-year median follow-up among patients aged ≥60 years with clear margins [31], the benefit

was lost after 20 years of follow-up [32], hence not recommended. Moreover, the benefits of reducing local recurrence have to be balanced against competing risks of non-breast cancer mortality and radiation-induced toxicities, particularly cardiac [33] and second malignancies [34].

Great interest was also directed towards accelerated partial breast irradiation (APBI) techniques in older patients. APBI could be an alternative not only to conventional WBRT, but also with respect to RT omission or ET alone. Currently, different APBI techniques are available based on postoperative approaches - brachytherapy or external beam, or intraoperative irradiation using low-energy photons or electrons.

Four phase III randomized trials on APBI have been published up to date, but none of these was specifically designed for older women [35-38], and no comparison can be made with other trials in which the omission of radiation therapy has been investigated [17, 29]. In the ELIOT trial, only 10% of the general population was elderly. The total number of local recurrence in the ELIOT arm was 35, and 4 out of 62 patients >70 years had relapsed at 5 years [35], with no statistical difference with younger patients. In GEC-ESTRO study, ~16% of patients included were aged >70 years [38]. The recurrence rate and safety profile on the older subset of patients included in the previously mentioned trial in Florence [37] has been reported separately, and revealed no difference in terms of local recurrence rate, DFS and cosmetic outcome. However, OS significantly differed between the groups, favoring APBI arm (p=0.047) [39].

Few phase II studies were designed to specifically address the role of APBI in older patients and none of them has yet published the results in terms of clinical outcomes. In TARGIT-E(lderly) trial, selected ≥70 years old patients with small and low-risk EBC

receive a single intraoperative dose of 20Gy [40]. In agreement with all the TARGIT trials, postoperative WBRT is added to complete the RT treatment if extensive intraductal component, lymphovascular invasion, and/or multifocality are present. In the GERICO-03 phase II trial, 40 older adults received high-dose rate brachytherapy (34Gy in 10 fractions for 5 days), and a good quality of life was reported [41]. Khan *et al*. have reported that APBI resulted in low toxicity, similar cosmesis and local control at 5 years in women >70 years compared with younger women, suggesting that omitting WBRT may be an option in older women with small volume disease [42].

In summary, omission of adjuvant RT following BCS is a reasonable option in women ≥70 years with low-risk, T1N0, hormone sensitive EBC, particularly when the risks of toxicities, advancing age, and comorbidities outweigh the risks of cancer recurrence. Prospective biomarker-assisted studies may be considered in eligible patients. APBI is well tolerated by older patients and may be considered a better alternative to WBRT, but definitive results are not yet available.

III. Role of Adjuvant Systemic Therapy in Early Breast Cancer

Endocrine Receptor positive, HER2-negative EBC

The decision to give adjuvant chemotherapy in addition to ET is debated among women with ER-positive, HER2-negative EBC. Similar decisional process should be made if the standard clinical, biological or genomic risks are to be used, irrespective of age. In a review data from the National Cancer Institute Surveillance Epidemiology and End Results (SEER) database of >40,000 women aged ≥65 years with EBC (11% received chemotherapy), no survival benefit was observed in ER-positive EBC [43]. Identifying patients with low-risk of recurrence having low absolute benefit from chemotherapy based on multi-gene testing, may reduce the unnecessary exposure and toxicity from chemotherapy. Unfortunately, very few data are available in older patients. A study on

trends in 21-gene recurrence score (RS) assay use among 132,222 women aged 66-74 and 75-94 years with BC post-surgery revealed no change in chemotherapy use despite increased RS testing and associated cost in patients ≥75 years [44]. Recent SEER database study (30% of patients aged ≥70years) reported a high BC-specific mortality for older patients with either no 21-gene assay performed or a RS ≥18, but not <18 [45]. In a randomised phase III study of 6,693 women with EBC, chemotherapy provided no 5-year survival or recurrence benefit among patients with high clinical but low genomic risk (1% were >70 years) using the 70-gene signature [46].

Triple negative EBC

Patients with triple negative EBC derive the most significant OS advantage with adjuvant chemotherapy. However in most patients, the decision to give chemotherapy to reduce the risk of recurrence in older population is never straightforward, as the risk-benefit ratio must be weighed in addition to the overall life expectancy. Online tools that provide estimates of benefit of systemic therapy have been studied in a population-based cohort of patients aged ≥65 years. Adjuvant! Online, despite taking into account the comorbidities, did not accurately predict OS and recurrence [47] while PREDICT can only accurately predict 5-year but not 10-year OS in older patients with EBC [48]. For fit, older patients, combination chemotherapy represents the standard of care. The combination of doxorubicin and cyclophosphamide (AC) x 4 cycles or cyclophosphamide, methotrexate, and fluorouracil (CMF) x 6 cycles have been prospectively evaluated in older women in clinical trials [49]. The lower incidence of non-hematological side effects and better compliance has made AC the preferred regimen over CMF. Substitutions with “less intensive” regimens are not as comparable, as capecitabine failed to show non-inferiority with AC in efficacy and tolerability [50], and docetaxel significantly led to increased toxicity and reduced quality of life

compared to CMF [51]. Nevertheless, taxanes may be given as an alternative to anthracyclines to alleviate cardiac risks. Use of docetaxel and cyclophosphamide (TC) has provided a significant survival benefit over AC after 7 years median follow-up, irrespective of age [52]. Although febrile neutropenia may be an issue, this can be minimized with granulocyte colony stimulating factors (G-CSF) primary prophylactic administration [53, 54]. More intensive regimens (both anthracycline- and taxane-based given either sequentially or concomitantly) have not been adequately and prospectively evaluated in older patients. Retrospective per-age subgroup analysis from major randomized clinical trials has shown a higher rate of hematological toxicity and treatment-related deaths [55] and more dose delays, reductions, hospitalizations, and treatment discontinuations in older patients [56]. Therefore, using these regimens are recommended only in fit, older patients with aggressive tumors [57]. Standard guidelines recommend giving primary prophylaxis G-CSF when using chemotherapy regimens yielding a ≥20% risk of febrile neutropenia [58]. However, older age per se is acknowledged as a risk factor interlinked with other factors, such as comorbidities, functional, and nutritional impairments, making primary prophylaxis administration relevant, even with a lower threshold, in this age group.

For older patients with aggressive and/or advanced stage disease but unfit or unsuitable for combination chemotherapy, personalized chemotherapy may be considered. Despite the single-agent paclitaxel failing to show non-inferiority to AC, favorable toxicity profile and only 1% OS absolute difference made paclitaxel a reasonable option for unfit patients needing chemotherapy [59].

HER2-positive EBC

Adjuvant trastuzumab, in combination with polychemotherapy, improves prognosis and is the gold standard treatment for patients with HER2-positive EBC. However,

cardiotoxicity may be an issue. There is a disparity in the cardiotoxicity rates reported in clinical trials and actual practice, perhaps due to strict patient selection, closer monitoring, and early cardiac toxicity recognition in the trial setting. A systematic review of randomized controlled trials on adjuvant trastuzumab (vs. chemotherapy alone) including patients >60 years noted only a 5% pooled proportion of cardiac events [60]. In contrast, population-based studies have reported higher incidence rates of cardiac events in older women given trastuzumab ± sequential anthracyclines [61, 62], with age >80 years, presence of coronary artery disease or hypertension, and weekly dose administration as contributory risk factors [63]. Strategies to minimize toxicities are therefore critical, such as use of anthracycline-free regimens, i.e. TC [64], or weekly paclitaxel in women unable to tolerate polychemotherapy or with Stage I (low risk) disease [65]. Paclitaxel with trastuzumab has yielded a lower rate of serious toxic effects (0.5% incidence of heart failure) and low risk of cancer recurrence (<2% at 3 years) [65]. There remains limited data for using docetaxel and carboplatin combination with trastuzumab in women ≥70 years. Trastuzumab-related cardiac events are linked with the duration of treatment exposure [66, 67] and therefore, shorter treatment duration might be an option especially in older patients to reduce cardiac risks. However, the PHARE trial has failed to show non-inferiority of 6 vs. 12 months of trastuzumab therapy, although more cardiac events were noted in the 12-month group at 3.5 years follow-up [68], and a more detailed age sub-group analysis is needed. Despite the low level of evidence from the literature, trastuzumab monotherapy might be a useful alternative in less-fit patients. Much hope is expected from strengthened action on HER2 pathway and/or associated pathways through dual blockade and/or combination with ET, especially in cases with ER-positive disease, deserving specific investigations.

In summary, personalized assessments of the risk-benefits are essential when considering older BC patients for adjuvant chemotherapy. Fit, older patients with EBC should receive standard adjuvant treatment, while less fit patients may be considered for personalized less toxic regimens if at high risk of relapse. In both situations, surveillance and proactive management of side effects should be guaranteed.

IV. Role of Geriatric Assessments in Breast Cancer Treatment Decisions

Performance status does not appear to be sufficient for differentiating the heterogeneous older population with cancer [69, 70]. Geriatric syndromes, i.e. functional limitations, malnutrition or cognitive impairments, can be present even in those with good performance status and are easily missed if not especially looked for. The 2005 SIOG Task Force recommends implementing a geriatric assessment (GA) in older cancer patients [69]. A GA is a systematic procedure used to objectively appraise the health status of older people, focusing on somatic, functional and psychosocial domains [69], and aimed at constructing a multidisciplinary treatment plan.

Only a limited number of studies have focused specifically on the role of GA in treatment decisions for older breast cancer patients [71]. In a pilot study, Extermann *et al*. found that a mean of six new issues were discovered with GA, issues which had not become apparent in the completed oncologic work-up. For 36% of patients, the treatment plan was revised based on the outcome of GA and for 55%, non-oncologic interventions were implemented to address issues that could influence the course of cancer treatment. Another study found that GA detected medical risks that could affect the patient's capacity for making a treatment decision: 17% of patients had cognitive impairments and 30% had depression [72].

For very old or frail patients with EBC, an important choice is between primary endocrine therapy (PET) and surgery. Previous studies in unselected older patients with

resectable breast cancer have demonstrated that the survival benefit of surgery compared to PET does not become clinically relevant until 3 years after diagnosis [73], which has led to the recommendation that PET should only be offered to women with ER+ tumors with limited remaining life expectancy, who are unfit for surgery, or at increased risk of serious surgical or anaesthetic complications if subjected to surgery [74]. In women, the average remaining life-expectancy at 75 years is 10-11 years, 7-8 years at 80 years, and 4-5 years at 85 years [75]. However, this can be significantly reduced in frail patients with multi-morbidity and poor general health.

Several studies have set out to determine factors predictive of mortality in older patients with EBC. Stotter et al. (n=328) [76] developed a mathematical model including cognitive function, basic and instrumental activities of daily living and American Association of Anaesthesiologists classification, for calculating the probability of death in 3 years. Clough-Gorr et al. (n=660) [77] used GA consisting of physical function limitations, comorbidities, obesity, general mental health, social support and financial resources. This study found a statistically significant and consistent increase in overall 5-year mortality with each additional deficit: 18% for no deficit, 25% for 1-2 deficits and 40% in ≥3 deficits. For 10-year mortality, results were similar: 42%, 58% and 75%, respectively [77]. Although not specifically developed for breast cancer, a well-known and extensively validated instrument for predicting middle-term mortality is the Lee-Index [78, 79], which predicts the 4- and 10-year mortality risk based on demographic variables, comorbidities and functional status. Other potentially useful instruments for patients in various settings (community-dwelling, hospitalized, nursing homes) and time frames can be found at *http://eprognosis.ucsf.edu*, which is based on a systematic review of prognostic instruments [80].

GA can also be used is for predicting chemotherapy toxicity. One instrument [81, 82], including assessment of functional status, level of social activity, neurosensory deficits and assistance in medication-taking, showed that the risk of grade 3-4 toxicity increased significantly with increasing risk scores: 37% in low-risk, 62% in medium-risk and 70% in high-risk patients (p<0.001). Another instrument differentiated between hematological and non-hematological toxicity and found several geriatric domains to be associated with each [83].

In summary, GA can aid in decision making for cancer treatment by highlighting previously unidentified health issues, predicting risk of chemotherapy toxicity and remaining life expectancy. However, data specific to breast cancer is limited.

Conclusion

The management of older patients with EBC can be challenging, as they are under-represented in clinical trials and at risk of both over- and under-treatment. There is enough evidence suggesting that older patients derive similar benefits from surgical, and systemic therapies as younger patients, in terms of reduction in breast cancer-specific mortality and recurrence, though the benefits of RT seem less defined in patients with low-risk disease. Older patients have a higher risk for developing treatment-related toxicity, compounded by the presence of any competing comorbidities, making a careful patient and regimen selection fundamental, as investigated for instance in the ASTER 70s trial [84]. A comprehensive assessment of the overall health status is recommended when weighing the expected absolute benefits of cancer treatment against tumor biology, potential toxicities, physiological age, patient preference, quality of life, and remaining life expectancy.

Footnote:

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