



Review article

Breast cancer treatment in women over the age of 80: A tailored approach

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ARTICLE INFO

Keywords:

Octogenarian
Age over 80
Breast cancer
Screening
Surgery
Adjuvant therapy

ABSTRACT

Breast cancer treatment in women over the age of 80 remains a complex issue due to pre-existing comorbidities, therapy-related toxicities, and the lack of evidence-based data in this population, leading to both overtreatment and under treatment. The average life expectancy of an 80-year-old woman is 9.7 years and chronologic age alone should not be a factor in withholding therapy.

Women over age 80 should be treated on an individual basis, taking into account their overall health and life expectancy, their risk of dying from breast cancer versus other causes, and the benefits versus toxicities of therapies for their tumor. Invaluable online tools are readily available to easily assess life expectancy (ePrognosis), as well as the absolute survival benefits for every tumor type and stage in individual patients (PREDICT, Ajuvant!). This information should be presented to the patient so that they are able to make an informed decision based on their goals, wishes and quality of life. Vulnerable patients should not be bullied or scared into taking unwanted or unnecessary treatments.

1. Introduction

Breast cancer is the most common cancer in women, increasing with age until 80 years. It is estimated that in 2017 in the US over 30,000 new breast cancer cases will be diagnosed in women over 80, accounting for 12% of all cases [1]. Management of breast cancer in this population remains controversial, as there is a lack of evidenced-based data to guide therapies. Women over 80 are often omitted or under-represented in clinical trials and treatment recommendations are often extrapolated from results in younger patients. Subgroup analyses of 'elderly' patients most often use age 65 or 70 as the lower age limit, and results might not be valid in women over 80 years of age. This lack of evidence often results in either overtreatment or under treatment. Treatment of the extreme elderly is further complicated by a wide variation in physical and mental comorbidities, which need to be addressed on an individual basis.

The purpose of this study was to examine existing data in women over age 80 on breast cancer screening, diagnosis, treatment and prognosis. Online tools are discussed, which can aid physicians in the clinical care of these complex patients in whom life expectancy and quality of life are major concerns.

2. Methods

A literature search was performed (Google Scholar, PubMed, Cochrane) using terms including breast cancer, DCIS and/or, screening, treatment, endocrine therapy, surgery, radiation therapy, chemotherapy, prognosis and elderly, octogenarian, age over 80, oldest. Further articles were obtained and evaluated from citations in relevant articles. Over 200 articles/abstracts were screened and over 155 articles were reviewed extensively by the co-authors. Articles were selected for octogenarians or age over age 80. Relevant articles were considered if subgroup analyses of included women over age 65, 70 or 75 y.

3. Results

3.1. Comorbidity and life expectancy

The average life expectancy of an 80-year old female is 9.7 years [2]. There are many healthy octogenarians who will tolerate conventional therapy and have a life expectancy of 10–15 years. Age alone should not be a factor in withholding treatment. Significant comorbidities affect life expectancy and alter the benefit/risk ratio from surgical and adjuvant therapies, and in particular, tolerance of chemotherapy. A comprehensive geriatric assessment is a useful tool to

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Table 1
Online tools with links.

Tool	Link
ePrognosis (Life expectancy) calculator	http://eprognosis.ucsf.edu/calculators/index.php/
ePrognosis Breast cancer screening calculator	http://cancerscreening.epronosis.org/screening/BreastCancerScreening.html
PREDICT – Adjuvant therapy	http://predict.nhs.uk/
Adjuvant! – Adjuvant therapy	http://www.newadjuvant.com/login.aspx

determine functional capacity, nutritional status, cognition, psychological status and social support, which can estimate life expectancy and guide therapy [3]. A weighted index of comorbidities (e.g., Charlson comorbidity index) takes into account the number and seriousness of comorbid conditions, and their effect on mortality [4]. Validated tools like the online ePrognosis calculator can quickly and accurately estimate the life expectancy of an individual patient, which can help with clinical decision-making (Table 1).

- The ePrognosis calculator is an invaluable tool in determining life expectancy in women over 80 years of age, which is critical in decision-making in this population.

3.2. Screening mammography

The incidence of breast cancer in women over 80 years of age is nearly 400 cases per 100,000 women in the US [1]. No one disputes that mammograms save lives through early diagnosis, with a reduction in breast cancer mortality of at least 15% in women over 50 years of age. However, screening mammograms also have ‘harms’, which must be conveyed to the patient. Although the American Cancer Society recommends continuing screening mammography in healthy women with a life expectancy of 10 years or longer [5], the U.S. Preventive Services Task Force concluded that there is insufficient evidence to assess the balance of benefits and harms in women aged 75 and older [6]. A controversial 2013 Cochrane review concluded that although there was an absolute risk reduction in mortality of 0.05%, screening led to 30% over diagnosis and over treatment (absolute risk of 0.5%). This translates to 1 life saved for 2000 women screened over 10 years, while 10 healthy women will be over diagnosed and treated unnecessarily. Furthermore, 200 women will experience psychological distress because of false positive findings [7]. If a healthy octogenarian or patient at increased risk for breast cancer is considering screening mammography, the physician should educate the patient on the actual benefits and harms so that an informed decision can be made.

Results of the ePrognosis Breast Cancer Screening calculator/tool (Table 1) concur with the results of the Cochrane review. For healthy 80-year old patients in excellent health, 100/1000 patients screened will experience harms in the first year including false positive exams (and subsequent unnecessary workups), false negative exams, over diagnosis, overtreatment, and psychological distress. After 10 years, 1/1000 80-year old women will avoid death from breast cancer due to screening and 200/1000 will die whether or not they got tested for breast cancer.

- There is no data supporting routine screening mammography in women over 80 years of age

3.3. Surgery

Mastectomy or breast conserving surgery remains the standard of care for women of any age, unless they are not surgical candidates, refuse surgery, or have a limited life expectancy (< 2–3 years). Surgery improves breast cancer-specific survival in octogenarians with early stage breast cancer [8,9], and has a low post-operative mortality rate,

i.e., 0.5% [10]. In contrast, in elderly women (70 y plus) with locally advanced disease (Stage III) breast cancer-specific survival was the same in surgical and non-surgical groups [9]. In frail elderly women with hormone receptor positive tumors who are unfit for surgery, or women who refuse surgery, primary endocrine therapy should be offered [11].

Most older women are candidates for breast preservation, and those with smaller, hormone receptor positive tumors and clinically negative axilla (on physical examination and imaging) are unlikely to benefit from sentinel node biopsy, which would not change management. Although there are no studies in women 80 years and older, a study in women over 70 showed that omission of axillary staging did not affect overall or breast cancer specific mortality [12]. Patients with clinically involved axillary nodes should be considered for axillary dissection to control disease [13].

Women over age 80 have a high incidence of ductal carcinoma in situ (DCIS). A study in octogenarians showed that although surgery did not provide an overall survival benefit in DCIS, it did provide a survival benefit for those with ‘high grade’ DCIS and should be considered in fit elderly [14].

- Surgical therapy should be considered in women over age 80 unless comorbidities and limited life expectancy are prohibitive

3.4. Radiation therapy

Though adjuvant radiation therapy after lumpectomy is the standard of care, there is a high rate (64%) of noncompliance in octogenarians [15]. The main benefit of radiation therapy is lowering the risk of local recurrence, which is 1% per year on average. Although no trial has exclusively investigated women over 80 years of age, the CALGB 9343 trial looked at women over age 70 with stage 1, estrogen receptor (ER) positive tumors [16]. At 10.5 years there was a 9% local recurrence with endocrine therapy alone versus 2% with the addition of radiation therapy. Less than 1/100 (0.67) women per year benefited from therapy. Omission of radiation therapy did not affect distant recurrence or overall survival. Morbidity was much higher in the radiation therapy group [16]. The PRIME II trial, which included women over 65 y, reported 4.1% versus 1.3% local recurrence at 5 years [17]. In addition, a 15-year non-randomized trial reported similar findings for stage 1 disease [18]. This study also included tumors up to 5 cm. For 2–5 cm (pT2) tumors, there was a 14.6% incidence of ipsilateral breast tumor recurrence at 15 years in untreated women. However, breast cancer mortality and distant metastasis did not differ significantly [18]. These results may be even more significant for octogenarians.

There are no studies investigating the absolute benefits versus risks of radiation therapy in women over 80 years of age with ER negative tumors and/or with more advanced disease. A fit octogenarian may tolerate radiation therapy and derive a benefit in local and regional control of disease and should not be undertreated. Mastectomy with or without axillary dissection would also be an option for local control of advanced disease. Although there is a lack of data in women over 80 years of age, post mastectomy chest wall radiation may be considered for fit elderly patients with four or more positive nodes or a tumor over 5 cm.

- Radiation therapy may be omitted in octogenarians with early stage, hormone receptor positive disease undergoing breast conservative surgery

3.5. Endocrine therapy

Over 85% of breast cancers in women over 80 years of age are ER positive (versus ER negative), which offers a survival advantage even in women unfit for surgery or chemotherapy [19,20]. Endocrine therapy is well tolerated in octogenarians. However, women in this age group are

often noncompliant with hormonal therapy [15]. There are no trials looking at the benefit of endocrine therapy, anti-HER 2 therapy, or chemotherapy specifically in women over 80. Results of studies in younger women are often extrapolated to this population. Online mathematical models like PREDICT and Adjuvant! (Table 1) allow physicians to easily calculate the overall 5 year and 10 year survival and ‘disease recurrence’ benefits of adjuvant therapies. However, these models have not been validated in women over 80 years of age and may overestimate the benefits of adjuvant therapies. Life expectancy, comorbidities, clinical judgment, and the patient’s wishes must be considered in treatment decisions. Patients over age 80 need to be informed of the actual benefit in terms of overall survival (e.g., 2 out of 100 women will be alive at 10 years because of therapy) using prognostic tools, as well as the actual risks and side effects of therapy before making an informed decision.

Tamoxifen or an aromatase inhibitor should be considered for most octogenarians with ER positive tumors. However, the benefit may be minimal for surgically treated small low-grade tumors, and in women with a limited life expectancy. The minimal benefit may not justify the side effects and risks of therapy. The BIG 1-98 trial demonstrated that although there was a slight benefit in disease free survival, there was no overall survival advantage in women over 75 y for aromatase inhibitors versus Tamoxifen [21]. Women with an intact uterus or at increased risk for thrombosis may better tolerate aromatase inhibitors. Whereas elderly women at increased risk for fractures may do better on Tamoxifen. In women over 75 years of age, 6.2% of patients treated with Letrozole and 1.4% of patients treated with Tamoxifen experienced lethal adverse cardiac events [21]. The optimum duration of endocrine therapy also remains unanswered in the extreme elderly, as efficacy may not outweigh risks and side effects of long-term therapy. After 2 years of therapy, severe toxicities appeared in 73% of women over 75 on Letrozole and 60% of women treated with Tamoxifen [21]. A shorter duration of therapy may be appropriate in this population.

Primary endocrine therapy may be considered in frail elderly patients or patients who refuse surgery [22]. Non-aromatizable androgens or testosterone in combination with an aromatase inhibitor may be considered, which can also improve quality of life in this patient population [23].

- On-line tools can help determine the absolute benefits and risks of endocrine therapy based on individual tumor characteristics, age, comorbidities, and life expectancy.

3.6. Locally advanced, metastatic disease and chemotherapy

Although there is no data on the use of chemotherapy specifically in women over 80 years of age, chemotherapy should not be omitted based on age alone. Healthy older patients may benefit from chemotherapy, but may also experience more treatment related toxicities. Single agent therapy and reduced doses of cytotoxic agents might need to be considered.

Most studies evaluating the benefits of chemotherapy in ‘older women’ use a lower cut off age of 65 or 70 with few phase II trials jointly assessing efficacy and tolerance to treatment, e.g., toxicity, quality of life etc. [24]. In frail patients or patients with multiple comorbidities, aggressive treatment may not result in a survival benefit compared to younger women. Women over age 80 may also be at a greater risk of cardiac toxicity, arterial thromboembolic events, and worsening of cognitive dysfunction (chemo brain) from therapies. A retrospective single-center cohort study including 2276 breast cancer patients found that omission of chemotherapy in patients over age 75 did not affect breast cancer specific or overall survival [25]. Despite more advanced stage at diagnosis compared to younger women, the majority (78%) of patients over age 80 do not die from breast cancer [19]. However, half of octogenarians with advanced disease, ER negative, and poorly differentiated tumors do die from breast cancer [26].

What is uncertain is the absolute benefit of adjuvant therapies in this patient population. Competing causes of death may influence prognosis, and chemotherapy may have less benefit on overall and disease specific survival.

In patients over age 80 considering chemotherapy biological age instead of chronological age should be considered. Life expectancy should be calculated (e-prognosis), and online tools (PREDICT and Adjuvant!) should be used to determine the absolute survival benefit of chemotherapy prior to the patient making an informed decision. Increased risks of toxicities and adverse effects on quality of life should be discussed in detail. Overestimation of disease prognosis and benefits from therapy should be avoided. Overtreatment near death (in all patients) should be avoided and palliative care considered.

- Morbidity and toxicities from chemotherapy often outweigh survival benefits in the elderly

4. Discussion

Our findings confirm the lack of evidence guiding breast cancer screening and adjuvant therapies in octogenarians, including the lack of validation of online adjuvant therapy tools. An attempt was made to review available data, which can help physicians in all specialties avoid both under treatment and overtreatment in this vulnerable age group.

Breast cancer patients of all ages should be evaluated and treated on an individual basis. The physician should make every effort to provide the patient with complete and accurate information and not overestimate or under estimate the benefits and risks of therapies. Clinical decision-making should not be based on age alone. The patient’s overall health and life expectancy should be considered and a geriatric consult obtained if indicated. The ‘ePrognosis’ life expectancy calculator (Table 1) is simple to use and can provide objective data that can help the physician and the patient understand the benefits and risks of therapies. Although not validated in women over the age of 80, ‘PREDICT’ and ‘Adjuvant!’ tools (Table 1) can assist in individualizing patient care, providing survival data that can be shared with the patient so an informed decision can be made and respected.

5. Conclusion

Despite the high incidence of breast cancer in women over 80 years of age, there is a lack of evidenced based data to guide clinical decision-making in this complex age group. Life expectancy and comorbidities of each patient must be considered as well as tumor characteristics and stage of disease. Understanding the full impact of breast cancer and cancer therapies on emotional, mental, and physical wellbeing will maximize the quality of life for elderly patients as well as their families and caregivers.

Research agenda

- Further research in breast cancer treatment in octogenarians is desperately needed in this under-represented population.
- Women over 80 years of age need to be included in prospective trials, which should be designed to jointly assess both efficacy and tolerance of therapies.
- Online predictive models can then be validated for this population, and designed to include adjuvant radiation therapy.

Contributors

All three authors participated in the literature search, analysis and interpretation of the data, and the writing of the manuscript.

All authors saw and approved the final manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

No funding was received for the preparation of this review.

Provenance and peer review

This article has undergone peer review.

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