



Treatment and patient related quality of life issues in elderly and very elderly breast cancer patients

Bengü Depboylu

Department of Radiation Oncology, Faculty of Medicine, Aydin Adnan Menderes University, 09100 Kepez Mevkii/Aydin, Turkey

Correspondence to: Bengü Depboylu, MD. Department of Radiation Oncology, Faculty of Medicine, Aydin Adnan Menderes University, 09100 Kepez Mevkii/Aydin, Turkey. Email: engu.depboylu@adu.edu.tr.

Abstract: As the number of aging population increases, a significant amount of elderly cancer patients need more personalized care for their cancer treatment. Breast cancer is the most common cancer in women, and almost half of the newly diagnosed patients are older than the age of 65 years. With their peculiar characteristics, elderly patients with breast cancer should be held with a comprehensive geriatric assessment. It is vital to make the choice of correct treatment more delicately, to better predict the prognosis of the patient and risks associated with specific treatments. The current article focuses on how various methods of treatment in elderly breast cancer affect their quality of life and the challenges they experience among age from 70 to 79 and age from 80 and over subgroups of this population. Treatment (surgery, radiation therapy, chemotherapy, and endocrine therapy) and patient-related (mental health, physical function, frailty, cognitive function, nutrition) quality of life issues are revisited in the light of recent literature.

Keywords: Breast cancer; elderly; frailty; geriatric assessment; quality of life

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Introduction

Cancer of the female breast is one of the top three cancer types in terms of incidence and ranked as fifth in terms of mortality. Since the prognosis is relatively favorable, when compared with other cancers types such as lung cancer, colorectal cancer, etc., at least in more developed countries, it is responsible for 627,000 deaths (6.6% of the total) according to the latest global cancer data in 2018 (1).

Age is an important risk factor for breast cancer. It is accepted by most of the developed world countries that chronological age of 65 years as a definition of “elderly” or “older person” (2). On the other hand, Breast International Group proposed age of 70 years if chronological age would be used as a frame of reference to define the elderly population (3) Therefore, “elderly patients” are mostly referred to patients as 65 or 70 for the lower age limit, however, there is no described age for the upper limit to this cohort of patients.

Given the fact that cancer is on the rise in the elderly

as well as other diseases (e.g., diabetes, cardiovascular conditions, pulmonary disease), patients older than 65 years of age are reported to comprise almost 45% of newly diagnosed breast cancer cases (4). An average 65-year-old patient is expected to live 20 years more, likewise, a 75-year-old patient is substantially expected to live 12 years more. For some types of breast cancer such as triple-negative pathology may frequently have an early relapse which put such patients at high risk for recurrence (5).

Until recently elderly breast cancer patients were used to be underrepresented in clinical trials (6,7). It is promising that more specific trials are being tailored mainly addressing older women with both localized and metastatic breast cancer (8-12). As more detailed information about clinicopathological features of breast cancer in the elderly is obtained, it becomes more important it is to understand that it differs in a unique way from the features of breast cancer in the younger population (13).

The elderly patient’s status of health should be assessed by using geriatric assessment tools which is a validated

instrument. Estimation of life expectancy and mortality are among aspects of it. It's a thorough challenge for oncologists to prescribe an appropriate treatment that strikes a delicate balance in a patient's quality of life (14).

The current article focuses on how various modalities of treatment in elderly breast cancer affect patients' QoL and the challenges they experience among age from 70 to 79 and age from 80 and over subgroups of this population. Treatment and patient-related QoL issues are revisited in the light of recent literature.

Breast cancer tumor characteristics in elderly and very elderly women

In a recent review article by Lodi *et al.*, clinicopathologic characteristics in elderly women showed a distinction between ages from 70 to 79 and from 80 and over. Analysis of thirteen articles showed that radiological cancer detection (38.7% *vs.* 22.2%, $P < 0.01$), small tumor size (T1) (57.7% *vs.* 42.9%, $P < 0.01$), lymph nodes were less frequently assessed (53.7% *vs.* 44.2%, $P < 0.01$), the presence of metastases were also less frequently assessed (94.1% *vs.* 92.0%, $P < 0.01$) ductal and lobular histological subtypes (66.8% *vs.* 61.5%, $P < 0.01$ and 10.0% *vs.* 6.9%, $P < 0.01$; respectively), histological tumor grade III was more frequent (25.5% *vs.* 21.5%, $P < 0.01$), presence of lymphovascular invasion (29.7% *vs.* 22.9%, $P < 0.01$) were all significant for the 70–79 years sub-group.

In the 80 and over sub-group clinical cancer detection (77.8% *vs.* 61.3%, $P < 0.01$), bigger tumor size T2 (43.5% *vs.* 33.0%, $P < 0.01$), less frequent lymph node assessment and more frequent unknown status (N_x) (12.5% *vs.* 4.0%, $P < 0.01$), more frequent lymph node metastasis with less N0 (56.0% *vs.* 50.5%, $P < 0.01$) and more N+ (44.0% *vs.* 49.5%, $P < 0.01$), more frequent distant metastasis (8.0% *vs.* 5.9%, $P < 0.01$) more frequent mucinous and other histological type carcinomas (4.3% *vs.* 3.7%, $P < 0.01$ and 27.3% *vs.* 19.6%, $P < 0.01$) more the histological tumor grade I (23.2% *vs.* 19.8%, $P = 0.01$) less grade III (21.5% *vs.* 25.5%, $P < 0.01$) more hormone sensitive tumors with more PR expression (72.6% *vs.* 67.3%, $P < 0.01$), less frequent lymph vascular invasion (22.9% *vs.* 29.7%, $P = 0.03$) were found.

Breast cancer mortality in these two different groups were also distinctive. In 70–79 years sub-group overall survival at 5 years were clearly inferior to 80 and over sub-group due to more frequent occurrence of tumors with aforementioned features (16.1% *vs.* 53.5%, $P < 0.01$). Interestingly, in the 80 and over sub-group an increase in

breast cancer-specific mortality is observed both at 5 and 10 years (25.8% *vs.* 17.2%, $P < 0.01$ and 32.7% *vs.* 26.6%, $P < 0.01$; respectively) (15).

With their peculiar characteristics, elderly patients with breast cancer should be held with a comprehensive geriatric assessment. This useful tool determines functional capacity, nutritional status, cognition, psychological status, and social support. It estimates life expectancy and guides therapy to make the choice of correct treatment more delicately. In this way, the prognosis of the patient can be better predicted and risks associated with specific treatments better foreseen.

Treatment-related quality of life issues: surgery for breast cancer in the elderly and very elderly

Surgical resection is the milestone for women with early-stage breast cancer, unless they refuse surgery, are not an appropriate candidate for surgery due to their comorbidities, have a short life expectancy less than 3 years. Breast-conserving procedures or mastectomy, with or without sentinel lymph node biopsy and/or axillary lymph node dissection are options for it.

The EORTC 10850 trial showed that in early breast cancer mastectomy and breast-conserving surgery are equally effective in terms of survival, but studies continue to show proof that patients undergoing breast-conserving surgery have a better QoL. Women undergoing lumpectomy plus tamoxifen did not differ from those that are undergoing a mastectomy in terms of fatigue, emotional functioning, fear of recurrence, social support, physical functioning and free time activities. Patients treated with mastectomy reported fewer arm problems ($P = 0.04$) and better feeling of body image ($P = 0.06$), but relations were statistically borderline. As better results were reported in QoL following conservative treatment, this modality can be utilized in elderly patients just like their younger counterparts (16).

The ACOSOG Z0011 (Alliance) Randomised Clinical Trial showed that among women with T1 or T2 invasive primary breast cancer, no palpable axillary adenopathy, and 1 or 2 sentinel lymph nodes containing metastases, 10-year overall survival for patients treated with sentinel lymph node dissection alone was noninferior to overall survival for those treated with axillary lymph node dissection (17).

According to the current literature, age is not considered a major risk for surgery in the elderly. Functional status is a better variable for postoperative complication prediction. Functional reserve of elderly cancer patients should be

evaluated by The Preoperative Assessment of Cancer in the Elderly (PACE) before the planned surgical resection (18).

Treatment-related quality of life issues: radiation therapy for breast cancer in the elderly and very elderly

The data relating to the effect of radiation therapy on QoL in elderly breast cancer patients is growing. It is controversial whether irradiation of the whole breast following the breast-conserving surgery in elderly women. In a meta-analysis by Clarke *et al.*, none of the randomized trials which were analyzed showed a decrease in overall survival when whole-breast radiotherapy (WBRT) was omitted (19).

The CALGB 9343 trial has primarily focused on women 70 years or older with clinical stage 1, ER-positive breast cancer. Locoregional recurrences were 1% for patients with WBRT and 4% for those without at 5-year median follow up (20). At 10-year median follow-up, LRRs were 2% and 10%, respectively, although with no overall survival difference (breast-cancer-specific survival 98% *vs.* 96%; overall survival 67% *vs.* 66%) was observed (21).

The effect of the omission of radiotherapy on quality of life is assessed by PRIME I (Postoperative Radiotherapy in Minimum-Risk Elderly) study which accrued 255 patients with T0-T2, N0, M0 axillary node-negative patients after breast-conserving surgery with clear margins. There were no significant differences in overall QoL during 15 months of follow-up, between irradiated and non-irradiated patients. Radiotherapy had an adverse effect on breast symptoms and social functioning (22). No difference in overall QoL scores was observed at 5-year median follow-up, although patients mentioned hospital transport and accommodation problems as important matters (23).

PRIME II Study which accrued 1,380 patients with T1-2 (≤ 3 cm), node-negative disease showed a significant but modest reduction in local recurrence for women aged 65 years or older with early breast cancer 5 years after randomization (1.3% *vs.* 4.1%; $P=0.0002$) (8). The potential effect of local relapse on QoL and psychological state in older patients should always be considered in the long term.

In the light of current literature, it can be concluded that no specific sub-group of patients in whom WBRT following breast-conserving surgery can be systematically omitted. Lacking overall survival benefit, surgical treatment options for local recurrences should be considered as alternative balancing with the logistics of daily visits to radiotherapy

clinic for treatment and patient's individual preference regarding the potential of local relapse (24).

Relating to women 80 and over Strader *et al.*, showed a high rate of (64%) noncompliance with recommendations of radiation therapy following breast-conserving surgery this group (25). The lack of trials which investigate the benefits and risks of radiation therapy in women 80 years and over with hormone-negative tumors and/or advanced disease directs clinicians to consider factors that include life expectancy, general health and functional status, risk for local recurrence plus mortality risk from heart related comorbidities, while deciding for breast irradiation. In the elder population, patients with a life expectancy of more than 5 years, those with large (5 cm) tumors, LN (+) or ER (-) hormone receptors may benefit most from radiation therapy.

Treatment-related quality of life issues: chemotherapy and endocrine therapy for breast cancer in the elderly and very elderly

The largest patient series of adjuvant chemotherapy in older women belongs to the SEER database with 41,390 cases aged 65 or over (stage I-III disease). Among these patients, only 4,500 (10.9%) were given adjuvant chemotherapy (aged 65-69, 21%; aged 70-74, 13%; aged 75-79, 8.6%; aged 80 or over, 2.4%). Patients with nodal involvement and ER-negative disease had most survival benefit. However, patients with nodal involvement and ER-positive disease had no survival benefit at all (26).

Risks and benefits of a chemotherapy regimen must be evaluated deliberately due to the increased potential risk for adverse effects. The cardiotoxic side effects of anthracyclines are higher in the elderly. Older women may experience higher rates of febrile neutropenia with docetaxel and cyclophosphamide, but both are superior for disease-free survival and overall survival (27). In HER2 overexpressing tumors, chemotherapy plus trastuzumab combination is preferred. The SEER data shows that elderly patients are less likely to complete 1-year standard trastuzumab treatment. Trastuzumab can be combined with docetaxel and carboplatin or paclitaxel in elderly patients as they can cope with such regimens better (10,28). In general, elderly breast cancer patients less likely undergo guideline-based treatments, thus their survival decrease (29). Nevertheless, studies have shown that elderly breast cancer patients can be tolerant to standard, even intensive, chemotherapies almost as good as younger patients (30).

However, it should be kept in mind that hospitalizations because of chemotherapy-related toxicity can be high due to functional status and survival decline (31).

Almost 85% of women with breast cancer aged 80 years and over are ER-positive status that brings a survival advantage even if the patient is unfit for surgery or adjuvant chemotherapy (32,33). Even though there is not enough data about the use of chemotherapy specifically in this patient population, chemotherapy should not be omitted only because of their old age. Chemotherapy can be beneficial for fit older patients age 80 and over, however, clinicians should be alert for more frequent chemotherapy-related toxicities. Generally, cardiac toxicity, arterial thromboembolic events increase, cognitive dysfunction gets worse. Chemotherapy with a single agent and attenuated doses of cytotoxic agents should also be considered.

Women with breast cancer aged 80 and over present with more advanced disease at diagnosis, interestingly 78% of these patients do not die from breast cancer (32). The absolute benefit of adjuvant therapies in patients aged 80 and over is uncertain. Chemotherapy may promote less overall survival and disease-specific survival. Increased risks of toxicity and impact of negative effects on QoL should be informed and discussed in detail with the patients and their caregivers.

Endocrine therapy is an integral part of systemic therapies in suitable breast cancer patients. It can be administered either in a neoadjuvant setting or an adjuvant setting. A growing body of literature advocate neoadjuvant endocrine therapy as a good alternative option for frail patients with limited life expectancy or refuse breast surgery (34-36).

Neoadjuvant endocrine therapy can be advised as a more effective option for luminal A type breast cancer patients, which is the predominant tumor type in the elderly. Aromatase inhibitors (AI) and selective estrogen receptor modulators (SERM) are utilized for these patients. Studies comparing the two types of agents showed that either both have equal efficacy or AI's are superior. A treatment period of 3-4 months is necessary to achieve a good clinical response (34-38).

Adjuvant endocrine therapy should be considered in most postmenopausal women with early breast cancer usually following surgery and radiation. Aromatase inhibitors and tamoxifen can be both used in this setting. Age-independent superior efficacy of AI's are proven over tamoxifen, therefore healthy patients who finished 5 years with tamoxifen should be considered for extended adjuvant therapy with an AI (like Letrozole) (9,39). Recently, the DATA, IDEAL, and NSABP B42 trials showed that extended adjuvant endocrine therapy with AIs beyond

5 years in postmenopausal women with early breast cancer reduces the occurrence of secondary breast tumors. But it has very little or no positive effect on survival without distant metastasis. Furthermore, the patients gradually leave the treatment due to the toxic side effects of adjuvant AI's, thus deaths out of breast cancer-related reasons increase. In conclusion, it is suggested that extended adjuvant treatment should be considered only in women who are fit in condition but have high-risk factors (40-43).

Endocrine therapy-related side effects should be delicately evaluated. Arthralgia, osteoporosis, vaginal dryness, dyspareunia, and loss of sexual interest are common side effects caused by two types of agents. However, vaginal bleeding or discharge, cold sweats, and thrombosis are reported more frequently with tamoxifen. Side effects of treatment may strongly impact a patient's quality of life. In case of poor management, they may even cause discontinuation of treatment thus worsening the outcome (44-46).

Endocrine therapy is well tolerated in women with breast cancer aged 80 and over because 85% of them have ER-positive hormone profile which allows them a survival advantage when they are not suitable for surgery or chemotherapy (32,33). Unfortunately, patients of this cohort are often noncompliant with endocrine therapy (47). Fifty percent of women with breast cancer aged 80 and over are prescribed tamoxifen by their physicians when compared with their younger counterparts. Women aged 85-92 are 25% less prescribed tamoxifen than those aged 80-84 years. The concerns regarding thromboembolic risk, treatment adherence, and other comorbidities might drive physicians to be reluctant for tamoxifen prescription. Moreover, the adverse effects and therapy-related risks may outweigh the expected benefits.

The optimum duration of endocrine therapy is not clear in women aged 80 and over, its efficacy may be inferior to the risks and side effects of long-term therapy. A shorter duration of therapy may be better in this patient population. Testosterone or nonaromatizable androgens can be combined with an aromatase inhibitor, which can also improve the QoL in this population, may be preferred (48,49).

Patient related quality of life issues in the elderly and very elderly breast cancer patients

While treating elderly women with breast cancer, it is essential for clinicians to understand the patient's specific personal needs for medical treatment, her values, and priorities for QoL. It becomes of critical importance as the

number of accompanying comorbidities increase and mental or physical functions decrease. Efforts should be made for patients and family members understand the possibilities for a cure, potential side effects of treatment, the impact of their consequences on quality of life.

Declines which are due to age in major physiologic functions such as cardiovascular, renal and hepatic functions and hemopoietic reserve may negatively affect the patient's ability to endure surgery, cytotoxic therapy, and irradiation. Poorer prognosis is associated with the number and severity of comorbidities as well as functional impairment. In the same way, mental, emotional and nutritional status, polypharmacy and poor family relations or social support can interfere with effectiveness and tolerability of treatment, with negative results for outcome and survival (50).

The decline in physical functioning is very important because it is associated with the inability to perform daily life activities, and it potentially prevents the independence of elderly patients. Physical activity has a positive effect on muscular strength and balance, thus functional decline may be prevented (51).

Frailty is a common concept in elderly breast cancer patients which can begin at any age. Falls, incident disabilities comprise an increased risk for growing numbers of hospitalization and mortality. Frailty is defined as "a clinical syndrome in which three or more of the following criteria are present: unintentional weight loss (5 kg in the past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity". Patients that have at least two criteria of those mentioned above have a high risk for progression to frailty (52,53). Frail or pre-frail elderly patients at the beginning of breast cancer diagnosis have increased the risk for long-term worse physical function and reduced social roles, as well as, more fatigue, depression, and sleep disturbances. Recently a secondary analysis of CALGB 369901 also proved, pre-frail and frail patients have elevated long-term all-cause and breast cancer-specific mortality (54).

Accelerated cognitive decline and memory problems are another patient related quality of life issue. Based on CALGB 369901 results and follow-up data Durá-Ferrandis *et al.*, reported that 7.6% of patients had accelerated the decline in cognitive function. This study also indicated that personality and social resources affect the course of the long-term emotional status in the elderly, while clinical factors are more important for physical, cognitive and functional outcomes. Patients with accelerated decline should be identified early and psychological support must be provided for them as soon as possible (55).

Mental health is a vital part of the quality of life. During the course of their treatment, cancer patients experience many different changes in their emotional status and mental health. Anxiety and depression are reported as the most prevalent mental health pathologies among this patient population. Emotional support is very important for mental wellbeing. Puigpinós-Riera *et al.* reported that patients with low emotional support were at greater risk for anxiety and depression (56). Moreover, Avis *et al.* suggest that social support promotes QoL by improving the mood and self-esteem, decreasing daily life born burden, and better improvising of information and resources (57). Fact is that the different dimensions of emotional support; tangible, emotional, affective and social interaction influence self-efficacy in deciding treatment-related matters and in the process of self-care (58).

In the light of published articles on diet and nutrition, there's a lack of information referring to the outcomes according to age differences. Malnutrition is more common in patients aged 70 and over (59). A majority of older breast cancer patients take supplements like multivitamins (60). Malnutrition in the elderly is associated with functional dependence, decreased cognitive function and depression (61). Poor oral hygiene and dental problems may cause disability in chewing and swallowing, eventually increasing the risk of malnutrition (62). A healthy diet rich in fruits and vegetables, whole grains, with less animal fat protects against the risk of breast cancer recurrence and other chronic conditions.

Conclusions

Due to the rapid advances in the field of medicine, the life expectancy of human gets longer, and the number of malignancies increases in the elderly population. Breast cancer risk rises with the age, plus almost half of the women diagnosed with breast cancer are over age 65 years and over. However, there is no consensus for standard therapy of this patient population, and they are either likely to have less treatment or discontinue the standard treatments. In the light of growing evidence, it is now advised that each elderly patient should be handled with comprehensive geriatric assessment tools and a multidisciplinary approach should be conducted. For fit elderly patients, standard treatments should be offered irrespective of age.

Clinicopathologic features of breast cancers in the elderly show a distinction between women aged 65 and over and women aged 80 and over. While offering the treatment choices, efforts should be made for patients and family

members understand the possibilities for a cure, potential side effects of treatment, the impact of their consequences on quality of life. Good QoL should be the primary concern in the treatment of elderly breast cancer patients. Treatment-related and patient-related quality of life issues should be evaluated diligently.

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