

# Breast cancer in women over 70 years of age: guidelines for diagnosis and treatment

## *Câncer de mama em mulheres acima de 70 anos de idade: diretrizes para diagnóstico e tratamento*

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### ABSTRACT

In Brazil, life expectancy among women is 75 years. The current population aged over 70 years exceeds 4.5 million, and is expected to grow even more in the coming years. Contrary to expectations, the clinical outcome of breast cancer appears to be similar in both younger and older women. Level I evidence randomized prospective studies involving patients older than 70 years with breast cancer are scarce. Early diagnosis using mammography enables less aggressive treatments. Therefore, the need for mammographies should not be overlooked in elderly women. Surgical treatment carries low morbidity and mortality even among elderly women. Nonetheless, comorbidities, impaired general health status and limited life expectancy are factors that limit systemic treatment and radiotherapy in these women. Thus, the elderly are more prone to under-treatment leading to reduced overall survival and disease-free survival. Whenever possible, the approach to breast cancer in women over age 70 should comply with protocols previously established for younger women. Comorbidities, performance status and life expectancy should be factored in planning for individualized treatment.

**Key words:** Women; Aged; Mammography; Breast Neoplasms/surgery; Breast Neoplasms/chemotherapy; Breast Neoplasms/radiotherapy; Women's Health.

### RESUMO

*No Brasil, a expectativa de vida para as mulheres é de 75 anos e a população acima de 70 anos, atualmente, ultrapassa os 4,5 milhões de mulheres com previsão de crescimento para os próximos anos. Ao contrário do que se imaginava, a evolução clínica do câncer de mama parece ser semelhante em mulheres idosas quando comparadas às mais jovens. Estudos prospectivos randomizados com nível I de evidência envolvendo pacientes com mais de 70 anos portadoras de câncer de mama são escassos. O diagnóstico precoce, por meio da mamografia, proporciona tratamentos menos agressivos. Portanto, a mamografia não deve ser negligenciada em idosas. O tratamento cirúrgico é de baixa morbidade e mortalidade mesmo em idosas. Por outro lado, comorbidades, estado geral comprometido e limitada expectativa de vida são fatores que limitam o tratamento sistêmico e radioterápico nessas mulheres. Diante disso, as idosas estão mais sujeitas ao subtratamento com prejuízo para a sobrevida global e sobrevida livre de doença. Sempre que possível, a abordagem do câncer de mama nas mulheres acima de 70 de idade deve respeitar os protocolos previamente estabelecidos para as mais jovens. Comorbidades, performance status e expectativa de vida devem ser consideradas para a definição do tratamento individualizado.*

**Palavras-chave:** Mulheres; Idoso; Mamografia; Neoplasias da Mama/cirurgia; Neoplasias da Mama/quimioterapia; Neoplasias da Mama/radioterapia; Saúde da Mulher.

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## INTRODUCTION

The World Health Statistics report of the World Health Organization presented at the 2007 60th World Health Assembly in Geneva reveals that the life expectancy of women has been increasing globally and has reached a current global average of 68 years. In Brazil, life expectancy for women is 75 years<sup>1</sup> and in western countries, for women aged over 70 to 80, it is 15.5 and 9.2 years, respectively.<sup>2</sup>

According to the IBGE, the Brazilian female population aged over 70 years has grown 128% in the last 20 years, from 2,082,342 to 4,750,292 women today. For the next 20 years, a growth of 122% is expected, reaching a total of 10,545,602 women.<sup>3</sup>

The aging process is highly individualized and multidimensional. Chronological age is not always enough to predict an individual's physiological decline, in part as a result of comorbidities. Perception of one's own health, limitations to activities daily living due to health problems, bed confinement, and cognitive functional levels are better indicators of quality of life in elderly women than the presence of specific diseases<sup>4</sup>. With recent socioeconomic and cultural developments, autonomy and independence are increasingly observed in elderly women.

Longevity brings a significant increase in the number of new cases of breast cancer in this age group. In the United States, probabilities for developing breast cancer until the age of 39, between 40 and 59, between 60 and 69 and over 70 years of age were 0.48, 3.98, 3.65 and 6.84%, respectively<sup>5</sup>. One in every 225 women aged less than 39 years and one in every 14 aged 60-79 years have breast cancer in the U.S.<sup>6</sup>

Overall mortality rate for breast cancer in Brazil in 2002-2006 was of 9.3/100,000 women. The rate was 16.2 for patients aged 40-49 years and of 84.1 for women over 80.<sup>7</sup> Increasing age is the determining factor in increased mortality. The clinical outcome of breast cancer in older women, contrary to what has been thought, appears to be similar to that of younger women when the same stages of disease are compared. Disease-free survival for women over 70 with negative axillary lymph nodes was worse than that of women aged less than 40 years with negative axillary lymph nodes and treated for breast cancer. This finding may be due to the fact that the standard treatment for controlling breast cancer is less frequently used for older women.<sup>5</sup> According to the American *National Cancer Institute*

women over 70 are less subjected to axillary dissection than younger women.<sup>8</sup>

Many elderly women have reduced access to screening programs, the latest diagnosis methods and more complex breast cancer treatments. The combination old age and cognitive dysfunction makes this population vulnerable to undertreatment.<sup>9</sup>

Most of the studies on mammographic screening, surgery, radiotherapy, and systemic treatments for breast cancer exclude women over 70 years of age. Large randomized prospective studies with elderly patients with breast cancer with evidence level I for treatment are scarce.<sup>10</sup>

Given the growth of the female population over 70 years, both worldwide and in Brazil, the improved quality of life and life expectancy, as well as the high incidence rates of breast cancer in these women, the Mastology Study Group at the UFMG Medical School (GEMA, in Portuguese) proposes guidelines for approaching this disease in women over 70 years. This article covers mammogram screenings and mammograms, surgical and systemic treatments, and radiotherapy.

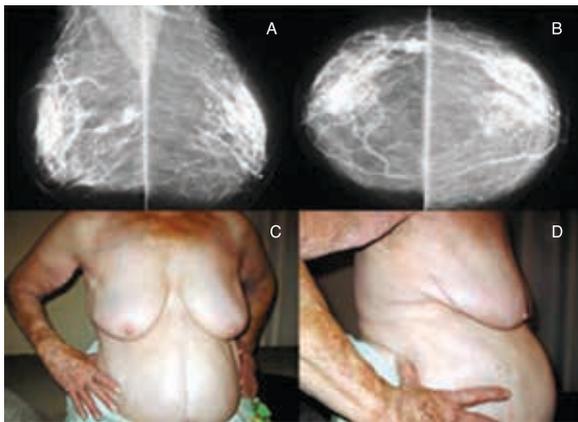
## MAMMOGRAM SCREENINGS AND MAMMOGRAMS

### Should elderly patients be exempted from mammogram screenings or mammograms?

Early diagnosis through mammograms can lead to less aggressive treatment. Nevertheless, no controlled studies showing a reduction in breast cancer mortality in women over 70 years of age submitted to mammographic screening programs are available. Women over age 75 do mammograms less often;<sup>11</sup> elderly women with cognitive disabilities likewise.<sup>12</sup> Stage at diagnosis was similar for older women who did periodic mammograms and younger women who were screened.<sup>13</sup> Mammograms can determine what other diagnostic tools can be used, such as complementary imaging exams, fine needle biopsy, *core biopsy*, stereostatic mammography (guided or not by mammograms or ultrasound), puncturing of non-palpable lesions, *Radioguided Occult Lesion Localization* (ROLL) and open biopsies. Many of these interventions add morbidities in elderly patients who may already have compromised health. The choice of

the best complementary diagnostic method must be evaluated individually.

Around 20% of the malignant neoplasms detected by mammograms are ductal carcinoma “in situ” (DCIS) and most do not progress to invasive carcinoma and thus do not modify survival. It yet is unclear which DCIS progress to invasive tumors. While mortality rates for breast cancer changed very little in the 1980s and 1990s, the incidence of DCIS grew 750% in the same period since the mammogram was developed.<sup>14</sup> A significant number of treatments performed for DCIS only contributed to increased morbidity, since many would never have reduced survival or increased mortality. Figure 1 illustrates the case of a DCIS carrying nulliparous patient, aged 90, with a ECOG performance score of 1, with no relevant comorbidities, diagnosed by routine mammogram and treated only with quadrantectomy under day-hospital regimen and local anesthesia, without radiation or hormone therapy. After a five-year follow-up the patient is disease-free and enjoys good quality of life.



**Figure 1** - 90 year-old patient suffering from DCIS. (A) CC Mammography. (B) OBL Mammography. (C) Front view. (D) Right view.

Patients aged 70+ years with advanced cognitive impairment, significant comorbidities or life expectancy of less than five years should be advised against routine mammogram and mammogram screening. Routine mammograms and screenings should only be recommended to elderly patients with normal results upon clinical breast examination if they are clearly able to understand the risks and benefits or are accompanied by family or a legal guardian (Figure 2). The decision must always be made by patients and their families.

## SURGICAL TREATMENT

### Should elderly patients undergo conservative surgery?

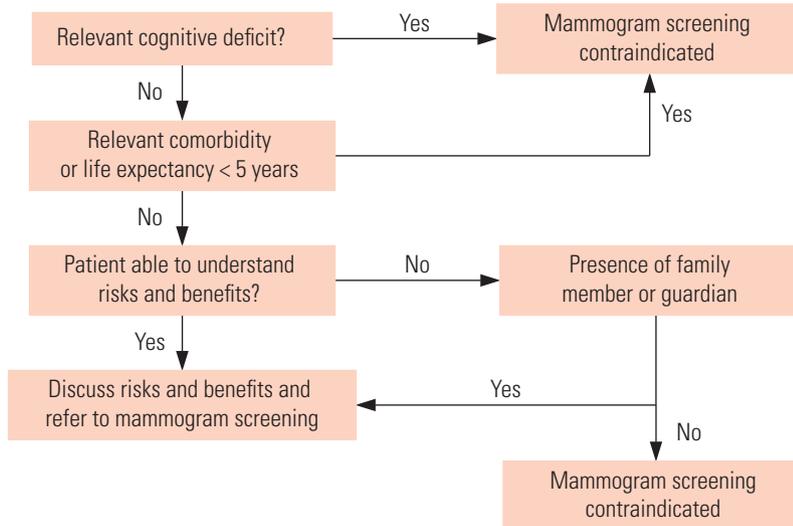
Surgical treatment is crucial to control breast cancer and it is often the first form of therapeutic intervention. For some elderly patients, it may also be the only one. The choice of surgical technique is directly related to disease presentation and not to patient's age.

Geriatric presurgical clinical assessment with strict comorbidity control is a priority before surgery. The preanesthetic evaluation is useful to inform the anesthesiologist of the case and for planning the type of anesthesia to be used. Clinical follow-up during hospitalization contributes to adequate postoperative outcome.

Mammary surgeries are procedures with low morbidity and even lower mortality. Data collected in the *National Surgical Quality Improvement Program*, a national benchmark for standards of care in the U.S., and published in 2007, showed mortality rates on the 30th day after conservative surgeries and mastectomies associated with axillary procedures to be of 0.24% and 0.0%, respectively, in 3,107 patients.<sup>15</sup> In the same study, the most frequent morbidity was related to surgical wounds and occurred in 3.63% of cases. Body mass index (BMI), hematocrit and albumin levels were more important than advanced age as factors for surgical wound complications.

Patients over age 70, with ECOG performance scores of 0, 1 or 2<sup>16</sup>, with controlled comorbidities and life expectancy of more than five years should be submitted to surgery according to the consensus protocols in the same way as younger patients.

Elderly women tend to be less subjected to axillary dissection and surgical treatments is much less frequent than what consensus protocols recommend. In women over 70 years of age, with clinically negative axillae, T1 tumors, who are estrogen receptor-positive and treated with tamoxifen, axillary dissection does not seem to bring radical impact on survival compared with similar patients not submitted to dissection.<sup>17</sup> The negative impact of this procedure on the quality of life of elderly patients suffering from arthritis is considerable.<sup>18</sup> Axillary dissection involving only Berg levels I and II or excision of the sentinel lymph node has very low morbidity and can be performed with ease in elderly patients.



**Figure 2** - Organization chart for mammogram and/or mammogram screening referrals in women over 70 years of age with normal mammary clinical examination.

While conservative surgery and mastectomy provide equal survival for women of all ages with tumors in early stages, studies have shown better quality of life in patients submitted to conservative treatment. Therefore, options such as local excision with or without tamoxifen, local excision with or without axillary lymph node dissection or sentinel lymph node, or local excision with or without radiation therapy should be considered according patient characteristics, risks and benefits involved, as well as comorbidities.<sup>18</sup>

Elderly patients show less interest in breast reconstruction than younger women. More complex breast reconstruction procedures, such as myocutaneous flap, must be contraindicated due to high morbidity and longer recovery time. Use of expanders and silicon prosthesis is simpler, tends to lead to lower morbidity, and can be done in selected cases.

## SYSTEMIC TREATMENT

### Can elderly patients be exempted from systemic treatment?

Systemic treatment is conditioned to the patient's clinical status. Before making decisions about systemic treatments, a comprehensive geriatric assessment must be performed considering the role of comorbidities and their effects on life expectancy.<sup>19</sup>

Generally speaking, elderly women are less tolerant to chemotherapy than younger women because of progressively reduced organ and system function associated with age-related comorbidities. For these reasons, women over 70 are excluded from or under-represented in most studies on the systemic treatment of breast cancer and end up receiving inadequate treatment or treatment untested in their age group. Moreover, increased age, compromised cognitive status and the presence of comorbidities are related to lower doses and chemotherapy interruption.<sup>20</sup>

Women with breast cancer associated with three important comorbidities are 20 times more likely to die of other causes than of breast cancer.<sup>21</sup> Diabetes, heart disease, stroke, kidney failure, liver disease, previous malignant tumor and smoking are significant in predicting early mortality in women with breast cancer<sup>8</sup>. While 16.4% of patients aged 70-74 years old have severe heart diseases, those aged between 55 and 59 years have them in less than 6% of cases.<sup>16</sup>

Age also directly influences pharmacokinetics, affecting absorption, distribution, metabolism and excretion of drugs. In elderly women, reduced intestinal motility, blood flow, and digestive secretions, as well as intestinal mucosal atrophy, lead to a decrease in the absorption rate. Drug delivery depends on body composition and concentration of plasma proteins, such as albumin, and of red blood cells (RBCs). Elderly women, compared with younger women, have double the amount of body fat and lower levels of intracellular water, which may reduce peak plasma

concentration and increase the half-life of chemotherapeutic drugs.

Correction of anemia is particularly beneficial for women over 70, since treatment with anthracyclines and taxanes depends on RBC concentration.<sup>21</sup> The *National Comprehensive Cancer Network (NCCN)*<sup>22</sup> guidelines suggest that a hemoglobin level of 12 g/dL is a reasonable goal for older patients in order to avoid toxicity. Although the literature does not agree regarding the effects of age on hepatic metabolism, there is a consensus that the liver decreases in size and that blood flow reduces with age. Enzymatic systems involving P450 cytochrome, located mainly in the liver, for example, are overloaded by the use of other, more common, drugs in elderly women, which can alter the metabolism of chemotherapeutic drugs. Paclitaxel and docetaxel should not be used in patients with liver failure because they demand high hepatic metabolism.<sup>23</sup> Due to decreased glomerular filtration rate, chemotherapy that is essentially excreted by the kidneys should be used with care in elderly women. Standard doses can be too toxic and individual adjustments must be made.

The side effects of chemotherapy in women over 70 years old deserve further consideration. Whether myelotoxicity increases with age is still controversial. Neutropenia, however, is more durable and offers greater risk of death in elderly patients. Taxane-induced leukopenia has been found in 65.5% of patients aged 65 years or more and in 55.3% of patients under 60.<sup>23</sup> Early correction based on the use of “growth factors” should be considered. Mucositis are more common in the elderly. Diarrhea can be particularly problematic because it leads to rapid volume depletion and cardiovascular collapse if not treated promptly.

Less toxic treatments such as those using only capecitabine produce results inferior to regimens with cyclophosphamide, methotrexate and fluorouracil (CMF) or adriamycin and cyclophosphamide (AC).<sup>24</sup> Age alone cannot be the decisive factor in the choice of chemotherapy regimen. The NORA<sup>25</sup> study, which assessed 1,042 patients aged 65+ years, showed that estrogen receptors (ER) and progesterone receptors (PR), simultaneously positive, increase with age. Hormone therapy with tamoxifen or aromatase inhibitors may be the only systemic treatment of choice after lumpectomy for ER-positive elderly women whose health is compromised by significant comorbidities.

There is no evidence that Her-2 positivity varies with age. Trastuzumab carries low morbidity and can be used in selected elderly patients.

In sum, patients over 70 years of age whose life expectancy is higher than the life expectancy with untreated breast cancer should receive the standard treatment so as to potentially prolong their survival.

## RADIOTHERAPY

### **Should radiation therapy be omitted from the treatment of elderly women?**

The few studies conducted on the role of radiotherapy in the treatment of elderly women reveal the need to use it in the same way it is used in younger patients.<sup>26</sup> Radiotherapy has a key role in controlling local disease, contributing effectively to the reduction of local relapse rate. In most cases, local relapse is the first manifestation of disease recurrence and can happen as early as the first few months or years after surgery. Thus, if life expectancy after breast cancer treatment is higher than two years, radiotherapy should not be omitted. A recent German cohort study involving 1,922 women over the age of 50 showed that the omission of radiotherapy was a factor that reduced overall survival and disease-free survival in women over the age of 70.<sup>27</sup>

Elderly patients with positive axillary lymph nodes have more chances of local relapse. Following mastectomy, radiotherapy reduces local relapse in elderly women by 60-70% and increases overall survival by 8-9%. When they are treated conservatively, radiotherapy reduces local recurrence from 20-25% to 5-8%.<sup>28</sup> A Canadian study analyzed 233 women aged 70+, after mastectomy, with tumors larger than 5 cm or with four or more compromised axillary lymph nodes, revealing a reduction in local relapse from 28 to 16% in a median 5.5-year follow-up ( $p = 0.03$ ).<sup>29</sup> Another research conducted in Canada involving 4,836 women with breast cancer treated with conservative surgery identified that radiotherapy was more often omitted with advancing age. For patients aged between 50 and 64 ( $n=2,398$ ) radiotherapy was omitted in 7% of cases, while for patients over age 75 ( $n=773$ ) it was omitted in 26%. After median follow-up of 7.5 years, this omission determined a significant loss in local control, decreasing five years in overall survival and five years in cancer-specific survival for women aged 75 years or more.<sup>30</sup>

Conversely, a prospective Italian study with a mean 15 years of follow-up monitored 354 women aged 70+,

with early breast carcinoma with clinically negative axillary lymph nodes and who underwent conservative treatment without axillary dissection or radiotherapy and with adjuvant tamoxifen. Results showed 8.3% ipsilateral tumor recurrence and 17% mortality from breast cancer. During follow-up, 268 patients died, with a total 222 (83%) dying from other causes, unrelated to breast cancer. The authors concluded that for elderly women with early stage breast cancer, clinically negative axillary lymph nodes and free resection margins, the only safe treatment is conservative surgery followed by tamoxifen without radiation.<sup>31</sup>

Radiotherapy is usually well tolerated as long as the total dose and fractioned dose limits are respected. Correct planning and use of adequate equipment are essential for low morbidity. Using dose fractionation in daily applications through a period of five weeks can be an obstacle when treating elderly women with reduced mobility, especially those who live far from treatment centers. Changes in dose fractionation aiming to reduce treatment period and new techniques such as targeted intraoperative breast radiation therapy and the use of MammoSite® may be beneficial for elderly women with reduced mobility.<sup>32,33</sup>

## DISCUSSION

The most significant element in treatment is the goal of the therapy given the context of the patient's general state of health. Defining whether the goal is increasing survival, remission, cure or palliative control of symptoms is essential. Tumor aggressiveness and availability of effective treatment are other important aspects of planning.

Breast cancer treatment in elderly women must be preceded by comprehensive and thorough geriatric evaluation assessing physical condition, presence of comorbidities, functional dependence, socioeconomic, emotional, and cognitive conditions, as well as life expectancy over the next five years. Among the numerous comorbidities, the most important are: heart conditions (CHF, arrhythmia, coronary and heart valve diseases), respiratory (COPD), kidney failure, liver failure, stroke, peripheral neuropathy, hypertension, diabetes, collagen diseases, severe arthritis, and other malignancies.

ECOG performance score, although not directly related with survival, is useful in planning treatment for elderly patients. Elderly patients with ECOG of 3 or 4

have significant impairments to their general condition, which limits the use of chemotherapy or radiotherapy. Another key factor is the approximate expected survival of elderly patients. Short life expectancy due to comorbidities limits the use of standard treatment.

Considering that the development of breast cancer seems to be similar for young and elderly women when matched by stage, the disease itself, and not the patient's chronological age, should be the reference point for treatment. Undertreatment, more common among the elderly, translates into loss in disease-free survival and overall survival. Conversely, more aggressive treatments, with many side effects that cause a decline, however temporary, in the patient's quality of life are much more liable to be abandoned by elderly patients and their families.

The presence of a family member or guardian, in addition to enabling adequate social assistance, is important from diagnosis until control follow-up of elderly patients. Every intended procedure must be clearly explained to patients and their families, including risks and benefits. The responsibilities of each agent must be previously defined and the signature of an informed consent term is essential.

Geriatric services also play a crucial role in adequately controlling, prior to cancer diagnosis, any pre-existing diseases, as well as in providing support in case of treatment-induced aggravation of any comorbidities.

Even though studies of breast cancer patients aged 70+ are scarce, it would seem that the availability, experience, and integration of the medical staff, as well as compliance with the standard treatment protocols, whenever possible, are crucial for better results.

Regardless of health impairment or limited life expectancy, the individual's dignity must be preserved, even when that only means doing simple surgical procedures with the appropriate hygiene protocols.

## CONCLUSION

The treatment of breast cancer in elderly women should be individualized. The same guiding principles used for treating younger patients should be considered, given that undertreatment in this elderly population impacts negatively on their survival. Comorbidities and performance status are key factors for prescribing chemotherapy. Complementary radiotherapy, when indicated, brings benefits in terms of locoregional control and overall survival. A subgroup

of patients with incipient breast cancer and well-differentiated tumors smaller than 2 cm, with clinically negative axilla, however, may benefit from just conservative treatment and hormone therapy, provided they have free surgical margins. Therefore, the oncological treatment of elderly women with breast cancer should be as complete as possible and take into consideration their life expectancy, treatment effectiveness, and potential adverse effects.

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