Breast cancer in the elderly

M Bellet, C Alonso, B Ojeda

Summary

Breast cancer in the elderly has attracted considerable interest in recent years for three main reasons. Firstly, information concerning the profile (clinical and biological) of the disease in the geriatric population is scarce; secondly, the number of patients is increasing, and thirdly there are conflicting data regarding the actual effectiveness of the different treatments. The present review attempts to outline the specific characteristics of this malignancy in the elderly in terms of histological pattern, stage at diagnosis, and outcome. The feasibility of standard therapies (mastectomy/lumpectomy, axillary clearance, and radiotherapy) in the elderly is carefully analysed, and compared to the efficacy of less aggressive procedures. The use of tamoxifen as a primary treatment, instead of surgery, is critically reconsidered, as well as its use as an adjuvant therapy. Finally, the effectiveness of systemic therapy in advanced disease is also discussed.

Keywords: elderly, breast cancer, management

Determinants of care applied to elderly breast cancer patients

- functional disability
- concomitant diseases
- scanty socioeconomic resources
- distance to radiotherapeutic centre
- difficulties regarding access to transport
- poor compliance

Box 1

Department of Medical Oncology,
Hospital Sta Creu i Sant Pau, Avda S
Antoni Ma Claret 167, 08025 Barcelona,
Spain

M Bellet
C Alonso
B Ojeda

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Breast cancer continues to be the most common neoplasm and is the second leading cause of malignant deaths in women.¹ According to statistics from western countries, breast cancer incidence substantially increases with age, at least until 85 years.² In recent years, the average age of women with newly diagnosed breast cancer has risen notably (from 55.5 to 62.5).³ As the elderly population increases compared to that of younger adults there is also a dramatic increase in the absolute number of new elderly breast cancer patients.^{4,5} Furthermore, for a variety of reasons (box 1) this group of elderly patients may not benefit from the therapeutic advances made in breast cancer.^{6–9}

Comorbidity precludes standard therapy being given in many cases:⁶ the proportion of women with two or more diseases is 45%, 61% and 70% for women of 60–69, 70–79, and ≥80 years old, respectively.¹⁰ The percentage of people requiring assistance in daily living activities ranges from 6–8% among those aged 65–74, to 25% among those over 85 years.^{11,12}

In other cases, age *per se* constitutes the only determinant of this 'suboptimal care'. Greenfield *et al*⁶ found that age was an independent risk factor for not receiving definitive treatment even in patients without comorbidity and with early disease. This finding has been corroborated by other studies^{7–9} and probably results from misjudging the life expectancy of the elderly woman (see box 2).¹³ For these same reasons, older patients have systematically been excluded from most clinical trials. The result is an alarming lack of specific data concerning this subset of patients.

Profile of breast cancer in the elderly

Does breast cancer in the elderly have specific biohistological characteristics?

Tumours in postmenopausal women, compared with those in premenopausal women show a lower proliferative index, measured by [³H]thymidine labelling index¹⁴ and S-phase fraction, a higher incidence of oestrogen receptor, and a higher degree of differentiation.^{15–17} Valentini *et al*,¹⁸ in a study of the breast cancer samples from 476 patients over 70, confirmed a high number of oestrogen and progesterone-receptor positivities (83% and 61%, respectively) for the tumours in this specific age-group. The authors also reported a notorious proportion of aneuploid tumours (74%, median DNA index: 3.7%) and a mild to moderate proliferative activity (median [³H]thymidine labelling index: 3.4%).

Are the elderly diagnosed in more advanced stages? Is the nodal involvement similar to that found in younger patients?

We analysed the data of several retrospective series and statistical sources.^{2,8,19–30} The results of this review can be summarised as follows:

- The most frequent stage for all age groups is II.²³
- Among women over 75 years of age, a greater number of stage III, IV and unknown stages are registered.^{2,23} The proportion of unknown stages ranges from 9.2%²⁶ to 21%.²¹
- Early studies^{20,21} suggested that a 'nonnodal variant' could be common among the elderly. More recently, Gazetas *et al*²⁶ describe 37% positive nodes among the elderly, which is only somewhat lower than the general 40–50% found among patients of all ages. However, due to the low number of nodal clearances carried out in aging patients in most reports, no definitive conclusions can be reached.

If elderly patients are more likely not to receive standard therapy, what treatment is usually administered?

Mastectomy (simple, total or radical) has been the most widely performed treatment, although the proportion of operated patients is clearly lower in the older group in all series.^{2,8} Standard conservative treatment has been carried out in few cases, with percentages as low as 0% in one series.²⁵

Life-expectancy of older women

- age 65, life expectancy 18.8 years
- age 75, life expectancy 11.9 years
- age 85, life expectancy 6.6 years

Box 2

Figure Craniocaudal and lateral mammograms of left breast in an old woman (88 years): several nodular images (the greatest measuring 2.5 cm) with malignant characteristics are seen, suggesting a multifocal carcinoma. Notice the low density of breast tissue in older patients, which allows a good contrast of tumoral lesions.

- Older patients receive a higher proportion of local excisions: 38% for women over 75 vs 2.6% for younger patients in one study.⁸ Axillary clearance is performed with variable frequency, ranging from 49%²³ to 90.8%.²⁶
- Radiotherapy for any use (first treatment, adjuvant setting) has been less employed in the elderly: 65% of patients under 75 years received radiotherapy compared with only 33% of older patients.⁸ Implant Ir techniques are seldom used, as this can imply a general anaesthesia.³¹
- Hormonotherapy has often been used as the only treatment among elderly patients with stage II breast cancer, but not in younger women with similar extent of the disease.⁸
- Chemotherapy has rarely been employed in aging patients, even in most recent reports, with percentages ranging from 3%²⁷ to 9%.²⁶
- Combined treatment modalities are not likely to be indicated in elderly patients: surgery and less often radiotherapy were used as the only therapy in the years prior to tamoxifen. Since then, surgery, surgery plus hormonotherapy or hormonotherapy alone have been the most frequently used strategies.

When can recurrence be expected? What are the prognostic factors affecting disease-free survival in elderly breast cancer patients?

Recurrent disease usually occurs between the second and third year after first treatment (mostly surgery and/or tamoxifen for operable disease, see table 1).^{21,26,28,32-34} In the recent series of Gazetas,³¹ which included 83.3% of early-stage patients, and with a widely applied adjuvant treatment, the average time to recurrence was 27.7 months. According to this, short- or median-term control of the disease cannot be guaranteed, even for early disease and when life-expectancy is believed to be short because of comorbid conditions.

Clinical tumour size,²⁷ ganglionic involvement,²⁶ clinical TNM stage,²⁷ and grade of tumour^{35,36} have been shown to influence local disease-free survival.²⁷ In some studies^{28,37} ‘suboptimal therapy’ (local excision or lumpectomy without complementary irradiation, no ganglionic treatment) has correlated with a higher proportion of local and regional recurrence, although in most cases it has not had a negative effect on survival.^{8,26,27}

Survival in elderly breast cancer patients. Are there any differences compared with younger patients?

Overall survival in elderly cancer patients at five years ranges from 30%^{21,24} to 50%²⁷ (box 3). In elderly populations, an accurate survival analysis must take into account the expected survival of the general population (relative survival) or the number of deaths due to any cause other than breast cancer (disease-specific survival, DSS). Most authors^{2,22,38} have reported five-year relative survival for elderly breast cancer patients to be slightly worse than for younger patients. Bergman *et al*,⁸ however, only found lower relative survival rate for the elderly at 10 years (<75:57%, >75:32%) and this difference disappeared after controlling for stage.

Similarly, a trend towards a worse disease-specific survival rate in older patients has been shown in several studies.^{24,25} Bergman²⁴, however, found a 7-year DSS of 55%, 65%, and 50% for women aged 55–64, 65–74, and over 75 years, respectively, so that a categorically worse DSS for the elderly could not be demonstrated.

Among the elderly, a noticeable proportion of deaths occur from causes other than neoplastic disease (from 11.6%²⁶ to 54.8%²¹). In spite of this, the impact of breast cancer on survival should not be underestimated. Davis reported a median survival of 20 months for patients who died from the disease, which was clearly lower than the 40 months observed among non-cancer deaths.²¹

Advanced stage^{8,19,21,22} and nodal involvement⁸ negatively influence survival. The hormonal status has shown statistical significance in survival only for node-negative patients, for whom the risk of dying from breast cancer seems to be 8.4-fold higher than in oestrogen-receptor-positive groups. In most^{8,26,27}, but not all²⁸ studies, suboptimal therapy applied to elderly patients did not modify survival.

Treatment of breast cancer in the elderly

EARLY-STAGE DISEASE

Nowadays,³⁹ partial mastectomy with axillary dissection plus postoperative breast irradiation is the preferred treatment for patients with early disease; total mastectomy should be reserved for multicentric tumours or when cosmetic results of partial mastectomy are likely to be poor.

Table 1 Time to treatment failure after first therapy (mainly operable disease) in elderly breast cancer patients

Ref	n	Age (years)	Early stage (%)	Treatment mainly performed (%)	Recurrences L/D (%)	Median time to failure from surgery (months)	Mean follow-up (months)
21	198	83 (80–94)	58.6	mastectomy: 74.8 adj RT: 23.2	21.7	58% recurrences before 36	NS
26	479	76 (70–95)	83.3	mastectomy: 78.2 adj HT/CT (node+): 73.9	21.3	27.7	55
28	150	84 (80–95)	71	mastectomy: 69*	6**	37.4	68
32	96	76	84	wide local excision (all cases) (no adj treatment)	35	31	47
33	109	79 (70–92)	89	wide lumpectomy adj TMX: 80.4 adj RT: 16	9.1/6.5	33 (L)/25 (D)	44
34	40	82 (68–93)	83	TMX	27.2	33	29

L: recurrence loco-regional; D: distant metastases (L + D if non-specified); adj: adjuvant; HT: hormonotherapy; CT: chemotherapy; RT: radiotherapy; TMX: tamoxifen; NS: not specified. *Mastectomy was performed in 85% of I-II staged-patients. **Referred only to stages I-II (clearly operable patients).

Survival of elderly breast cancer patients

- 30–50% of overall survival at 5 years
- trend to worse relative and disease-specific survival than younger patients
- 12–55% of ‘non-cancer deaths’
- double median survival for older breast cancer patients who died from non-malignant causes

Box 3

Management of primary tumour

- mastectomy is a safe surgical procedure
- axillary dissection could be obviated if all older patients were to receive adjuvant tamoxifen
- suboptimal therapy may be acceptable in selected cases
- postoperative irradiation also reduces local recurrence in elderly patients
- primary tamoxifen is not as effective as surgery in operable patients
- after first treatment (surgery, tamoxifen), recurrences begin to appear between the second and third year

Box 4

These recommendations are based on three large randomised trials^{40–42} that compared total mastectomy with breast-conserving surgery plus postoperative irradiation. No differences in disease-free survival or overall survival were found between treatment groups in any of these three trials. Unfortunately, the conclusions of these trials are not easily applied to elderly patients due to the low number of women over 65 years included.

Surgery

Mastectomy has proven to be a safe surgical procedure in older patients, with mortality (0–5%) and morbidity (13–25%) rates similar to those reported for younger patients.^{27–30}

Axillary clearance can be followed by local pain, paresthesias and lymphedema. Ganglionic dissection must be essentially considered as a staging rather than a therapeutic procedure. It becomes crucial when the decision to deliver adjuvant treatment is based on pathological node involvement. On the contrary, if all postmenopausal women were to receive complementary treatment with tamoxifen, in accordance with the latest recommendations of the US National Institutes of Health,³⁹ the axillary clearance performance could be obviated.

As breast-conserving treatment and mastectomy show a similar efficacy, other factors, such as quality-of-life and perception of body image, must be taken into consideration. According to one⁴³ of the few studies specifically addressing the issue in the elderly, familial support was more relevant in the quality-of-life than the surgical procedure chosen. ‘Wide local excisions’ in a short-admission regimen^{32,33} or under local anaesthesia⁴⁴ have been reported as an alternative treatment for older breast cancer patients, even for those with clinical positive nodes.³² Adjuvant treatment (tamoxifen, radiotherapy) was added in few cases.³³ After an average follow-up of 45 months, recurrence rates ranged from 9.1%³³ to 35%³² These alternative procedures may be an acceptable first treatment for patients reluctant to spend a long stay in the hospital,³³ unfit to undergo major surgery⁴⁴ or with difficulties in complying with radiotherapy protocols.³² Otherwise, standard therapy is preferable.

Radiotherapy

Postoperative irradiation is a well-tolerated procedure in any age group.^{28,30,45} Among women under 70 years, there is currently strong evidence for the efficacy of postoperative irradiation in reducing local recurrence, without affecting survival.^{42,45,46} As for elderly women, less local recurrence with aging in the absence of postoperative radiotherapy has been noted,^{45,47,48} with rates as low as 3% in one series.⁴⁷ The results led some authors to suggest that this procedure could be reasonably obviated in this group of patients, for whom daily transfer to a radiotherapeutic centre might imply an additional burden. Nevertheless, an undoubted benefit in terms of local recurrence-free survival (39.1% vs 4%) and breast preservation (54% vs 12%) for women over 60 receiving postoperative irradiation has been observed.⁴⁵

Primary tamoxifen

Tamoxifen has been widely investigated as first treatment in elderly patients with operable disease. According to criteria developed by the International Union

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Adjuvant therapy

- complementary treatment with tamoxifen reduces local regional failures and, when given for a long period, positively influences survival
- at present, adjuvant chemotherapy cannot be considered as standard therapy, even in node-positive patients

Box 5

Against Cancer, an average of 60% of positive overall responses has been noted, with an additional 20% of ‘stable disease’.^{49–54} Despite these response rates, an increasing percentage of relapse is found during longer follow-up, requiring additional local treatment. In the retrospective series with longest follow-up,⁵⁵ the disease was not controlled by tamoxifen to the time of death or most recent follow-up in 62% of patients.

Three randomised studies have compared surgery *vs* tamoxifen as initial therapy in early disease^{35,36,56–58} (see table 2). Local progression or relapse was more frequent in the tamoxifen group in the three trials. The difference reached statistical significance in two of them, including the study with the longest follow-up.³⁶ No differences with regard to overall survival^{35,36,57,58} or quality of life were detected. Nevertheless, recent up-dated data from one of these series⁵⁸ have also disclosed a marginal benefit on survival for the surgically treated group. In the light of these data, tamoxifen cannot currently be considered an equally effective alternative to surgery for elderly patients with operable breast cancer.

Adjuvant tamoxifen (hormonotherapy)

The benefit of adjuvant tamoxifen in older women has been demonstrated by a worldwide meta-analysis⁵⁹ and by at least four randomised trials^{60–63} specifically carried out in older patients. According to these data adjuvant tamoxifen, given for one year or until progression, was useful in significantly reducing the number of local regional recurrences and contralateral breast cancer and in extending the time to treatment failure,^{61,62} although it did not modify survival. The benefit was evident even for patients whose oestrogen receptors were negative⁶¹ or unknown.⁶² Adjuvant tamoxifen for five years after mastectomy positively influenced survival when compared to the drug given at first recurrence. The benefit was only evident after three years of randomisation.⁶³

An increased rate of cardiovascular deaths was found in one trial⁶¹ among patients receiving the drug. This finding has not been reported in the other studies. On the contrary, due to its partial oestrogenic properties, tamoxifen has proven useful in preventing osteoporosis, reducing levels of low-density cholesterol, and even decreasing the risk of myocardial infarction when given over a long period.⁶⁴ Therefore, ‘non-cancer arguments’ favouring tamoxifen’s use in the elderly can be made.

Adjuvant chemotherapy

In a recent meta-analysis,⁶⁵ the use of adjuvant chemotherapy in women aged 60–69 years implied a significant reduction of recurrences, although the mortality rate was only 10% lower. Chemotherapy in the adjuvant setting did not seem to be beneficial in the 366 women over 70 included in the meta-analysis.

As for individual trials addressing the question, nearly all have been centred on positive node patients aged 50–70 years. Most of these studies have found that complementary chemotherapy is useful at increasing disease-free survival, but has no clear effect on overall survival. The trials using cyclophosphamide/methotrexate/5-fluorouracil (CMF)-based regimens^{66–68} have failed to demonstrate a benefit in overall survival, while two studies^{69,70} using doxorubicin-containing regimens, found a reduction in mortality ranging from 38%⁶⁹ to 45%.⁷⁰

In conclusion, adjuvant chemotherapy cannot be considered as standard treatment in node-positive women over 70 years old. It might be useful, however, in certain subsets of patients with aggressive disease.

Table 2 Randomised studies comparing surgery (S) to tamoxifen (T) as initial therapy in older patients with operable disease

Ref	n	Age (years)	Comparison	Median follow-up (months)	Outcome (T/S)			Comments
					LR	D	OS	
56	116	75 (70–95)	T <i>vs</i> S*	–	25/38 NS	13/18 NS	63/65 NS	Included 20% T ₃ –T ₄ in T-arm, 36% T ₃ –T ₄ in S-arm Excess of recurrences in surgical group
36	135	75 (70–88)	T <i>vs</i> S**	65	46/20 p<0.0001	24/34 NS	63/59 NS	Included only T≤5 cm Longest follow-up
58	434	>70	T <i>vs</i> T + S†	42	45/21†† p<0.0001		29/21 p = 0.048	No differences in quality-of-life or distant metastases in preliminary report ⁵⁷

T: tamoxifen; S: surgery; NS: non-statistical significance; LR: locoregional failure; D: distant failure; OS: overall survival. *Mastectomy/lumpectomy; **wedge mastectomy ± axillary clearance; †most adequate surgery according to surgeon; ††locoregional failure measured by need to change treatment.

Side-effects of hormone-therapy
<i>Tamoxifen</i> <ul style="list-style-type: none">• hot flushes• nausea• mild thrombocytopenia/leucopenia• increased risk of deep vein thrombosis in women over 65 years old (rare) <i>Progestin agents</i> <ul style="list-style-type: none">• weight gain• fluid retention• mild congestive heart failure• hypertension• hyperglycemia (usually transient and easy to manage) <i>Aminoglutethimide</i> <ul style="list-style-type: none">• lethargy• skin rash• orthostatic dizziness• ataxia• hypotension (possible palliation with addition of corticoid therapy)

Box 6

ADVANCED DISEASE: PALLIATIVE SYSTEMIC TREATMENT
The realistic goal of treatment for women with recurrent or overt distant disease is palliation of symptoms and secondly, improvement of survival. With this concept in mind, efficacy, and particularly toxicity of the different treatments, hormone therapy or chemotherapy, must always be accurately assessed.

Hormonotherapy
The percentage of breast tumours sensitive to hormonal treatment increases with advancing age. The anti-oestrogen tamoxifen is the drug of choice, as it is also the best tolerated. Hot flushes are the most common adverse effect.^{71,72} Tamoxifen can induce a remission rate of 30–40% in advanced disease when used in previously untreated patients,⁷³ with a median duration of response of 1 to 2 years.
Progestational agents such as megestrol acetate or medroxyprogesterone acetate, and aromatase inhibitors such as aminoglutethimide^{74,75} have proven to be nearly as effective as tamoxifen in terms of response, but with somewhat more toxic effects, which can be particularly relevant in older patients. They should be regarded as second or third-line drugs.

Chemotherapy
Commonly used chemotherapy regimens include cyclophosphamide, methotrexate, 5-fluorouracil and doxorubicin. Before starting a cytotoxic regimen in an elderly patient, any organ dysfunction that may increase toxicity must be ruled out. The use of methotrexate, either as monotherapy or in combination, demands correct renal function, which is often impaired in advanced age. Concomitant treatment with non-steroidal anti-inflammatory drugs (frequently prescribed in geriatric populations) must be avoided, because of their negative effect on methotrexate renal plasma clearance. Cardiac function must be monitored before giving a doxorubicin-containing schedule. Cardiac toxicity of doxorubicin is dose- and age-dependent. On the other hand, the drug is considered the most active single agent for breast carcinoma. Therefore, among elderly patients with increased risk for congestive heart failure, alternative schedules such as lower doses of doxorubicin once weekly, or the use of related and also active drugs (4-epirubicin, idarubicin, mitoxantrone) with less cardiotoxicity, must be considered. Mitoxantrone appears to be a particularly suitable drug in elderly patients, since it causes less cardiac toxicity, less nausea and vomiting, and less alopecia.

There is little experience about combination chemotherapy regimens in elderly breast cancer patients, especially in those over 70 years. Begg *et al*⁷⁶ reported that the frequency of severe toxicity in terms of sepsis, bleeding, vomiting or neurological or cardiac dysfunction, was the same in women under 60 years and in those aged 60 to 65. Only a minor increase in haematological toxicity was seen in the older group.

In spite of these results, initial dosage of classical schedules continues to be a matter for debate. Gelman and Taylor⁷⁷ recommended a CMF dosage based on creatinine clearance to neutralise potential increments in toxicity of cyclophosphamide and methotrexate in elderly patients. Beex⁷⁸ suggested that, among the elderly, and because of the haematological toxicity, the median doses of CMF administered during the first three cycles can rarely overcome the 75% of classical doses. Christman *et al*⁷⁹ found similar non-haematological toxicity in women over 70 receiving total doses of doxorubicin-containing schedules as compared to their counterparts treated with an intended dose of 75%. Haematological toxic effects were also similar within age groups, but the elderly had twice the frequency of life-threatening neutropenia and the only drug-related septic deaths. These authors recommended caution in extrapolating these results, as the otherwise healthy population studied, might not be representative of all older patients. Based on data published elsewhere,⁸⁰ reporting the same degree of benefit for both elder and younger patients with erythropoietin or GM-CSF treatment, the authors also suggested the possibility of diminishing neutropenia by using this kind of haematological support.

Effectiveness of chemotherapy in elderly patients was also discussed in Christman's work.⁷⁹ In the multivariate analysis performed, age was not significantly associated with response to cytotoxic treatment. In Gelman's experience,⁷⁷ doses of cyclophosphamide and methotrexate were adapted to renal function and the dose of 5-fluorouracil was reduced. The authors found a 38% overall response, which was lower than the response rate observed in younger patients using classical CMF doses.

Chemotherapy vs hormonotherapy

Chemotherapy is generally considered for patients with massive liver metastases, lymphangitic involvement of lung or skin, failure to third hormonal line or simply rapidly growing disease. Taylor *et al*⁶¹ compared tamoxifen to CMF as initial therapy for inoperable, recurrent or metastatic breast cancer disease in older women. A cross-over to the alternative treatment was performed at progression. Response rates were 45% and 38% on first-line treatment, and 29% and 31% upon cross-over to tamoxifen and CMF, respectively. Survival tended to favour tamoxifen as initial treatment, even among oestrogen-receptor-negative patients, although this was not statistically significant. The authors reported that initiation with tamoxifen rather than CMF chemotherapy was justified in almost all situations.

Future directions

An increasing volume of affected patients on one hand, and poorly defined patterns of care on the other, make breast cancer in the elderly a major healthcare issue, demanding special social and health efforts and intensive clinical research. The investigation should be focused on defining the effectiveness of standard treatments in older women with breast cancer. In particular, four main areas need to be studied: the value of radiotherapy and axillary clearance after breast-conserving surgery, the optimal duration of adjuvant tamoxifen, the indications for adjuvant chemotherapy and, finally, the role of less aggressive therapies for patients with poor performance status.

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