

ORIGINAL ARTICLE

## Breast cancer in women 80 years of age and older: A comprehensive analysis of an underreported entity

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### Abstract

**Background.** Approximately 10% of breast cancer (BC) patients are over the age of 80. We present the first comprehensive review on this particular group of patients. **Patients and methods.** The treatments and disease courses of an unselected cohort of patients, whose age at first diagnosis was  $\geq 80$  years ( $n = 151$ ), were compared to those of a group of women, who were aged 56–66 years ( $n = 372$ ). **Results.** The group of elderly patients had larger tumors at first diagnosis (25 mm vs. 18 mm,  $p < 0.001$ ) and higher disease stages (I: 31.1% vs. 44.1%, IV: 11.9% vs. 5.4%; each  $p < 0.001$ ). There were no significant differences between both groups in terms of histologic subtype, grading, hormonal receptor status and HER2 status. The tumors of older patients were more often detected by clinical examination (38.9% vs. 17.0%,  $p < 0.001$ ) and less often by mammography/sonography (10.4% vs. 29.9%,  $p < 0.001$ ). The rate of patients who died of BC were similar in both groups (21.2% vs. 21.5%,  $p = 1.00$ ). In the patients who had no evidence of metastases and who opted for primary non-surgical management ( $n = 21$ ), the tumor could be stabilized without considerable morbidity in only 42.9%. Persistence to adjuvant endocrine therapy was comparable (83.0% vs. 88.3%,  $p = 0.357$ ). In the adjuvant as well as in the palliative settings, elderly patients received less chemotherapy than younger ones (adjuvant: 1.6% vs. 23.3%; palliative: 32.3% vs. 68.4%; each  $p < 0.001$ ). For palliative treatments only, elderly patients received fewer treatment regimens ( $\geq 3$  therapy lines: 16.0% vs. 54.9%,  $p < 0.001$ ). In those patients who died of BC, elderly women had inferior overall (25 vs. 54.5 months,  $p < 0.001$ ) as well as metastatic-disease survival (11.5 vs. 19 months,  $p = 0.062$ ). **Conclusion.** It must be ensured that appropriate standard therapies should not be routinely withheld in older patients based on erroneous perceptions regarding the biological nature of BC in the elderly and lack of knowledge about available therapy regimens. Physicians should consider that preservation of current life circumstances and maintenance of quality of life are frequently more important than “classical” hard medical facts such as survival times.

### How old is old?

In recent years, the issue of “breast cancer in the elderly” has become an increasing focus of interest [1–6]. However, there is considerable inconsistency of the data which is mainly due to the fact that there has been no generally accepted definition for what an “elderly patient” is [7] (“how old is old?”). When considering which patients could be undeniably considered as elderly ones, the term “age-dependent frailty” [8] comes to mind. It is well recognized that chronological age does not necessarily determine the frailty of older patients. Therefore, the comprehensive

geriatric assessment (CGA) was designed to evaluate the functional age of an individual, to derive an estimation of survival and tolerance of therapy as well as to recognize health problems that might affect life expectancy [9]. Geriatric assessment tools consider multiple domains such as co-morbidity, mobility/agility, continence, auditory and visual capabilities, activities of daily living, cognition, psychological and emotional states, nutritional status, and familial and social support. If one categorizes an “old patient” as someone who has experienced cumulative declines in a considerable number of these factors, then it

does not make sense to include individuals in their 50s or 60s in this group; in the Western world, even a considerable number of individuals in their 70s are still active and in good health. However, when reviewing the literature which explicitly reports on BC therapy in the elderly, it becomes quickly apparent that most studies analyzed patients in their 60s and 70s, and women older than 80 were often not included or comprised a negligible minority of the cohorts analyzed [1–6,10]. Studies focusing on patients who are  $\geq 80$  years of age and thus represent the oldest 10% of the entire BC cohort are scarce [4,7,11–13]. To our knowledge, our study is the first comprehensive description of an unselected cohort of this particular subgroup of patients. Furthermore, we compared the subgroup of older BC patients with a standard BC subgroup which was defined as being either up to five years older or younger than the median age of a typical Western BC cohort, which is 61 years. By doing so, we were able to correct some commonly accepted truisms such as “older BC patients have less aggressive tumors” or “in older patients, disease progresses more slowly”.

### Patients and methods

Data from the prospective relational Basel Breast Cancer Database (BBCD), which includes all newly diagnosed primary invasive BC cases treated at the University Women's Hospital Basel, Switzerland since 1990, provided the basis for this study. This institution comprises the largest breast center in the canton of Basel and represents the population of the region. For this study, patients who had initial BC diagnosis up to and including 2009 were considered. Data collection methods and study design were approved by the institutional review board.

In this study, we analyzed a cohort of BC patients who were  $\geq 80$  years at initial diagnosis ( $n = 151$ ; mean age 84.3 years, range 80–95 years; 10.3% of the entire cohort of all BC patients) and compared them with a standard BC patient cohort ( $n = 372$ ; mean age 61.0 years, range 56–66 years; 24.9% of the entire cohort of all BC patients, 36–60th age percentile). We had complete follow-up for 518 patients of our study cohort (99.0%); five patients (1.0%) were lost to follow-up after a median observation time of 14 months (range: 1–25 months).

Our analysis considered: 1) Clinical, histo- and pathomorphologic features: tumor size, tumor category and stage according to the current (7th edition) American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) TNM Classification, histological subtype, grading, and hormone-receptor (HR) status. HER-2 status has been routinely assessed for all patients since 2002

and was available for approximately 48% of the entire cohort; 2) Tumor detection method: self-detection vs. clinical breast examination by a physician vs. standard radiological breast examination (mammography and/or sonography) vs. other method; 3) Adjuvant therapy: type of surgery including an analysis of patients who chose non-operative management; physician's recommendation and patient's compliance to radiotherapy after breast-conserving therapy (BCT); systemic therapy including an analysis in terms of compliance and persistence to endocrine therapy (ET); and 4) Palliative systemic therapy with particular attention to the number of therapy lines and outcome.

### *Non-operative management*

For this particular aspect, we studied patients who had HR-positive non-metastatic primary BC and who did not want to undergo surgery as initial therapy but were treated with ET with the intended long-term goal to avoid surgery. We analyzed how often the goal of non-operative management was met. In accordance with a previous study [14], we defined the therapy goal as reached when the treatment managed to control the locoregional disease and long-term avoidance of surgery was assured. We defined the following situations as failure to meet the therapy goal: 1) secondary surgery had to be performed due to progressive disease; 2) in the case of no surgery, the development of advanced locoregional clinical morbidity which significantly impaired quality of life such as large ulcerating and fungating lesions or severe lymphedema.

### *Compliance and persistence with adjuvant therapy*

The treatment recommendations for all patients were based on the decision of the interdisciplinary tumor board of the University Hospital Basel. All patients received a comprehensive consultation at the departmental oncology unit, during which treatment indication and duration, as well as the potential adverse effects, were extensively discussed. As of 1997 ET has been the standard recommendation for all HR-positive patients, with few exceptions, and we included patients who had BC diagnosis since that time to analyze non-compliance and non-persistence to ET.

According to previous studies [15,16], we defined non-compliance and non-persistence to therapies as an intentional action of the patients. “Compliance” was defined as the readiness to accept a proposed therapy; in our particular case, to accept starting radiation or a long-term adjuvant ET. When the patients started ET, we used the term “persistence” for the further intake of the drug regimen. Following the

above mentioned principle, the following situations, where the discontinuation of therapy was not chosen but was mandatory or inevitably, were not defined as “non-persistent”: 1) Patients who had to stop therapy due to local or systemic BC recurrence; 2) Cases where a physician decided to stop the therapy for serious medical reasons other than BC (e.g. in palliative situation of malignant diseases, dependence on nursing care, severe dementia); and 3) Patients who died within the planned five years of treatment from intercurrent illness and took the medication shortly before death.

As non-persistence to adjuvant ET occurs in most cases within the first two years of therapy [15,16], we also included patients with an ongoing therapy who took their medication for at least 30 months and considered these patients as being persistent with therapy.

### Statistical analysis

Comparisons between nominal parameters were made with the Fisher exact test. Comparisons between metric parameters were made with the Wilcoxon rank sum test. A *p*-value < 0.05 was considered significant.

## Results

Compared with a standard group of BC patients who were 56–66 years old at initial diagnosis, older patients presented significantly more often with larger tumors (median tumor size: 25 mm vs. 18 mm, *p* < 0.001; T1: 38.4% vs. 56.5%, *p* < 0.001; Table I) and lesions with non-inflammatory skin involvement (T4b: 13.3% vs. 2.9%, *p* < 0.001). They were less likely to have a favorable disease stage at presentation (Stage I: 31.1% vs. 44.1%, *p* < 0.001; Stage IV: 11.9% vs. 5.4%, *p* < 0.001). There were no significant differences between both groups in terms of histologic subtype, grading, hormonal receptor status and HER2 status (Table I).

In older patients, tumors were more often detected by a clinical breast examination (38.9% vs. 17.0%, *p* < 0.001) and less often by radiologic procedures (10.4% vs. 29.9%, *p* < 0.001; Table II).

Analysis of the overall outcome of all patients revealed that the rate of patients who died of BC were similar in both groups (21.2% vs. 21.5%, *p* = 1.00; Table II).

When older patients underwent BC surgery, they were more often treated by mastectomy (58.6% vs. 41.1%, *p* < 0.001) and received less surgical axillary staging (57.6% vs. 95.3%, *p* < 0.001; Table III). More older patients who had BCT refused the recommended standard adjuvant radiotherapy (49.0% vs. 6.8%, *p* < 0.001; Table III).

A greater proportion of older patients received no surgical therapy (11.9% vs. 1.9%, *p* < 0.001; Table III). In the group of elderly patients who had no evidence of metastases and who opted for primary medical (non-surgical) management (*n* = 21, 15.8% of the cohort of old BC patients), the tumor could be stabilized without considerable morbidity in only 42.9% (*n* = 9) for a moderate period of time (median time: 20 months; Table III).

In the adjuvant setting, older patients were more likely to have no systemic therapy (41.9% vs. 17.3%, *p* < 0.001; Table IV). Of the patients who had HR-positive BC and were eligible for adjuvant ET, older patients more commonly declined the recommended therapy and never began treatment (non-compliance: 13.0% vs. 4.9%, *p* < 0.026; Table IV). Of the patients who initiated ET, only a minority of the older patients fully completed the planned therapy duration of five years (39.6% vs. 65.3%, *p* < 0.001). However, applying our inclusion criteria for non-persistence, an intended discontinuation of therapy was found in comparable frequency (non-persistence: 17.0% vs. 11.7%, *p* = 0.357; Table IV). While cessation of ET due to BC recurrence was similar in both groups (11.3% vs. 12.2%, *p* = 1.000), medication was more often discontinued by the physician due to serious medical reasons independent of BC (17.0% vs. 4.7%, *p* = 0.003).

In the adjuvant as well as in the palliative treatment contexts, elderly patients received significantly less chemotherapy (adjuvant: 6% vs. 23.3%; palliative: 32.3% vs. 68.4%, each *p* < 0.001; Tables IV and V). With regard to palliative systemic treatments alone, elderly patients received fewer treatment regimens than younger ones ( $\geq 3$  therapy lines: 16.0% vs. 54.9%, *p* < 0.001; Table V). In those patients who died of BC, elderly women demonstrated lower overall (25 vs. 54.5 months, *p* < 0.001) as well as metastatic-disease survival (11.5 vs. 19 months, *p* = 0.062).

## Discussion

It has been widely documented that a considerable number of very elderly BC patients do not receive standard therapies [4,13,17,18]. The effect of such an undertreatment was assessed well and it was found that sub-standard care results in a large excess of preventable BC mortality [13,17]. Most authors attributed physician's attitudes as the main reason for undertreatment and advocated that, based on previously demonstrated safety of surgery, radiation and ET in the very elderly, multimodality therapy should not be withheld in these patients [4,13,17]. This recommendation, however, ignores the fact that an important reason for undertreatment is not only due to the doctor's hesitation to recommend a therapy

Table I. Comparison between a cohort of breast cancer patients who are  $\geq 80$  years at initial diagnosis and a standard breast cancer cohort (56–66 years old): Clinicopathologic characteristics.

| Variable                        | 56–66 years<br>n = 372 (%) | $\geq 80$ years<br>n = 151 (%) | p-value          |
|---------------------------------|----------------------------|--------------------------------|------------------|
| Mean age (years)                | 61.0                       | 84.3                           |                  |
| Tumor size <sup>1,2</sup>       |                            |                                |                  |
| Median (mm) (range)             | 18 (0–220)                 | 25 (2–220)                     | <b>&lt;0.001</b> |
| Tumor category                  |                            |                                |                  |
| T0                              | 1 (0.3)                    | –                              |                  |
| T1                              | 210 (56.5)                 | 58 (38.4)                      | <b>&lt;0.001</b> |
| T2                              | 125 (33.6)                 | 61 (40.4)                      |                  |
| T3                              | 20 (5.4)                   | 10 (6.6)                       |                  |
| T4b                             | 11 (2.9)                   | 20 (13.3)                      | <b>&lt;0.001</b> |
| T4d (inflammatory carcinoma)    | 5 (1.3)                    | 2 (1.3)                        |                  |
| Bilateral synchronous carcinoma | 9 (2.4)                    | 5 (3.3)                        | 0.56             |
| AJCC/UICC stage <sup>1,2</sup>  |                            |                                |                  |
| I                               | 164 (44.1)                 | 47 (31.1)                      | <b>0.008</b>     |
| II                              | 135 (36.3)                 | 61 (40.4)                      |                  |
| III                             | 53 (14.2)                  | 25 (16.6)                      |                  |
| IV                              | 20 (5.4)                   | 18 (11.9)                      | <b>0.015</b>     |
| Histologic subtype              |                            |                                |                  |
| Ductal invasive                 | 269 (72.3)                 | 107 (70.9)                     | 0.75             |
| Lobular invasive                | 63 (16.9)                  | 26 (17.2)                      |                  |
| Rare types                      | 40 (10.8)                  | 18 (11.9)                      |                  |
| Grading                         |                            |                                |                  |
| G1/2                            | 214 (59.8)                 | 87 (62.1)                      | 0.68             |
| G3                              | 144 (40.2)                 | 53 (37.9)                      |                  |
| Not available                   | 14                         | 11                             |                  |
| Hormonal receptor status        |                            |                                |                  |
| ER+PR positive                  | 225 (62.0)                 | 94 (65.7)                      | 0.47             |
| ER+PR negative                  | 51 (14.1)                  | 27 (18.8)                      | 0.17             |
| Not available                   | 9                          | 8                              |                  |
| HER2 status, 2002–2009          | n = 169 (%)                | n = 81 (%)                     |                  |
| Positive                        | 25 (14.9)                  | 15 (18.8)                      | 0.46             |
| “Triple-negative” carcinoma     | 17 (10.1)                  | 10 (12.5)                      | 0.66             |
| Not available                   | 2                          | 1                              |                  |

AJCC, American Joint Committee on Cancer (7th edition); ER, estrogen receptor; PR, progesterone receptor; UICC, International Union Against Cancer (7th edition).

<sup>1</sup>In 25 patients ( $\geq 80$  years: n = 13; 56–66 years: n = 12), where neoadjuvant therapy was performed, the ypT and ypN status were used for stage grouping.

<sup>2</sup>In cases with bilateral synchronous carcinoma, the tumor with the more advanced stage or the more advanced tumor size (“reference lesion”) was considered for analysis.

Table II. Comparison between a cohort of breast cancer patients who were  $\geq 80$  years at initial diagnosis and a standard breast cancer cohort (56–66 years old): Tumor detection and outcome.

| Variable                                                    | 56–66 years<br>n = 372 (%) | $\geq 80$ years<br>n = 151 (%) | p-value          |
|-------------------------------------------------------------|----------------------------|--------------------------------|------------------|
| Tumor detection method                                      |                            |                                |                  |
| Self-detection                                              | 190 (52.0)                 | 69 (47.9)                      | 0.43             |
| Clinical breast examination (by physician)                  | 62 (17.0)                  | 56 (38.9)                      | <b>&lt;0.001</b> |
| Standard radiologic examination (mammography or sonography) | 109 (29.9)                 | 15 (10.4)                      | <b>&lt;0.001</b> |
| Other method                                                | 4 (1.1)                    | 4 (2.8)                        |                  |
| Unknown                                                     | 7                          | 7                              |                  |
| Follow-up status                                            |                            |                                |                  |
| Alive, no evidence of disease                               | 244 (65.6)                 | 50 (33.1)                      | <b>&lt;0.001</b> |
| Alive, metastatic disease                                   | 7 (1.9)                    | 5 (3.3)                        | 0.19             |
| Died of metastatic breast cancer                            | 80 (21.5)                  | 32 (21.2)                      | 1.00             |
| Died of other causes                                        | 37 (9.9)                   | 63 (41.7)                      | <b>&lt;0.001</b> |
| Lost to follow-up                                           | 4 (1.1)                    | 1 (0.7)                        |                  |

Table III. Comparison between a cohort of breast cancer patients who were  $\geq 80$  years at initial diagnosis and a standard breast cancer cohort (56–66 years old): Surgical therapy and adjuvant radiotherapy.

| Variable                                                              | 56–66 years          | $\geq 80$ years        | p-value          |
|-----------------------------------------------------------------------|----------------------|------------------------|------------------|
| Surgery                                                               | n = 372 (%)          | n = 151 (%)            |                  |
| Mastectomy                                                            | 150 (41.1)           | 78 (58.6)              | <b>&lt;0.001</b> |
| BCT                                                                   | 215 (58.9)           | 55 (41.4)              |                  |
| Surgical axillary staging (SLND/ ALND)                                | 348 (95.3)           | 87 (57.6)              | <b>&lt;0.001</b> |
| No surgery                                                            | 7 (1.9) <sup>1</sup> | 18 (11.9) <sup>2</sup> | <b>&lt;0.001</b> |
| Non-operative management                                              |                      | n = 21 (%)             |                  |
| Therapy goal reached; median follow-up (mths)                         |                      | 9 (42.9); 20           |                  |
| Therapy goal failed; median follow-up (mths)                          |                      | 12 (57.1); 32.5        |                  |
| Adjuvant radiation following BCT                                      | BCT, n = 211 (%)     | BCT, n = 53 (%)        |                  |
| Radiation not recommended due to severe comorbidity                   | 3 (1.4)              | 4 (7.5)                | <b>0.031</b>     |
| <b>Compliance</b>                                                     |                      |                        |                  |
| Radiation recommended                                                 | n = 208 (%)          | n = 49 (%)             |                  |
| Radiation not done; patient died before the intended start of therapy | 1                    | –                      |                  |
| Patient received radiation                                            | 193 (93.2)           | 25 (51.0)              | <b>&lt;0.001</b> |
| Non-compliance:                                                       |                      |                        |                  |
| radiation refused by the patient                                      | 14 (6.8)             | 24 (49.0)              |                  |

ALND, axillary lymph node dissection; BCT, breast-conserving therapy; SLND, sentinel lymph node dissection.

<sup>1</sup>In all cases (n = 7), surgery was not performed in palliative situation (stage IV at initial diagnosis).

<sup>2</sup>In eight cases, surgery was not performed in palliative situation (stage IV at initial diagnosis); in nine cases, therapy goal of a non-operative approach was reached; in one further case, non-operative approach was applied but the defined therapy goal was not reached (development of advanced locoregional clinical morbidity, i.e. large ulcerating and fungating lesion, which significantly impaired quality of life).

but also to the patient's decision not to accept a recommended treatment. Our data shows that, with regard to radiation after BCT and adjuvant ET for HR-positive BC, a certain percentage of patients were not recommended a treatment by their doctor (radiation: 7.5%; ET: 12.7%). However, the percentage of patients who did not initiate a recommended therapy is similarly high (ET: 13.0%) or even considerably higher (radiation: 49.0%).

A typical example for the process of non-compliance to a standard therapy, which results in an undertreatment in very elderly BC patients, is non-operative management in non-metastasized disease. Today, with the current standards of anesthesia and postoperative surveillance, it is possible for the vast majority of elderly and frail women to safely undergo breast surgery, and only a clear minority of the patients must be categorized as "inoperable" or "unfit for surgery". In our opinion, there is a clear role for surgery in preventing or palliating breast or chest wall symptoms, in particular for older women and those with severe comorbid conditions. Considering the fact that a non-operative approach is not successful in nearly half of the cases and is generally associated with poorer outcome [14,19–21], this procedure must be called an undertreatment. One could assume that non-compliance, i.e. the patient's refusal of surgery, is the result of a confrontation between patient and physician. This is not so in our experience. It is more often the case that patients in oncological consultations tend to be wary and reluctant towards oncological therapies. In further discussions,

the physician can address the anxieties and reservations of the patients. Factors such as average life expectancy, presence of comorbidities and an analysis of potential treatment benefits versus risks of the proposed treatment strategy must be carefully weighed and the option of a conservative non-operative management can be offered to the patients. In our experience, in the majority of cases, non-operative management is the result of shared decision making and clear communication that acknowledges the values and preferences of patients and their families and not the patient's categorical refusal of medical advice [14].

When discussing the implications of undertreatment in very elderly women, it must be emphasized that the term "undertreatment" pertains to the oncologist's view. This, however, may not necessarily represent the patient's perspective. Physicians must take into account that for many older patients, "classical" hard medical facts such as disease-specific and progression-free survival are only one component of total care. The priorities of these women more often lie with retaining their current life circumstances and their quality of life plays a more significant role in determining their treatment options rather than aiming solely for curative treatment [22].

Taking into account that a certain degree of undertreatment might result from an autonomous choice of the patients, efforts should be made to ensure that undertreatment does not result from medical care which does not reflect the most current evidence in the literature. In particular, older patients

Table IV. Comparison between a cohort of breast cancer patients who were  $\geq 80$  years at initial diagnosis and a standard breast cancer cohort (56–66 years old): Adjuvant systemic therapy and compliance and persistence to adjuvant endocrine therapy.

| Variable                                                                                       | 56–66 years | $\geq 80$ years | p-value                                                   |
|------------------------------------------------------------------------------------------------|-------------|-----------------|-----------------------------------------------------------|
| Adjuvant systemic therapy                                                                      | n = 352 (%) | n = 124 (%)     |                                                           |
| No therapy                                                                                     | 61 (17.3)   | 52 (41.9)       | <b>&lt;0.001</b><br><b>CT:&lt;0.001</b><br><b>ET:0.75</b> |
| Chemotherapy (CT) only                                                                         | 24 (6.8)    | 1 (0.8)         |                                                           |
| Endocrine therapy (ET) only                                                                    | 195 (55.4)  | 68 (54.8)       |                                                           |
| CT + ET                                                                                        | 58 (16.5)   | 1 (0.8)         |                                                           |
| Not known                                                                                      | 1           | –               |                                                           |
| Adjuvant ET in HR-positive BC, 1997–2009                                                       |             |                 |                                                           |
| Total number of patients                                                                       | n = 275 (%) | n = 79 (%)      |                                                           |
| Therapy was not recommended                                                                    | 11 (4.0)    | 10 (12.7)       | <b>0.012</b>                                              |
| <b>Compliance</b>                                                                              |             |                 |                                                           |
| Therapy recommended                                                                            | n = 264 (%) | n = 69 (%)      |                                                           |
| Non-compliance: patients refused to initiate therapy                                           | 13 (4.9)    | 9 (13.0)        | <b>0.026</b>                                              |
| Lost to follow-up                                                                              | 1 (0.4)     | –               |                                                           |
| <b>Persistence</b>                                                                             |             |                 |                                                           |
| Patients who initiated oral ET and had complete (at least 30 months) follow-up <sup>1</sup>    | n = 213 (%) | n = 53 (%)      |                                                           |
| I. Therapy completed                                                                           | 188 (88.3)  | 44 (83.0)       | 0.36                                                      |
| Therapy fully completed                                                                        | 139 (65.3)  | 21 (39.6)       | <b>&lt;0.001</b>                                          |
| Therapy discontinued due to death                                                              | 13 (6.1)    | 8 (15.1)        | <b>0.036</b>                                              |
| median duration of therapy (mths)                                                              | 16 (4–52)   | 16 (4–33)       |                                                           |
| Therapy discontinued due to BC recurrence                                                      | 26 (12.2)   | 6 (11.3)        | 1.000                                                     |
| median duration of therapy (mths)                                                              | 20.5 (3–58) | 28 (13–39)      |                                                           |
| Therapy stopped due to medical reasons independent from BC and therapy-related adverse effects | 10 (4.7)    | 9 (17.0)        | <b>0.003</b>                                              |
| duration of therapy (mths)                                                                     | 25 (1–52)   | 27 (1–52)       |                                                           |
| II. Non-persistence                                                                            | 25 (11.7)   | 9 (17.0)        |                                                           |
| Non-persistence due to therapy-related adverse effects                                         | 19 (8.9)    | 7 (13.2)        |                                                           |
| median duration of therapy (mths)                                                              | 8 (1–46)    | 21 (1–38)       |                                                           |
| Non-persistence due to other reasons                                                           | 6 (2.8)     | 2 (3.8)         |                                                           |
| median duration of therapy (mths)                                                              | 39.5 (6–47) | (6,44)          |                                                           |

BC, breast cancer; CT, chemotherapy; ET, endocrine therapy; HR, hormone receptor.

<sup>1</sup>The following number of patients, who were diagnosed during 2008/2009, started oral endocrine therapy but had no follow-up time longer than 30 months at the time of data analysis and were therefore not considered in the analysis of therapy persistence: Group “56–66 years”, n = 37; Group “ $\geq 80$  years”, n = 7.

are treated by primary care physicians and a better strategy should be developed to improve collaboration between specialized oncologists and primary care physicians [23]. In doing so, it should be made clear that the chemotherapy situation has changed in such a way that even older women can receive therapy regimens with safer profiles (e.g. weekly taxane regimens, newer less cardiotoxic anthracycline formulations, capecitabine, gemcitabine, and vinorelbine) and might derive similar benefits as their younger counterparts [2]. As a part of this collaboration, it is necessary to correct some old wives' tales regarding BC in the elderly such as “older BC patients have less aggressive tumors” or “in older patients, disease progresses more slowly”. These truisms, partly supported by an age-biased literature might play a role in deciding against therapy. In accordance with the study of Schonberg et al. [4], our data show that older patients have similar tumor characteristics compared to a standard cohort of BC patients. There

is little evidence to support that BC in elderly patients, which appears to have similarly aggressive features and is treated less aggressively, will have a slower, more indolent pattern of growth and progression, in fact the opposite is true. Our data shows that the percentage of patients who died of BC are similar in both groups analyzed and that from the patients who died of BC, older women had shorter overall and metastatic disease survival.

One further very important role for primary care physicians must be emphasized: the detection of BC. Older patients usually do not undergo screening mammography (we found that only 10% of the tumors diagnosed in older patients were detected by radiologic procedures) [2]. Accordingly, a comparatively high percentage of tumors were found by clinical breast examination. It is well documented that there is a strong association between older age and a delay of BC diagnosis, which is associated with larger tumors and more advanced stage at presentation

Table V. Comparison between a cohort of breast cancer patients who were  $\geq 80$  years at initial diagnosis and a standard breast cancer cohort (56–66 years old): Palliative therapy.

| Variable                                                   | 56–66 years  | $\geq 80$ years | p-value                                      |
|------------------------------------------------------------|--------------|-----------------|----------------------------------------------|
| Patients with distant metastases                           | n = 91 (%)   | n = 37 (%)      |                                              |
| Died on metastatic breast cancer                           | 79 (86.8)    | 31 (83.8)       |                                              |
| Alive, metastatic disease                                  | 7 (7.7)      | 3 (8.1)         |                                              |
| Died of other causes                                       | 5 (5.5)      | 3 (8.1)         |                                              |
| Palliative systemic therapy <sup>1</sup>                   | n = 79 (%)   | n = 31 (%)      |                                              |
| No therapy                                                 | 8 (10.1)     | 6 (19.4)        | 0.21                                         |
| CT only                                                    | 25 (31.7)    | 6 (19.4)        | <b>CT: 0.001</b>                             |
| ET only                                                    | 17 (21.5)    | 15 (48.4)       | ET: 0.83                                     |
| CT + ET                                                    | 29 (36.7)    | 4 (12.9)        |                                              |
| Number of therapy lines <sup>1</sup>                       | n = 71 (%)   | n = 25 (%)      |                                              |
| 1                                                          | 21 (29.6)    | 17 (68.0)       |                                              |
| 2                                                          | 11 (15.5)    | 4 (16.0)        | <b>1/2vs. <math>\geq 3</math>: &lt;0.001</b> |
| 3–4                                                        | 19 (26.8)    | 4 (16.0)        |                                              |
| 5–6                                                        | 15 (21.1)    | –               |                                              |
| 7–8                                                        | 5 (7.0)      | –               |                                              |
| Mean number of therapy lines                               | 3.2          | 1.6             | 0.29                                         |
| Median age at the start of palliative therapy              | 65 (56–75)   | 84 (80–92)      |                                              |
| Survival time for patients who died of BC (months) (range) |              |                 |                                              |
| Overall survival                                           | 54.5 (3–102) | 25 (2–91)       | <b>&lt;0.001</b>                             |
| Metastatic disease survival                                | 19 (1–98)    | 11.5 (1–74)     | 0.062                                        |

BC, breast cancer; CT, chemotherapy; ET, endocrine therapy.

<sup>1</sup>Considered were only the cases in which the patient died on BC, i.e. who had completed palliative therapy courses.

[24]. It must be emphasized that many larger tumors have easily detectable breast symptoms (e.g. breast lump, change in shape or dimpling of breast, nipple retraction or discharge) over a longer time. These clinical signs can be found at a clinical breast examination. We propose that an annual clinical breast examination should be an integral part of general medical care in older women. In our cohort, approximately 20% of the older patients had tumors larger than 5 cm or lesions with non-inflammatory skin involvement; with an easily performed clinical examination, the primary care physician can prevent their patients from developing advanced locoregional clinical morbidity which significantly impairs quality of life.

The limitations of our study must be considered. Firstly, our study population originates in a single region of a small country with a high socioeconomic status. All inhabitants of Switzerland have universal access to health care and free access to all prescribed and approved drugs. These facts must be considered while interpreting our results. Secondly, our study analyzes retrospective data. In our view, however, prospective randomized trials are an unsuitable trial design for addressing this issue. Clinical trials focus on the evaluation and comparison of defined therapy options, but in doing so, they can only evaluate therapy options in pre-selected groups of patients in certain situations. In particular studies which include older patients mostly have a high bias because they usually include patients who were deemed “fit for

therapy”. Thus, their ability to give a universally valid description of the entire cohort of elderly patients is limited. In our opinion, the goal of our study, i.e. to depict a clear and cohesive picture of the oldest 10% of BC patients, is very well achievable through a clinical database of a single institution, such as the one used in this study, which records data prospectively for all patients and provides solid individual-based follow-up data (lost to follow-up rate of our study cohort: <1%). We think that our approach is even better suited to reach the study goal than the analysis of large population-based databases such as National Cancer Registries. These sources have the following weak points: 1) They often exclude patients treated conservatively, limiting their validity for analysis in this group of patients. In the particular group of older patients, those who chose a non-operative management are high: in our study cohort, these patients comprised approximately 16% of all patients with non-metastatic BC. These patients are under-represented in larger databases: Schonberg et al., who used the SEER-Medicare data set and analyzed nearly 50 000 patients with stage I/II disease, found that only 1.7% of women did not receive surgery [4]; 2) They are not able to provide detailed information regarding the individual situations which lead to undertreatment. However, analyses of non-compliance and non-persistence to therapy, which in principle try to illuminate the complex field of personal motivation to therapy and mirror individual motivations and life

concepts, requires the readiness to engage with individual histories. This is of particular importance when analyzing the group of the oldest old in which the therapy decisions of sometimes very opinionated patients are strongly shaped by individual perceptions.

In order to report clinically meaningful data on non-compliance and non-persistence to therapy, it is essential to clearly categorize reasons of therapy cessation in clinically meaningful subgroups: in our view, non-compliance and non-persistence to therapy is not simply the act of not starting or stopping a therapy, but rather the manifestation of an intentional behavior [15,16]. Therefore, we applied a clear discrimination between situations where patients refused the recommended therapy or stopped therapy (whose attitude and behavior may be potentially influenced) and those whose therapy had to be stopped due to BC recurrence or other serious medical reasons (i.e. discontinuation of the therapy was unavoidable). Analyzing the cohort of the oldest old, it is apparent that situations in which ongoing therapies are stopped by physicians due to severe age-related comorbidity occur in approximately one fifth of the patients who started adjuvant ET. This is a factor which is negligible in younger patients, but common in an aged cohort and up until now has been widely ignored as a reason for non-persistence/non-adherence in the literature [15,16].

## Conclusions

The oncological care of elderly patients demands a high level of medical expertise and compassionate consideration. On the one hand, it must be ensured that appropriate standard therapies are not be routinely withheld in these patients based on erroneous perceptions regarding the biological nature of BC in the elderly and lack of knowledge about available therapy regimens. On the other hand, physicians must take into account that for many older patients "classical" hard medical facts, such as survival times, are only one component of total care. Preservation of current life circumstances and maintenance of quality of life, rather than aiming solely for curative treatment, are often of more importance. Physicians must be aware that well intentioned therapy recommendations are not always accepted, because some patients and families view their situation with broader psychosocial and spiritual meaning, shaped by a lifetime of experiences [25].

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