Undertreatment in older patients with breast cancer

Alessandra Surace [1], Lucia Idda [2], Elisabetta Trino [3], Anna Turletti [4], Cristina Capello [4], Lorenza Mairone [4], Chiara Perono Biacchiardi [5], Stefano Guzzetti [6], Maria Grazia Baù [7], Massimiliano Bortolini [8]

[1] Gynecology and Obstetrics 2, Department of Surgical Sciences, City of Health and Science, University of Turin, Via Ventimiglia 1, Turin, Italy; [2] Surgical Sciences Department, Turin University, Italy; [3] Radiotherapy, Mauriziano Hospital, Turin, Italy; [4] Oncology, Martini Hospital, Turin, Italy; [5] Gynecology, Martini Hospital, Turin, Italy; [6] Pathological Anatomy, Martini Hospital, Turin, Italy; [7] Gynecology and Obstetrics 3, Department of Surgical Sciences, City of Health and Science, Corso Spezia 60, Turin, Italy; [8] General Surgery, Martini Hospital, Turin, Italy

ABSTRACT

Background and purpose: As older patients with breast cancer are often not included in clinical trials, we currently have a limited number of specific recommendations available for their management.

Methods: Our retrospective analysis concerned patients older than 75 years treated between January 2010 and December 2018 at the Breast Unit of Martini Hospital in Turin. We evaluated the effect of undertreatment on overall survival (OS), local recurrence-free survival (LRFS), systemic recurrence-free survival (SRFS), and disease-free survival (DFS) in elderly people. Undertreatment was defined as any deviation of the treatment from the Italian and international guidelines, based on stage and biological sub-type.

Results: We selected 408 patients aged >75 years and affected by primary breast cancer. In this whole sample, worse OS ($p < 0.001$), LRFS ($p = 0.008$) and SRFS ($p = 0.042$) were observed in the undertreated group as compared with the standard treatment group, while no difference was found in DFS. In the older subgroup of patients (>85 years old), OS and LRFS did not appear to be affected by undertreatment ($p=0.476$ and $p=0.834$, respectively). While SRFS was seen to be worse in the undertreated patients aged >85 years ($p=0.031$), it did not appear to be affected by undertreatment in the subgroup aged 75-85 years ($p=0.119$).

Conclusion: Although undertreatment affects survival in a statistically significant way, age itself is the main factor affecting five-year survival and is the main risk factor for mortality in elderly patients. In fact, the over-85 group showed no statistically significant difference in OS according to omission or otherwise of axillary surgery or radiotherapy. So, in this group of patients, de-escalation therapies could be a reasonable choice.

KEYWORDS

Breast cancer, elderly, de-escalation treatment, undertreatment, geriatric oncology.

Background and purpose

Since older patients (≥ 70 years) are often excluded from clinical trials, we lack strong evidence-based recommendations for the management of breast cancer in these individuals.

Older patients often receive modified management strategies; however, this approach is not supported by the literature and it leads to undertreatment. Updated recommendations regarding breast cancer in older patients were recently published by EUSOMA (the European Society of Breast Cancer Specialists) and SIOG (the International Society of Geriatric Oncology): the topics covered include primary endocrine therapy (PET) and surgical management in older patients [1]. Undertreatment occurs in up to 19% of all newly diagnosed breast cancer patients: 13.6% are patients aged between 75 and 84 years, and 5.4% are patients older than 85 years [2]. In Italy, screening programs are regulated on a regional basis and usually include patients aged 50 to 75 years, thus excluding those older than 75 years. Our Breast Unit is part of a city hospital that does not carry out breast screening activities: most of our patients are diagnosed based on clinical symptoms. The aim of our study was to investigate the outcomes of older patients treated in our Breast Unit.

Article history
Received 5 Aug 2021 - Accepted 4 Jan 2022

Contact
Alessandra Surace; alessandra.sur@gmail.com
Gynaecology and Obstetrics 2, Città della Salute e della Scienza
University of Turin, Corso Spezia 60, Turin (Italy)
Tel. +39 011 3131822.

Methods

In this retrospective study, we analyzed data of consecutive patients aged over 75 years treated for invasive and in situ breast cancer between January 2010 and December 2018 at the Breast Unit of the Martini Hospital in Turin (Italy): any kind of treatment was included, i.e., both medical and surgical ones.

We selected 408 patients aged over 75 who met the above inclusion criteria. The exclusion criteria were: presence of metastasis at the time of diagnosis, follow up shorter than six months, and a history of breast cancer disease. For each patient, we collected personal and clinical data, such as age and presence of comorbidities, neoplasm characteristics, tumor staging according to the TNM system [3], tumor grading, histological

type, biological sub-type, data on the overall treatment adopted and on any undertreatment. Undertreatment was defined as any deviation of the treatment from the Italian and international guidelines, based on stage and biological sub-type. We recorded the presence of local or systemic relapses and the last known follow-up date. Patients were divided into two groups: 75-85 years old and over 85 years old. Patients were also defined as "fit" or "unfit" (if they presented associated medical conditions, i.e., at least one of: cardiovascular disease, major neurological disease, renal insufficiency, diabetes mellitus, chronic obstructive pulmonary disease, obstructive or central apnea syndrome). We set out to analyze the possible impact of undertreatment on overall survival (OS), local recurrence-free survival (LRFS), systemic recurrence-free survival (SRFS), and disease-free survival (DFS) in patients older than 75 years.

The National Cancer Institute definitions of these oncological outcomes are as follows [4]:

- OS: the length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive.
- RFS: the length of time after primary treatment for a cancer ends that the patient survives without any signs or symptoms of that cancer. RFS could refer to local (LRFS) or systemic (SRFS) relapse/recurrence.
- DFS: the length of time after primary treatment for a cancer ends that the patient survives without any signs or symptoms of that cancer.

Data were analyzed using IBM SPSS Statistics. OS, LRFS, SRFS and DFS between different analysis sub-groups were compared using the Kaplan-Meier method and the log-rank test. A value of $p < 0.05$ was considered statistically significant. The secondary endpoints were:

1. To evaluate the effects of undertreatment by stratifying patients by age (75-85 years old vs. over 85 years old);
2. To evaluate the effects of undertreatment by stratifying patients by comorbidities, biological sub-types and TNM staging at diagnosis.

Results

Patients

Out of all the cases we treated during the study period, we selected 408 patients with primary breast cancer aged 75 years and older. Their mean age was 80.3 years (range: 75-97). Among the selected patients, 356 (87.3%) were aged 75 to 85, while 52 (12.7%) were aged over 85. The median follow-up duration was 52.6 months (range 6-138 months). Among all the patients, 277 (67.9%) had comorbidities (232 in the group aged 75-85 years and 45 in the over 85s).

Tumors

As regards the staging of the cancer, most of our patients were diagnosed with T1c or T2, in 32.4% and 41.6% of cases, respectively, and axillary involvement was identified in 37% of cases. Most of the tumors in our sample were luminal A or luminal B breast cancer (62.6% and 23.7%, respectively), while only a few showed positive HER2 expression (2%). In patients

Table 1 Tumor characteristics at diagnosis (tumor staging based on AJCC, 2018). DCIS= ductal carcinoma in situ; NST= non special type; IC= invasive carcinoma; cN+: clinically involved nodes, without a histological confirmation.

		All	75-85 y/o	Over 85
Histological type (breast biopsy)	DCIS, n (% of the subgroup)	15 (3.68%)	15 (4.21%)	0 (0%)
	NST IC, n (% of the subgroup)	301 (73.77%)	263 (73.88%)	38 (73.08%)
	Lobular IC, n (% of the subgroup)	53 (12.99%)	46 (12.92%)	7 (13.46%)
	Others, n (% of the subgroup)	39 (9.56%)	32 (8.99%)	7 (13.46%)
Tumor size (breast specimen)	Tis, n (% of the subgroup)	10 (2.45%)	10 (2.81%)	0 (0%)
	T1a, n (% of the subgroup)	20 (4.90%)	20 (5.62%)	0 (0%)
	T1b, n (% of the subgroup)	36 (8.82%)	35 (9.83%)	1 (1.92%)
	T1c, n (% of the subgroup)	128 (31.38%)	114 (32.02%)	14 (26.92%)
	T2, n (% of the subgroup)	164 (40.20%)	137 (38.48%)	27 (51.93%)
	T3, n (% of the subgroup)	26 (6.37%)	20 (5.62%)	6 (11.54%)
	T4, n (% of the subgroup)	10 (2.45%)	9 (2.53%)	1 (1.92%)
	Unknown, n (% of the subgroup)	14 (3.43%)	11 (3.09%)	3 (5.77%)
Axillary involvement	N0, n (% of the subgroup)	230 (56.37%)	212 (59.55%)	18 (34.62%)
	N1mic, n (% of the subgroup)	13 (3.19%)	12 (3.37%)	1 (1.92%)
	N1 (N1mic excepted), n (% of the subgroup)	71 (17.40%)	65 (18.26%)	6 (11.54%)
	N2, n (% of the subgroup)	19 (4.66%)	16 (4.49%)	3 (5.77%)
	N3, n (% of the subgroup)	20 (4.90%)	19 (5.34%)	1 (1.92%)
	cN+, n (% of the subgroup)	12 (2.94%)	9 (2.53%)	3 (5.77%)
	Unknown, n (% of the subgroup)	43 (10.54%)	23 (6.46%)	20 (38.46%)
Tumor grading	G1, n (% of the subgroup)	82 (20.10%)	72 (20.22%)	10 (19.23%)
	G2, n (% of the subgroup)	190 (46.57%)	167 (46.91%)	23 (44.23%)
	G3, n (% of the subgroup)	92 (22.55%)	84 (23.60%)	8 (15.39%)
	Unknown, n (% of the subgroup)	44 (10.78%)	33 (9.27%)	11 (21.15%)
Biological sub-type	Luminal A, n (% of the subgroup)	251 (61.52%)	216 (60.67%)	35 (67.31%)
	Luminal B +, n (% of the subgroup)	21 (5.14%)	20 (5.62%)	1 (1.92%)
	Luminal B -, n (% of the subgroup)	74 (18.14%)	63 (17.69%)	11 (21.15%)
	Triple-negative, n (% of the subgroup)	47 (11.52%)	44 (12.36%)	3 (5.77%)
	HER2-positive, n (% of the subgroup)	8 (1.96%)	6 (1.69%)	2 (3.85%)
	Unknown, n (% of the subgroup)	7 (1.72%)	7 (1.97%)	0 (0%)

Table 2 Treatment in the study population.

		All	75-85	Over 85
Surgical therapy	No surgery, n (% of the subgroup)	32 (7.84%)	23 (6.46%)	9 (17.31%)
	Breast conservative surg, n (% of the subgroup)	270 (66.18%)	240 (67.42%)	30 (57.69%)
	Mastectomy, n (% of the subgroup)	106 (25.98%)	93 (26.12%)	13 (25%)
	No axillary surgery, n (% of the subgroup)	83 (20.34%)	55 (15.45%)	28 (53.85%)
	Sentinel lymph node, n (% of the subgroup)	232 (56.86%)	215 (60.39%)	17 (32.69%)
	Axillary dissection, n (% of the subgroup)	91 (22.30%)	85 (23.88%)	6 (11.54%)
	Axillary surgery unknown, n (% of the subgroup	2 (0.50%)	1 (0.28%)	1 (1.92%)
Adjuvant therapy	Hormone therapy (HT), n (% of the subgroup)	301 (73.77%)	270 (75.84%)	31 (59.62%)
	Chemotherapy (CT), n (% of the subgroup)	59 (14.46%)	57 (16.01%)	2 (3.85%)
	Trastuzumab (T), n (% of the subgroup)	21 (5.15%)	19 (5.34%)	2 (3.85%)
	Radiotherapy (RT), n (% of the subgroup)	255 (62.50%)	240 (67.42%)	15 (28.85%)
Undertreatment	Omission of HT, n (% of the subgroup)	50 (12.25%)	34 (9.55%)	16 (30.77%)
	Omission of CT, n (% of the subgroup)	100 (24.51%)	85 (23.88%)	15 (28.85%)
	Omission of T, n (% of the subgroup)	4 (0.98%)	1 (0.28%)	3 (5.77%)
	Omission of RT, n (% of the subgroup)	51 (12.50%)	34 (9.55%)	17 (32.69%)
	Omission of axillary surg., n (% of the subgroup)	75 (18.38%)	46 (12.92%)	29 (55.77%)
	Omission of breast surg., n (% of the subgroup)	30 (7.35%)	20 (5.62%)	10 (19.23%)
	Any undertreatment, n (% of the subgroup)	201 (49.26%)	156 (43.82%)	45 (86.54%)

older than 85, the luminal A and luminal B cancers represented together accounted for 90.3% of the cases (luminal A: 67.3%; luminal B: 23%). These results are shown in Table 1.

Management and oncologic outcomes

In our study population, 30 patients underwent PET, without any surgical treatment. Among these 30 patients, only seven were aged over 85. Two patients did not receive medical or surgical treatment. Further management details are shown in Table 2. During the study period, 125 patients (30.6%) died. Recurrence was experienced by 69 patients (16.9%); of these, 52 had a local recurrence (12.7%) and 17 had a systemic recurrence (4.2%).

We analyzed oncologic outcomes (OS, LRFS, SRFS and DFS) in the whole sample and in the different subgroups. In the whole sample, average OS was 56.8 months (range 6-160 months); other average data were 51.9 months for LRFS, 53.1 months for SRFS, and 51.3 months for DFS. When we evaluated all patients older than 75, not further stratified by age, worse OS (p<0.001), LRFS (p=0.008), and SRFS (p=0.042) were observed in the undertreated group as compared to with the standard treatment group, while DFS showed no changes difference (p=0.229; figure 1).

We subsequently considered the two age groups separately (75-85 vs >85 years). In the older group of patients (>85), OS and LRFS did not appear to be affected by undertreatment (p=0.476 and p=0.834, respectively). On the contrary, these outcomes appeared to be worse in the undertreated patients aged 75-85 years (p<0.001 and p=0.007, respectively; figure 2).

Moreover, while worse SRFS was observed in the undertreated patients aged >85 years (p=0.031), this parameter did not appear to be affected by undertreatment in the subgroup aged 75-85 years (p=0.119). Similarly, undertreatment appeared to have no impact on DFS when the two age groups were considered separately (p=0.567 and p=0.152).

We found a statistically significant association between

Figure 1 All patients. Difference in OS and LRFS between the standard therapy group and the undertreated group.

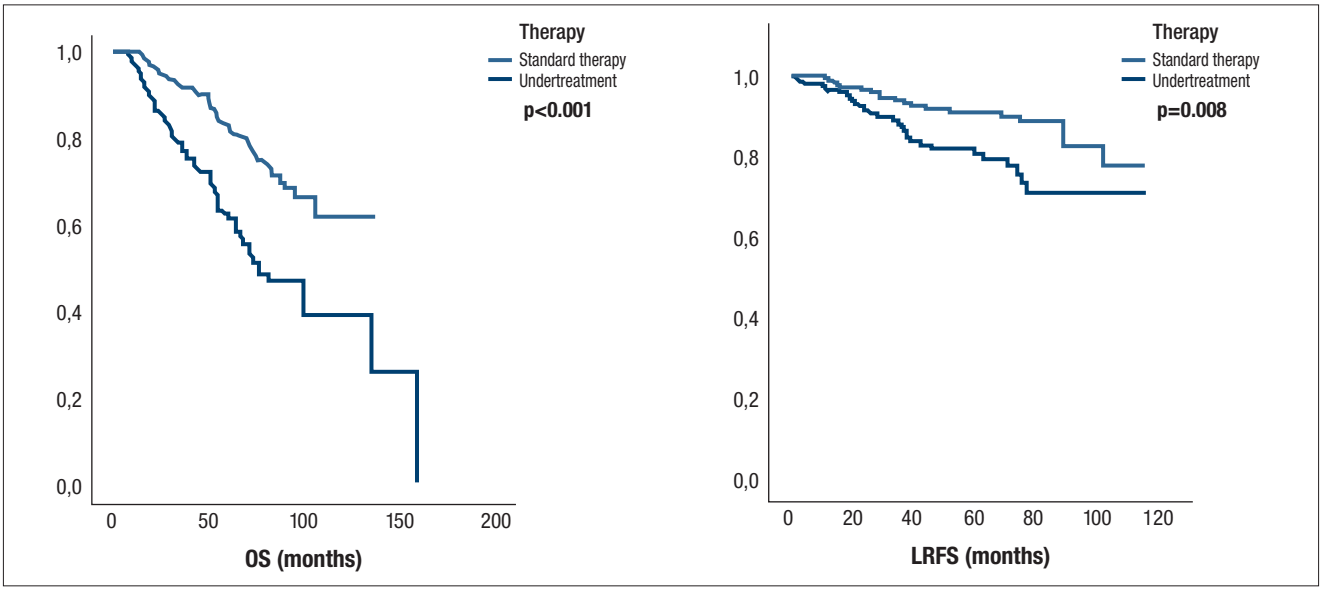


Figure 2 Patients stratified by age: 75-85 years and over 85 years. Difference in OS and LRFS between the standard therapy group and the undertreated group.

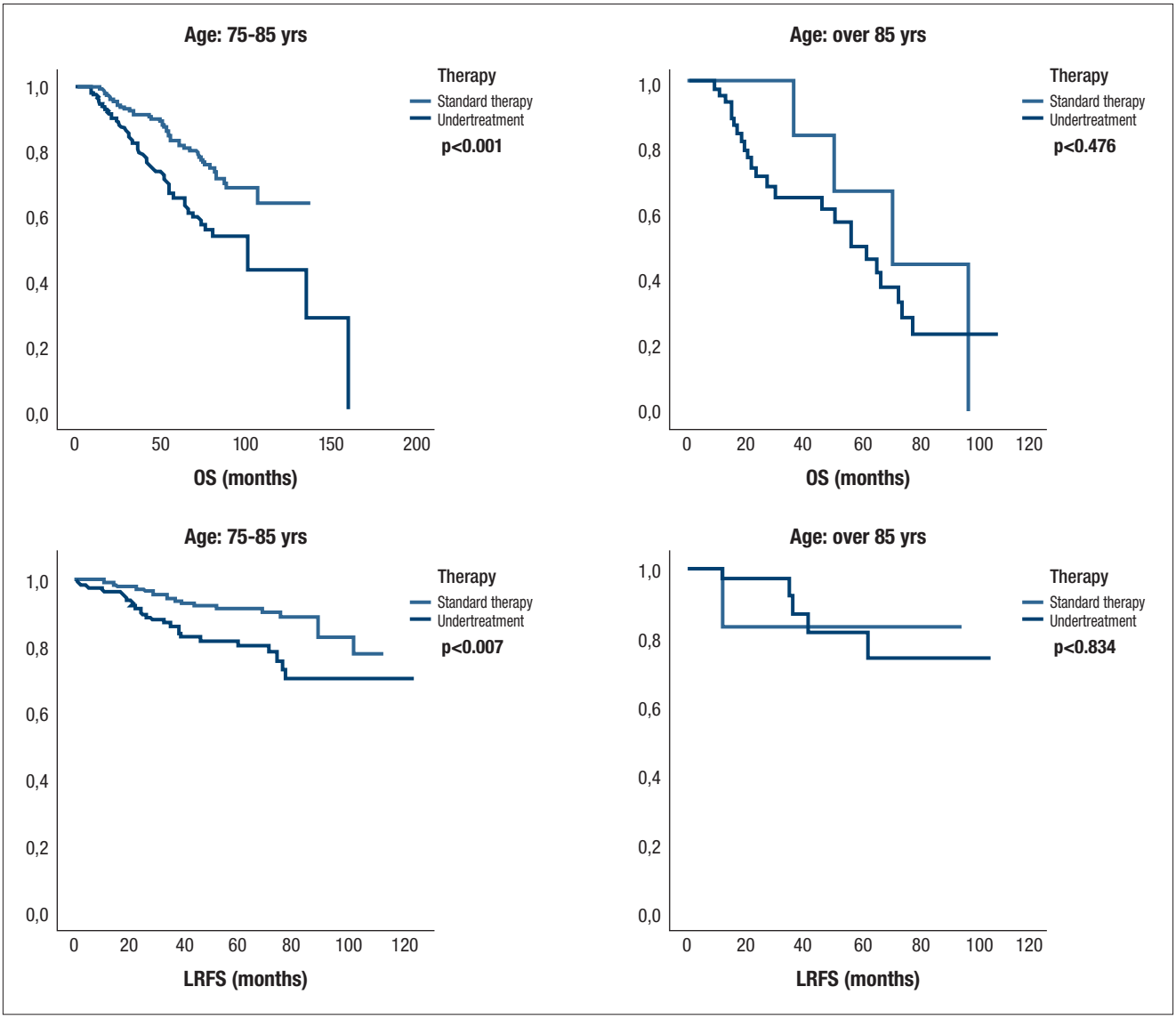
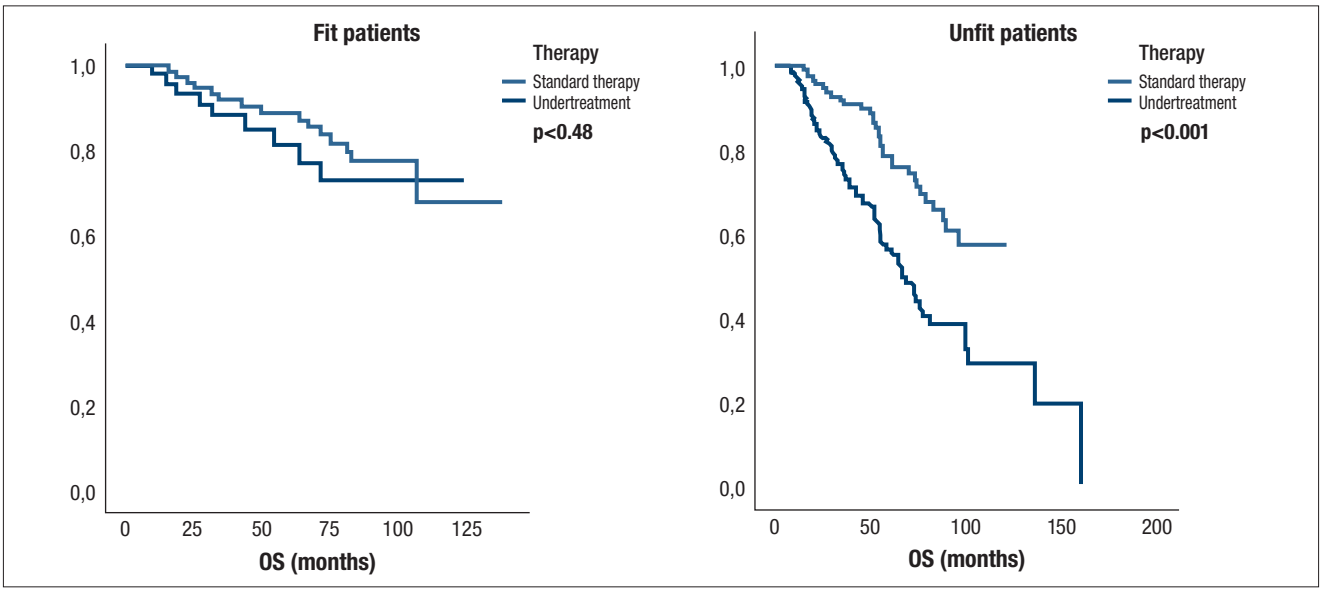


Figure 3 Fit and unfit patients. Difference in OS between the standard therapy group and the undertreated group.



the presence of comorbidity and undertreatment (χ^2 p<0.01). Evaluating the outcomes stratified by health status, we found that in unfit patients, undertreatment had a worse impact on OS (p<0.001; figure 3).

Our analysis of undertreatment in relation to the different biological sub-types appeared to show significantly worse (p<0.01) OS in undertreated luminal A patients, while there appeared to be no correlation with any outcome (LRFS, SRFS, DFS or OS) for the other sub-types.

We stress that these data must not be taken to mean that undertreatment has a strong impact only in the luminal A biological sub-type: this group of patients, being the most represented, was the only one in which statistically significant data could be obtained. In the other biological types, the comparison curves confirmed a worse prognosis in undertreated patients, but statistical significance was not achieved due to the poor numerical representation of the more aggressive biological types in elderly patients.

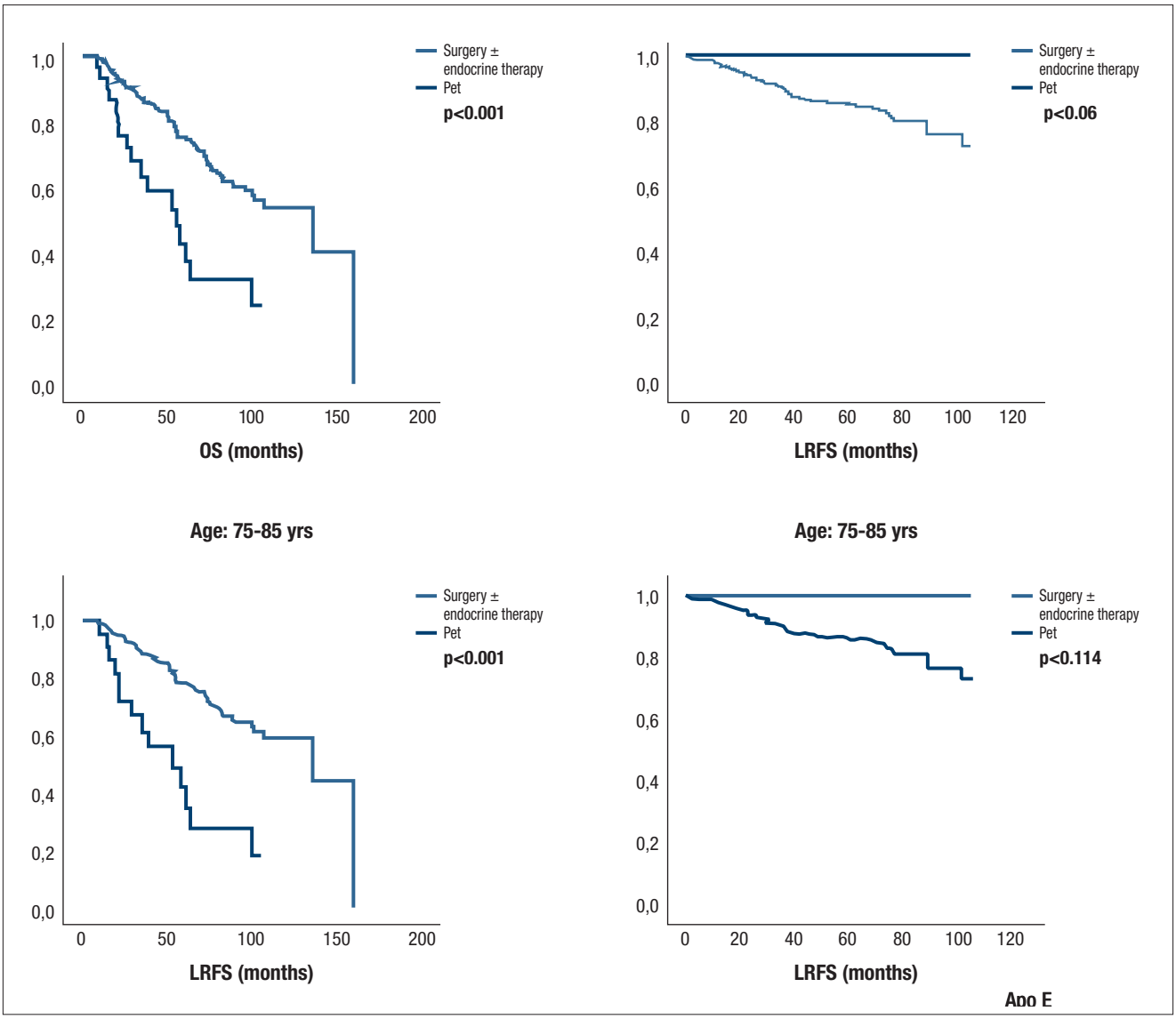
As regards the relationship between the TNM classification and survival, we detected a significant worsening of survival for the T stages T2 (p< 0.01) and T3 (p=0.019), and for the N stages N0 (p=0.002), N2 (p=0.001), and N3 (p=0.038). We observed that only systemic recurrence affected OS (p=0.001).

In comparison with the PET group, we identified better OS in patients who underwent surgical treatments plus hormone therapy, both in the entire population and in the group aged 75-85 years. No differences in LRFS were found when comparing the hormone therapy group and the surgery group, with or without adjuvant hormone therapy. This result was obtained both in the entire study population and in each of the subgroups (Figure 4).

Discussion

In our patient population, undertreatment had no impact on overall survival in patients aged over 85 years. The reasons for this may be related to the small number of patients in this age

Figure 4 All patients and patients aged 75-85 years. Difference in OS and LRFS between the surgery group and the PET group.



group, for whom statistics are not reliable, or to their limited life expectancy due to age and comorbidities.

This retrospective study evaluated patients of senile age, whose tumors often showed similar clinical and biological peculiarities. None of them were included in any national screening program, and their breast cancer was diagnosed clinically. Most of the breast cancers in our cases were palpable and axillary involvement was detected in a large proportion of the sample (37% of cases).

Similar data are also reported in the literature: Wildiers *et al*. [5] showed that older women are more likely to present larger tumors at the time of diagnosis and that their risk of lymph node involvement is high. Bergman *et al*. [6] confirmed that poor prognosis in older women is largely related to their unfavorable tumor stage at diagnosis, characterized by a larger tumor size, more common lymph node involvement, and more metastatic breast cancer. These findings are mostly explained by delayed diagnosis in this age group.

Anderson *et al*. [7], in agreement with our results, found that older women had more frequent estrogen receptor (ER) positivity, which constitutes a favorable tumor characteristic. The proportion of ER-positive cancer increased from 55.9% among women aged 30-34 to 85.1% among women aged 80-84. Additionally, HER2 positivity decreased with age (only 10% in women aged 70 or older). Other literature data confirmed that older patients, compared with younger postmenopausal patients, have tumors with more favorable biological characteristics, i.e., a higher degree of hormone receptor expression (81% of patients aged >70 years in the study by Pierga *et al*. [8]), lower HER2 expression [9], and lower proliferative rates [10].

Increasing age is independently associated with decreased compliance with standard of care, decreased likelihood of surgical procedures, less frequent use of adjuvant radiation therapy following breast-conserving surgery, increased use of PET, and decreased use of adjuvant chemotherapy, even in "fit" patients. It is nevertheless true that vulnerable older patients treated with intensive therapy may actually show higher all-cause mortality as a result of treatment toxicity, even if their cancer-specific mortality is lower. Therefore, a change in the definition of "undertreatment" is mandatory, as pointed out by DuMontier *et al*., who proposed the following new definition of the term: "the use of less intensive cancer treatment in a fit older adult who would otherwise derive a greater net benefit from more intensive cancer treatment". According to the author, "less intensive" means "some reduction in a recommended/standard treatment regimen normally used in younger, fit patients", "fit" is defined by a geriatric assessment (GA) score, and "benefits" are jointly defined by the physician and patient and outweigh the similarly defined harms resulting from the cancer treatment [11].

Our data show that, although undertreatment affects survival in a statistically significant way, age itself is the main factor affecting five-year survival and is the main risk factor for mortality in elderly patients. This is also reported in the literature: according to Roder *et al*. [12], patients aged 70-79 with breast cancer showed five-year survival of 82.4%, versus 74% for patients aged 80 and older. Data presented by Agborbesong *et al*. [13] pointed out that most breast cancer patients without standard therapy were aged over 80 and that there was no significant difference in breast cancer-related deaths between the two treatment groups (standard care vs. undertreatment). All-cause mortality rates were significantly higher in the undertreated patients (46.4% vs. 27.5%, p =0.011).

This finding is also consistent with the fact that more women in the undertreatment group were over the age of 80. Since age is a non-modifiable risk factor, we must select older patients based on their ability to receive cancer therapies. A GA is mandatory. We have been carrying out GAs in our breast center since 2017. The benefit of cancer therapy in individuals likely to die at an early stage from non-cancer-related causes is questionable; however, it is difficult for clinicians to identify these individuals. Also, underestimation of life expectancy and fitness for therapy might result in age-related undertreatment which is, in turn, a risk factor for breast cancer recurrence and death. In order to help cancer specialists determine the best treatments for their older patients, the US National Comprehensive Cancer Network (NCCN) [14], the SIOG [15], the EUSOMA [16], and the European Organization for Research and Treatment of Cancer (EORTC) [17] have recommended that some form of GA should be conducted in all older patients for whom aggressive therapy is considered.

Despite these recommendations, there is no solid evidence regarding either the best type of GA for use in the oncology setting or how outcomes are improved as a result of GAs. Since GAs can be time consuming and need to be carried out by a geriatrician, an abbreviated screening method has been recommended to identify patients who would benefit from a full GA. When screening suggests potential frailties, a comprehensive GA (CGA) allows identification of risks and consequently, where possible, their correction [18]. A CGA is "a multidimensional, multidisciplinary process which identifies medical, social and functional needs, and the development of an integrated/coordinated care plan to meet those needs" [19]. Completing a CGA in clinical practice takes approximately 30-60 minutes per patient and requires expertise in both its conduction and its interpretation [20]. In geriatric oncology there is therefore a need for specialized healthcare professionals in order to improve medical treatments of older patients: recent literature supports the creation of a special gerontology curriculum for both medical doctors and nurses [21-23].

The importance of GA is to assess the "functional" age of our patients, beyond their chronological age, which has implications for treatment outcome and tolerance [24].

Our analysis of two different groups of patients (fit and unfit) revealed that the unfit patients always showed worse OS than the fit ones. Furthermore, undertreatment greatly affects the prognosis of this subgroup of patients. However, we suggest that our results are not based on an appropriate definition of "unfit". In fact, until 2017, no GA was conducted for breast cancer patients in our Breast Unit and only a subjective evaluation of medical status determined which patients were considered "fit" and "unfit".

As regards the issue of surgery omission, PET is often considered as a possible alternative to surgery. A Cochrane Review published in 2006 [25] evaluated women aged 70 and older affected by operable breast cancer: the authors compared the

effectiveness of surgery (with or without adjuvant endocrine therapy) with that of PET both in terms of LFRS and mortality. They observed no statistically significant difference in either arm in terms of survival; instead, there was less recurrence in the surgical arm (with or without adjuvant endocrine therapy). Comparison of our population with that review showed quite different results. We identified better OS in patients who underwent surgical treatments plus hormone therapy, both in the entire population and in the subgroup aged 75-85 years. The worse OS in the hormone treatment alone (PET) group was probably due to a selection bias: the higher mortality was likely closely related to other causes of death.

As regards axillary surgery, in "Five Things Physicians and Patients Should Question" [26], the Society of Surgical Oncology reports that routine sentinel node biopsy can be avoided in specific care settings. Omission of sentinel lymph node biopsy does not result in worse locoregional recurrence and has no impact on breast cancer mortality in a specific subgroup of patients (women > 70 years old, ER positive and HER2 negative, early stage, no axillary involvement, adjuvant endocrine therapy).

Most of our patients who underwent axillary surgery showed better OS. Only the over-85 group showed no statistically significant difference. Furthermore, no statistically significant data emerged from the analysis of the effects of omission of axillary surgery on LRFS and DFS. Also in this case, we can suppose that the absence of statistically significant data is due to the small number of cases in the examined sub-sets.

In recent years, the benefit of adjuvant radiation therapy in older women with early-stage breast cancer has been evaluated in two randomized controlled trials: CALBG9343 [27] and the PRIME II trial [28]. These studies demonstrated that the risk of recurrence in older patients with early-stage cancer is low, so the possible side effects of radiation therapy could outweigh the benefit of local recurrence prevention. Also, the NCCN guidelines [14] state that breast radiation may be omitted in patients aged ≥70 years with ER-positive, clinical node-negative, T1 tumors who receive adjuvant endocrine therapy. Most of our patients underwent adjuvant radiotherapy after conservative breast surgery, and showed better OS. Only in the over 85s was no statistically significant difference identified when radiotherapy was omitted.

Conclusions

According to our results, in the age group 75-85 years, adherence to standard therapy allows for survival in line with that observed in younger patients and must always be pursued. In the older group (over 85 years of age), a less intensive treatment is a valid choice and should be considered. Considering the small numbers of patients, it would be difficult to set up a more reliable prospective study: indeed, the therapeutic choice cannot be randomized for ethical reasons, but must be decided on the basis of the characteristics of the single patient and tumor. Future studies should focus on individualizing treatments based on concomitant competing mortality and toxicity of treatments.

References

1. Biganzoli L, Battisti NML, Wildiers H, et al. Updated recommendations regarding the management of older patients with breast cancer: a joint paper from the European Society of Breast Cancer Specialists (EUSOMA) and the International Society of Geriatric Oncology (SIOG). Lancet Oncol. 2021;22:e327-e340.
2. National Cancer Institute; The Surveillance, Epidemiology, and End Results (SEER) Program 2013-2017: Cancer Stat Facts. Female Breast Cancer. Available at: https://seer.cancer.gov/statfacts/html/breast.html. Accessed September 11, 2021.
3. Amin B, Edge SB, Greene F, et al., eds. American Joint Committee on cancer (AJCC). Cancer Staging manual. Eighth Edition. New York, Springer; 2017.
4. National Cancer Institute. NCI Dictionary of Cancer Terms. Available at: https://www.cancer.gov/publications/dictionaries/cancer-terms. Accessed September 11, 2021.
5. Wildiers H, Van Calster B, van de Poll-Franse LV, et al. Relationship between age and axillary lymph node involvement in women with breast cancer. J Clin Oncol;27:2931-7.
6. Bergman L, Kluck HM, van Leeuwen FE, et al. The influence of age on treatment choice and survival of elderly breast cancer patients in south-eastern Netherlands: a population-based study. Eur J Cancer. 1992;28A:1475-80.
7. Anderson WF, Katki HA, Rosenberg PS. Incidence of breast cancer in the United States: current and future trends. J Natl Cancer Inst. 2011;103:1397-402.
8. Pierga JY, Girre V, Laurence V, et al; Institut Curie Breast Cancer Study Group. Characteristics and outcome of 1755 operable breast cancers in women over 70 years of age. Breast. 2004;13:369-75.
9. Laird-Fick HS, Gardiner JC, Tokala H, Patel P, Wei S, Dimitrov NV. HER2 status in elderly women with breast cancer. J Geriatr Oncol. 2013;4:362-7.
10. Diab SG, Elledge RM, Clark GM. Tumor characteristics and clinical outcome of elderly women with breast cancer. J Natl Cancer Inst. 2000;92:550-6.
11. DuMontier C, Loh KP, Bain PA, et al. Defining undertreatment and overtreatment in older adults with cancer: a scoping literature review. J Clin Oncol. 2020;38:2558-69.
12. Roder D, Farshid G, Kollias J, et al. Female breast cancer management and survival: the experience of major public hospitals in South Australia over 3 decades-trends by age and in the elderly. J Eval Clin Pract. 2017;23:1433-43.
13. Agborbesong O, Helmer SD, Reyes J, Strader LA, Tenofsky PL. Breast cancer treatment in the elderly: do treatment plans that do not conform to NCCN recommendations lead to worse outcomes? Am J Surg. 2020;220:381-4.
14. National Comprehensive Cancer Network guidelines for breast cancer. Version 6.2020.
15. Wildiers H, Heeren P, Puts M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol. 2014;32:2595-603.
16. Biganzoli L, Wildiers H, Oakman C, et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). Lancet Oncol. 2012;13:e148-60.
17. Pallis AG, Fortpied C, Wedding U, et al. EORTC elderly task force position paper: approach to the older cancer patient. Eur J Cancer. 2010;46:1502-13.
18. Extermann M, Aapro M, Bernabei R, et al; Task Force on CGA of the International Society of Geriatric Oncology. Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). Crit Rev Oncol Hematol. 2005;55:241-52.
19. Parker SG, McCue P, Phelps K, et al. What is Comprehensive Geriatric Assessment (CGA)? An umbrella review. Age Ageing. 2018;47:149-55.
20. Okoli GN, Stirling M, Racovitan F, et al. Integration of geriatric

assessment into clinical oncology practice: a scoping review. Curr Probl Cancer. 2021;45:100699.
21. Lim SYS, Koh EYH, Tan BJX, Toh YP, Mason S, Krishna LKR. Enhancing geriatric oncology training through a combination of novice mentoring and peer and near-peer mentoring: a thematic analysis of mentoring in medicine between 2000 and 2017. J Geriatr Oncol. 2020;11:566-75.
22. Burhenn P, Economou D, Uranga C, et al. Geriatric Oncology Workshop (GrOW): development and evaluation of a nationwide nursing curriculum. J Geriatr Oncol. 2021;12:649-57.
23. McKenzie GAG, Bullock AF, Greenley SL, Lind MJ, Johnson MJ, Pearson M. Implementation of geriatric assessment in oncology settings: a systematic realist review. J Geriatr Oncol. 2021;12:22-33.
24. Kikuchi R, Broadwater G, Shelby R, et al. Detecting geriatric needs in older patients with breast cancer through use of a brief geriatric screening tool. J Geriatr Oncol. 2019;10:968-72.
25. Hind D, Wyld L, Beverley CB, Reed MW. Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus). Cochrane Database Syst Rev. 2006;(1):CD004272.
26. Society of Surgical Oncology. Five Things Physicians and Patients Should Question. Released July 12, 2016; Updated June 20, 2019. Available at: https://www.choosingwisely.org/wp-content/uploads/2016/07/SSO-5things-List_2021-Updates.pdf. Accessed September 11, 2021.
27. Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. J Clin Oncol. 2013;31:2382-7.
28. Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM; PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. Lancet Oncol. 2015;16:266-73.

Conflict of interest statement: *the authors declare that there are no conflicts of interest.*
Funding: *none.*