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Original Article

Frailty-Independent Undertreatment Negative Impact on Survival in Older Patients With Breast Cancer

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ABSTRACT

Purpose: The management of older adults with breast cancer (BC) remains controversial. The challenging assessment of aging idiosyncrasies and the scarce evidence of therapeutic guidelines can lead to undertreatment. Our goal was to measure undertreatment and assess its impact on survival.

Methods: Consecutive patients with BC aged 70 years or older were prospectively enrolled in 2014. Three frailty screening tools (G8, fTRST, and GFI) and two functional status scales (Karnofsky performance score and Eastern Cooperative Oncology Group Performance Status) were applied. Disease characteristics, treatment options, and causes of mortality were recorded during a 5-year follow-up. In addition, we defined undertreatment and correlated its survival impact with frailty.

Results: A total of 92 patients were included in the study. The median age was 77 (range 70–94) years. The prevalence of frailty was discordant (G8, 41.9%; fTRST, 74.2%; GFI, 32.3%). Only 47.8% of the patients had a local disease, probably due to a late diagnosis (73.9% based on self-examination). Thirty-three patients (35.6%) died, of which 15 were from BC. We found a considerably high proportion (53.3%) of undertreatment, which had a frailty-independent negative impact on the 5-year survival (hazard ratio [HR], 5.1; 95% confidence interval [CI], 2.1–12.5). Additionally, omission of surgery had a frailty-independent negative impact on overall survival (HR, 3.9; 95% CI, 1.9–7.9).

Conclusion: BC treatment in older adults should be individualized. More importantly, assessing frailty (not to treat) is essential to be aware of the risk-benefit profile and the patient's well-informed willingness to be treated. Undertreatment in daily practice is frequent and might have a negative impact on survival, as we report.

Keywords: Breast Neoplasms; Geriatrics; Survival; Undertreatment

Conflict of Interest
The authors declare that they have no competing interests.

Author Contributions
Conceptualization: Osório F; Data curation: Osório F, Barradas AR, Urbano J; Formal analysis: Osório F, Barros AS, Peleteiro B; Funding acquisition: Osório F; Investigation: Osório F, Fougo JL; Methodology: Osório F, Barros AS, Peleteiro B, Leite-Moreira A; Project administration: Osório F, Leite-Moreira A; Software: Barros AS; Supervision: Peleteiro B, Fougo JL, Leite-Moreira A; Validation: Barros AS, Peleteiro B, Fougo JL, Leite-Moreira A; Writing - original draft: Osório F; Writing - review & editing: Osório F, Barros AS, Peleteiro B, Fougo JL, Leite-Moreira A.

INTRODUCTION

The population-extended lifespan is an emerging reality. In Portugal, for the last 60 years, the population aged 65 years or over almost tripled from 8% in 1961 to 22% in 2019. In 2050, the over-65 population in the European Union (EU) will reach 28.5%, with women outnumbering men [1].

The increased longevity of older adults has led to a growing cancer incidence, a disease associated with aging. A higher proportion of women will warrant the foreseen rising incidence of breast cancer (BC), reaching a peak in women aged 70–84 [2-4]. BC is the most common cancer affecting European women, with significant survival improvements in the last decades. The 5-year relative survival rate is 82% in the EU, 83% in Portugal, and 90% in the USA, but with pronounced differences between age groups and significantly worse in older adults (50% in over-75 women) [2-4]. Despite competing non-cancer mortality, in over-80 women at diagnosis, up to 40% of women die from BC [5].

The best multimodality therapeutic strategy for older patients with BC has always been and remains controversial [5,6]. Chronological age should not be used as the sole indicator of therapeutic strategy [5-7]. Decision-making at the multidisciplinary meeting (MDM) should be standardized and supported by level 1 evidence and simultaneously individualized after a multidimensional evaluation. Therefore, it is crucial to standardize the widely recommended geriatric assessment strategies in oncology [6-9]. Too many different tools described in the literature to assess the functional, nutritional, cognitive status, comorbidities, polymedication, and geriatric syndromes hamper a consensus about the MDM's best daily practice solution for a tailored plan [8,9]. Moreover, the well-known underrepresentation of older adults in randomized controlled trials evaluating cancer treatments due to the heterogeneity of their vulnerable physiology, confounding comorbidities, or drug interactions, and the likely lower adherence to therapy or the competing non-cancer mortality hinder the development of evidence-based guidelines [10-12]. Women older than 70 years were excluded from the paradigm-changing Veronesi Milan trials that validated breast conservative surgery (BCS) [13].

In older women, the myth of BC is biologically less aggressive, and the stigma of chronological age and the unknown benefit of several treatments (standard for younger patients) are the main reasons for frequent undertreatment that might affect cancer lethality [11,14]. Defining undertreatment in older patients, especially those with frailty, is not consensual [10]. Knowing when and how to treat, compliance with the proposed treatment, its potential adverse effects, avoiding undertreatment with impact on survival, and knowing individual patient preferences require clear clinical communication with the patient and her caregiver and family.

This study aimed to evaluate undertreatment and its potential impact on a 5-year survival in an older adult population aged 70 years or over, with BC treated in 2014 at the Breast Center of São João University Hospital (CM-CHUSJ).

METHODS

Patients over 70 years with *de novo* BC diagnosis were eligible for our study if they were not admitted with locoregional or distant recurrences of a previous BC. Our study enrolled 92 consecutive patients between January and December of 2014. Data were obtained prospectively during routine medical visits and retrieved from the patients' digital records. The patient, namely, their sociodemographic and clinical features, tumor characteristics, Surveillance, Epidemiology, and End Results (SEER) and anatomic disease extent (tumor, node, and metastasis; TNM) staging, and information on therapeutic options were collected. Tumors were classified according to the TNM classification of the Union for International Cancer Control (7th edition, 2009). To define the molecular subtypes, we used the immunohistochemistry (IHC) definition of estrogen receptor (ER) and progesterone receptor (PR), the detection of human epidermal growth factor receptor 2 (HER2) IHC overexpression and/or HER2 gene amplification as defined by *in situ* hybridization (ISH) and Ki-67 labeling index, with a pre-defined cut-off of 14%. The 5-year follow-up period ended on December 31, 2019. Disease progression and causes of death during follow-up were recorded.

As part of the usual care at our center, two functional assessment scales, the Karnofsky performance score (KPS, from 10% to 100%) [15] and the Eastern Cooperative Oncology Group Performance Status scale (ECOG-PS, from 0 to 4) [15] were applied. For a total of 70 patients, the activities of daily living (ADLs) were evaluated using the Lawton–Brody scale (scores 0: dependent and 1: autonomous) [16]. We also assessed the psychological context among these patients, using the Hospital Anxiety-Depression Scale, focusing our measurement on its depressive component (scores 0–7: healthy, 8–11: borderline and ≥ 12: psychopathology) [17]. The questionnaires were performed in person or by telephone, and a family member was the source of information in 20% of the cases. The application time had an average of 7 (range 5–12) minutes.

A geriatric assessment was made in an additional hospital visit before the MDM by applying three frailty screening tools: Geriatric 8 (G8) [18] (score ≤ 14: frailty, ≥ 15: risk absent), Flemish version of the Triage Risk Screening Tool (fTRST) [19] (frailty if ≥ 1 point, risk absent if 0 points), and the Groningen Frailty Indicator (GFI) [20] (4–15 points: frailty, 0–3 points: risk absent). Sixty-two patients agreed to this additional evaluation, which took, on average, 15 (range 11–18) minutes.

MDM decisions were based on CM-CHUSJ written protocols that followed national and international standards. In older patients, specifically those with frailty and luminal BC, we begin treatment with primary endocrine therapy (PET). We then propose surgery 3 to 6 months after a clinical and ultrasonographic re-evaluation and, eventually, adjuvant radiotherapy. Regarding more aggressive tumors, chemotherapy is recommended for patients with grade 3 luminal-B tumors, triple-negative (TN) BC, or lymph node-positive tumors. In addition, a combination of chemotherapy and trastuzumab was considered for HER2-enriched tumors.

In our study, we defined undertreatment: 1) when the patient refused the MDM proposal, 2) when, due to intolerance, it was not possible to complete the treatment defined in the MDM, and 3) when a standard treatment was not proposed in the MDM given the advanced chronological age or limiting physiological vulnerability.

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Statistical analysis

For continuous variables, normality was assessed by visual inspection of the data distribution, supported by QQ-plot analysis. If normally distributed, the results were summarized by the mean and standard deviation; otherwise, the median and interquartile range were used. Student's *t*-test was used to assess differences in the independent variables between the 2 groups (standard treatment and undertreatment) once normality was demonstrated; otherwise, the Wilcoxon rank-sum test was applied. Absolute (number) and relative (%) frequencies were reported for categorical variables. The χ^2 and Fisher's exact tests were used to assess the association between the independent categorical variables and the defined groups. Propensity score matching (PSM) was used to reduce covariates' bias, such as frailty, SEER, and TNM scores, to assess the effect of treatment on survival. PSM [21] was used to reduce covariates' bias, such as frailty, SEER summary stage system, and TNM stage, to assess the effect of treatment on survival. PSM includes the information provided by the baseline factors into a propensity score (PS) used to balance the treatment groups and mitigate bias. This procedure starts by using logistic regression to estimate the patients' propensity (predict probability) to receive treatment based on relevant clinical covariates such as frailty (including KPS, ECOG-PS, G8, fTRST, GFI), age, SEER summary staging system, and TNM stage. Then, the PS was used to match patients from both groups using a 1:1 ratio and based on a caliper matching of 0.2 standard deviations of the PS. Survival analyses were performed using Cox proportional hazards models and the Kaplan–Meier method. All statistical analyses were performed using the Survminer (version 0.43.1) and survival (version 2.43.3) packages in R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/).

Ethics approval

The study *("Geriatric evaluation in older patients with breast cancer—a clinical pathway validation")* was approved by the Ethics Committee of São João University Hospital on June 28th, 2013 (CES 111-13). Written study information was provided and written informed consent was obtained from all participants. Study enrolment took place in 2014.

RESULTS

Our observational study included 92 patients (one male), representing 26.1% of new BC cases treated at CM-CHUSJ in 2014. The median age was 77 (range 70–94) years.

Seventy (76.1%) patients agreed to answer sociodemographic, psychological, and ADL questionnaires: 64 patients (91.4%) mentioned having a "taste for life"; 33 (47.1%) reported feeling "younger" than they were; 35 (50.0%) lived with her husband and 15.7% lived alone; most patients (77.1%) assessed themselves as autonomous and 32 patients (45.7%) were completely independent in their ADLs. We assessed the occurrence of falls in the last year, which is one of the first indicators of frailty. Fifty (71.4%) had not suffered any fall; however, half of them emphasized that they were "afraid of falling." Most patients (71.4%) were classified as healthy in the psychological assessment, and 15.7% were depressed (**Supplementary Table 1**).

Sixty-two (67.4%) patients agreed to undergo a geriatric evaluation: the categorization of frailty on the three scales was discordant (G8, 41.9%; fTRST, 74.2%; GFI, 32.3%). The traditional functional scales applied to all patients showed a higher agreement (ECOG-PS 0, 45.7%; KPS 90%–100%, 47.8%) (**Table 1** and **Supplementary Table 2**).

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Most patients presented with a palpable mass (73.9%) detected by the patient or by a family member during hygiene care. Surveillance imaging exams detected only 23.9%, and of these,

Table 1. Patient's characteristics

Characteristic	Overall (n = 92)	No.	Standard treatment (n = 43)	Undertreatment (n = 49)	*p*-value*
5-yr follow-up status		92			< 0.001
Alive	59 (64.1)		37 (86.0)	22 (44.9)	
Dead	33 (35.9)		6 (14.0)	27 (55.1)	
Age	77 (73–83)	92	76 (72–80)	78 (74–85)	0.056
Diagnosis		92			0.003
Imaging	21 (22.8)		16 (37.2)	5 (10.2)	
Mass screening	1 (1.1)		0 (0.0)	1 (2.0)	
Self-examination	68 (73.9)		27 (62.8)	41 (83.7)	
Symptomatic M1 disease	2 (2.2)		0 (0.0)	2 (4.1)	
KPS		92			< 0.001
90%–100%	44 (47.8)		30 (69.8)	14 (28.6)	
70%–80%	19 (20.7)		9 (20.9)	10 (20.4)	
50%–60%	23 (25.0)		4 (9.3)	19 (38.8)	
30%–40%	6 (6.5)		0 (0.0)	6 (12.2)	
ECOG-PS		92			0.044
0	42 (45.7)		27 (62.8)	15 (30.6)	
1	27 (29.3)		12 (27.9)	15 (30.6)	
2	11 (12.0)		3 (7.0)	8 (16.3)	
3	11 (12.0)		1 (2.3)	10 (20.4)	
4	1 (1.1)		0 (0.0)	1 (2.0)	
G8		62			0.9
Fit	36 (58.1)		23 (71.9)	13 (26.5)	
Frail	26 (41.9)		9 (28.1)	17 (34.7)	
fTRST		62			0.9
Fit	16 (25.8)		9 (28.1)	7 (14.3)	
Frail	46 (74.2)		23 (71.9)	23 (46.9)	
GFI		62			0.12
Fit	42 (67.7)		25 (78.1)	17 (34.7)	
Frail	20 (32.3)		7 (21.9)	13 (26.5)	
Comorbidities		92			0.2
1	11 (12.0)		6 (14.0)	5 (10.2)	
2	21 (22.8)		13 (30.2)	8 (16.3)	
3	25 (27.2)		12 (27.9)	13 (26.5)	
4+	35 (38.0)		12 (27.9)	23 (46.9)	
Bloom and Richardson grading		86			0.012
Grade 1	23 (26.7)		15 (40.5)	8 (16.3)	
Grade 2	34 (39.5)		15 (40.5)	19 (38.8)	
Grade 3	29 (33.7)		7 (18.9)	22 (44.9)	
SEER Summary Stage system		92			< 0.001
In situ	6 (6.5)		6 (14.0)	0 (0.0)	
Local stage	42 (45.7)		24 (55.8)	18 (36.7)	
Regional stage	37 (40.2)		13 (30.2)	24 (49.0)	
Distant stage	7 (7.6)		0 (0.0)	7 (14.3)	
TNM stage		92			< 0.001
Stage 0	6 (6.5)		6 (14.0)	0 (0.0)	
Stage I	29 (31.5)		20 (46.5)	9 (18.4)	
Stage II	33 (35.9)		14 (32.6)	19 (38.8)	
Stage III	17 (18.5)		17 (39.5)	3 (6.1)	
Stage IV	7 (7.6)		0 (0.0)	7 (14.3)	
Molecular subtypes		86			0.7
Luminal	47 (54.7)		23 (53.5)	24 (49.0)	
Luminal_HER2_missing	18 (20.9)		7 (16.3)	11 (22.4)	
Luminal_HER2+	6 (7.0)		1 (2.3)	5 (10.2)	
HER2	5 (5.8)		2 (4.7)	3 (6.1)	
TN	10 (11.6)		4 (9.3)	6 (12.2)	

(continued to the next page)

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Table 1. (Continued) Patient's characteristics

Characteristic	Overall (n = 92)	No.	Standard treatment (n = 43)	Undertreatment (n = 49)	*p*-value*
Surgery		92			< 0.001
No	18 (19.6)		0 (0.0)	18 (36.7)	
Yes	74 (80.4)		43 (100.0)	31 (63.3)	

Statistics presented as number (%) or median (interquartile range).
KPS, Karnofsky performance score; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; G8, Geriatric 8; fTRST, Flemish version of the Triage Risk Screening Tool; GFI, Groningen Frailty Indicator; SEER, Surveillance, Epidemiology, and End Results; TNM, tumor, node, and metastasis; HER2, human epidermal growth factor receptor 2.
*Statistical tests performed χ^2 test of independence; Wilcoxon rank-sum test; Fisher's exact test.

only one patient was referred from the mass screening program (**Table 1** and **Supplementary Table 2**). Eighteen patients (19.6%) were referred for genetic counseling: the only man, 8 women with previous contralateral tumors, 5 with bilateral synchronous tumors, 3 with suggestive family history, and 1 with previous ovarian cancer. Only 1 patient was *BRCA2* positive.

Most patients were in stage IA (27.2%) and IIA (26.1%) in TNM staging, in contrast to 6.5% in stage 0 and 7.6% in stage IV. Using the SEER summary staging system to classify invasive tumors leads to a similar distribution between local (48.8%) and regional disease (43.1%). The predominant histological subtype of invasive tumors was "no special type" (75.6%); the Bloom-Richardson grading was evenly distributed (33.7% were G3, 39.5% G2, and 26.7% G1), and lymphovascular invasion was present in 31.4%. Regarding IHC, 83.0% were ER-positive, 71.0% were PR-positive, and 12.8% were HER2 positive. Regarding molecular classification, 82.6% had luminal-like tumors, 5.8% were HER2-enriched, and 11.6% were TN. A more specific subdivision of luminal tumors was not possible, as HER2 status was not studied in 18 or Ki67 in 16 cases (**Table 1** and **Supplementary Table 2**).

MDM decision-making was consensual in 61 patients (66.3%) but controversial and adapted in 31 patients (33.7%) due to frailty in 18 patients and advanced chronological age in 13. One patient, the only male, refused treatment. Seventy-four (80.4%) patients underwent surgery (55.4% underwent BCS), and 18 (19.6%) did not undergo surgery. Of these, 15 (16.3%) patients underwent PET, four refused surgery, and 11 had limiting comorbidities. Seven (7.6%) patients underwent neoadjuvant chemotherapy, and two of them, with stage IV luminal B-HER2 positive tumors, were not proposed for surgery afterward. Of the 68 patients with invasive tumors who underwent surgery, only two frail patients (aged 90 and 83 years) with TN tumors were not proposed for adjuvant treatment. The remaining patients were treated with various combinations of adjuvant treatment: 55 (80.9%) to endocrine therapy, 46 (67.6%) to radiotherapy, 21 (30.9%) to chemotherapy, and 9 (13.2%) to trastuzumab.

According to our pre-specified definition, 49 patients (53.3%) were undertreated (**Supplementary Tables 3** and **4**). KPS and ECOG-PS showed significant differences between the undertreatment and standard treatment groups. Conversely, the chronological age, with the three frailty screening tools applied, and comorbidities were not associated with undertreatment or standard treatment. Regarding the diagnosis and staging (TNM and SEER), we found a significant difference between the undertreatment and standard treatment groups. Analyzing by molecular subtypes, no relevant differences were found regarding undertreatment (**Table 1**).

Our patients' overall 5-year survival rate was 66.1% (95% CI: 57.0%, 76.5%) (**Supplementary Figure 1**). Thirty-three (35.9%) patients died: 15 (45.5%) due to BC, most with M1 bone plus visceral disease (**Supplementary Table 3**). Eighteen (54.5%) patients died from a non-cancer

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cause; however, 4 of these (22.2%) had stable M1 disease. Of the 33 patients who died, 27 (81.8%) were undertreated in contrast to the 52 patients who were alive without any evidence of oncological disease at the end of the follow-up, in which only 30.8% were undertreated. No significant differences in survival status were found when comparing death from BC and death from other causes (**Supplementary Figure 2**). Thus, the vital status was aggregated.

Undertreatment had a significant impact on 5-year survival (hazard ratio [HR], 5.1; 95% confidence interval [CI], 2.1–12.5) (**Figure 1A**). Our undertreated patients had an overall 5-year mortality rate of 55.1% (and 24.5% of cancer lethality rate) in contrast to the standard treatment group, in which the overall 5-year mortality rate was only 13.9% and 7.0%, respectively. To mitigate the contribution of frailty to the overall survival (OS) status, the PSM of patients using frailty scores highlights the worse prognosis for the undertreatment group (HR, 9.3; 95% CI, 2.7–32.0) (**Figure 1B** and **Supplementary Table 5**). A subanalysis regarding the omission of surgical treatment showed a significant association with undertreatment well

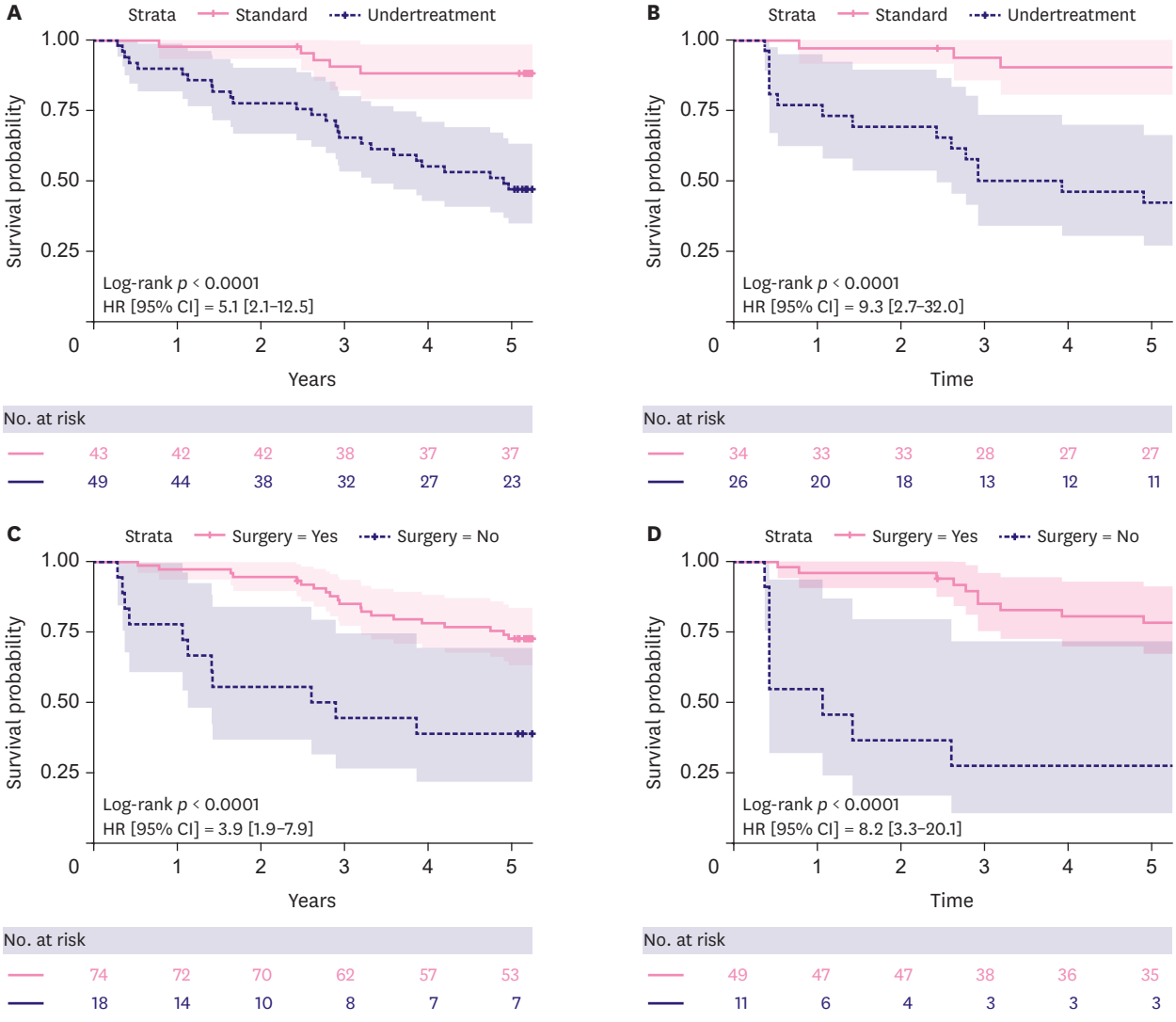

Figure 1. Kaplan–Meier survival curve. (A) For undertreatment; (B) for undertreatment—matched for frailty; (C) for omission of surgery; and (D) for omission of surgery—matched for frailty.
HR, hazard ratio; CI, confidence interval.

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supported by the clear negative impact on survival—held, even after frailty-matching of non-operated patients (**Figure 1C and D**).

DISCUSSION

Geriatric age should be defined according to chronological age, biological age, social role change, or functional capacity. We used (as stated by International Society of Geriatric Oncology, European Organisation for Research and Treatment of Cancer, or National Comprehensive Cancer Network) the 70 years' cut-off; however, this landmark lacks consensus [1,5,6].

Half of our patients had a good self-perceived health. Indeed, the self-assessment question in the G8 tool [18] showed that 51.6% considered their health status to be as good or better than others of the same age, similar to the reported (49.7%) healthy EU population aged 65–74 with good self-perceived health in a recent aging study [1]. Therefore, we can consider that our patients were resilient: 91.4% liked to live, 71.4% did not suffer any fall, 47.1% felt younger than their chronological age, and 45.7% were completely independent in their ADLs and ECOG-PS 0. The ability to translate this resilience into daily practice—the mirror-image of frailty—with a more positive connotation, more than a taxonomic debate, allows us to refocus on a subgroup of fit patients and to provide them with better MDM guidance [22].

Contrary to the current (screening-driven) trend in BC diagnosis, a late diagnosis was found to be mostly clinically based. As in other studies, only 23.9% of patients were diagnosed with periodic surveillance imaging, explaining why only 6.5% of ductal carcinoma *in situ* cases were observed (instead of the expected 16%–18%) [2-5]. Given the mentioned generational change, it is time to offer women over 70 years of mass mammography screening because evidence has shown a survival benefit for older women with a life expectancy of more than 10 years [23]. A late diagnosis consequence was more advanced TNM staging (51.2% were N+). Indeed, this is clear through the SEER summary staging applied to our invasive tumors: 49% had local disease (instead of the expected 64%) and 43% had regional disease (more than the estimated 27%) [3]. Contrary to other studies [11,24], a more favorable tumor biology was not found (33.7% were G3 and 31.4% had lymphovascular invasion), which, in addition to an incomplete IHC study (HER2 missing in 20.9% due to an advanced age preconceived intention-not-to-treat) might constrain the MDM decision. Our worst 5-year OS compared to all-ages 2019–2020 American Cancer Society statistics (76% vs. 99%, 57% vs. 86%, and 14% vs. 27% for local, regional, and distant disease, respectively) [3]. Even assuming a worse prognosis for older BC patients, the aforementioned late diagnosis and divergent tumor-stage distribution may explain these differences in survival. Variations were also observed among our TN tumors (50% vs. 77%), as well as in ER positive/HER2 negative cases (64% vs. 92%). The latter could be explained by the high proportion of missing data regarding HER2 status.

The best BC diagnostic and treatment strategy in older women remains challenging to define [5,10,11,14,25,26]. Likewise, the definition and mainly the clinical impact assessment of BC undertreatment is also elusive as it involves more than one sequential therapeutic modality [10,14,25]. In older women, more than assessing frailty for treatment conditioning, the key question is whether we can tailor the treatment, knowing the physiological reserve, comorbidities, vulnerabilities, and patient will. The geriatric evaluation performed, and the explanation of its goals allowed us to create a time-consuming, difficult-to-measure

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but rewarding open discussion with our patients about their cancer diagnosis and the risk-benefits of their treatments that will provide proper support for MDM therapeutic management [7,8,14]. Several geriatric tools and strategies have been recommended in the literature [5-9,27,28]. A comprehensive geriatric assessment was not yet conducted by us in 2014. The G8 screening tool, chosen for the EORTC trials, consensually emerged as a good predictor of geriatric risk and OS [28]. As seen in other studies [9], the categorization of frailty in the three applied screening tools was discordant, and none of them showed an association with undertreatment.

Age is a proven independent risk factor for non-standard BC treatment [5,24,26,27]. A significant, albeit variable, amount (in some studies, well above 50%) of older adults with BC are undertreated [11,25,26]. In our cohort, it was 53.3%. Our study's key answer is whether age-related BC undertreatment is itself a determinant of the worst 5-year survival or a consequence of limiting fragility. Co-morbid illnesses and functional status probably influence older patients' life expectancy more than BC [14,27]. Age, frailty, and comorbidities are non-modifiable risk factors that predict overall mortality. In contrast, tumor biology and TNM stage are modifiable risk factors for cancer mortality. We clearly show a negative impact of BC undertreatment, independent of frailty, on 5-year survival (**Figure 1A and B**, **Supplementary Table 5**). An unfit older patient with luminal BC and a short life expectancy are adequately treated with PET. Surgery in these patients will offer better local control but probably has no impact on OS. Instead, fit older adults must undergo standard treatment to avoid shortening their life expectancy [25,29,30]. An unproven survival benefit of the different therapeutic modalities due to ageing idiosyncrasies does not allow an accurate prognosis evaluation in older patients [24-26]. Despite the variability of our cohort [29,30], we show a frailty-independent negative impact of the omission of surgery on 5-year survival (**Figure 1C and D**).

The main limitations of our study are the small sample size, incomplete IHC characterization, a single-center study, and the lack of a formal assessment of patient-reported outcomes or health-related quality of life. As for strengths, we emphasize being a real-world study with complete clinical data, a resilient cohort with no loss to 5-year follow-up, and all causes of death verified.

In conclusion, the concept and clinical impact of undertreatment remain challenging in older adults with BC. Indeed, 53.3% of undertreatment was found in our study, with a significant negative impact on 5-year survival. Additionally, we observed this effect independent of frailty and found a frailty-independent positive impact of surgical treatment on OS.

Older adults' centered-care needs time and dedication. An integrated geriatric evaluation is mandatory to assess the patient's risk-benefit profile and well-informed willingness to be treated. Multidisciplinary decision-making should minimize undertreatment and its potential adverse effects on survival.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Sociodemographic, ADLs, and psychological characterization

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Supplementary Table 2
Frailty and tumor characterization

Click here to view

Supplementary Table 3
Undertreatment and mortality characterization

Click here to view

Supplementary Table 4
Undertreatment and mortality association

Click here to view

Supplementary Table 5
Patient's characteristics matched for frailty

Click here to view

Supplementary Figure 1
OS probability.

Click here to view

Supplementary Figure 2
Kaplan–Meier curve regarding death due to other causes vs. death by breast cancer.

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