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ORIGINAL ARTICLE

Breast Cancer in the Elderly: Treatment of 1500 Patients

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■ **Abstract:** There is a significant difference in the extent of treatment offered to the elderly with breast cancer; in the United States, while 98% of patients less than 65 years of age receive standard treatment, 81% of those older than 65 years were treated according to protocol. This study's goal was to evaluate disease-specific survival and local-regional recurrence in breast cancer patients more than 65 years of age at diagnosis. A total of 1500 patients with invasive breast carcinoma were treated consecutively from May 1971 to July 2002 at the University of Florence, Florence, Italy. All patients were more than 65 years of age. The median age was 70.6 years (range 65.1–87.3 years).The median follow-up was 8.7 years (range 1–30 years). The crude probability of survival (or relapse occurrence) was estimated using the Kaplan–Meier method and survival (or relapse occurrence) comparisons were carried out using Cox proportional hazard regression models. The Cox regression model by stepwise selection showed as independent prognostic factors for disease-specific survival (DSS), the occurrence of a local relapse ($p < 0.0001$), pN status ($p < 0.0001$), the type of surgery ($p < 0.0001$), and the use of radiotherapy ($p < 0.0006$) and chemotherapy ($p = 0.01$). For local disease-free survival (LDFS), the Cox regression model by stepwise selection showed that mastectomy ($p < 0.0001$), histotype ($p < 0.0001$), pN status ($p < 0.0001$), and pT status ($p = 0.001$) were the only independent prognostic factors. Age was not a prognostic factor for DSS nor LDFS. We suggest treating patients with appropriate treatment for their prognostic factors. ■

Key Words: breast cancer, elderly, radiotherapy

Breast cancer remains the most common cancer in women, with an estimated risk of new breast cancer at 1 in 14 women age 60–79 years, compared with 1 in 24 women age 40–59 years and 1 in 228 women age 39 years and younger (1). As a result, an estimated 35% of women are more than 70 years of age at the time of invasive breast cancer diagnosis (2). Usually the main decision-making factor in the elderly patient with breast cancer is that of life expectancy. The estimated life expectancy for a 65-year-old woman in the United States is estimated at 17.5 years. An 80-year-old woman is anticipated to live on average an additional 8.6 years (3). An appreciation of this nonlinear relationship between age and life expectancy and the concept of "functional age" is crucial in clinical decision making (4).

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The goal of this study was to evaluate outcome in terms of disease-specific survival (DSS) and local disease-free survival (LDFS) in 1500 patients more than 65 years of age at diagnosis and to investigate if these patients need an adjuvant treatment adequate to prognostic factors independent of age at presentation.

MATERIALS AND METHODS

A total of 1500 patients with histologic invasive breast carcinoma were treated from May 1971 to July 2002 at the University of Florence, Florence, Italy. All patients were more than 65 years of age at presentation. The median age was 70.6 years (SD ± 4.23; range 65.1–87.3 years; median 69.8 years). The median follow-up was 8.3 years (SD ± 5.9; range 1–31 years). The main series characteristics are reported in Table 1.

Breast-conserving surgery was performed in 800 patients (53.3%) and radical mastectomy in 700 patients (46.7%). Total axillary dissection and level I–II axillary lymph node dissection was performed in 1366 and 20

Table 1. Distribution of 1500 Elderly Breast Cancer Cases According to Selected Clinicopathologic Features

Clinicopathologic characteristic	Patients *N* (%)
Age group (years)	
65.1–69.9	793 (52.9)
70.0–74.9	460 (30.7)
≥75	247 (16.4)
Surgery	
Conservative	800 (53.3)
Mastectomy	700 (46.7)
pT	
1	572 (38.1)
2	687 (45.8)
3	83 (5.5)
4b	158 (10.6)
pN	
Negative	874 (58.3)
1–3 positive	348 (23.2)
>3 positive	216 (14.4)
Not available	62 (4.1)
Histotype	
Ductal NOS	1058 (70.5)
Lobular	124 (8.3)
NOS + lobular	190 (12.7)
Other types	128 (8.5)
Tamoxifen use	
Yes	818 (54.5)
No	682 (45.5)
Radiotherapy	
Yes	917 (61.1)
No	583 (38.9)
Chemotherapy	
No	1408 (93.9)
Yes	92 (6.1)
Anthracycline	29 (1.9)
CMF	58 (3.9)
Other	5 (0.3)
Total	1500 (100.0)

NOS, not otherwise specified.

patients, respectively; 52 patients underwent sentinel lymph node biopsy only, while in 62 patients, axillary dissection was not performed.

All patients who underwent breast-conserving surgery were treated with external beam radiotherapy only to the whole breast using tangential fields with 6 MV photons. The mean dose was 50 Gy (range 46–52 Gy). The tumor bed boost was administered by electrons. A total of 117 patients who underwent radical mastectomy were treated with radiotherapy (mean dose 45 Gy; range 42–56 Gy).

Chemotherapy was recommended in 92 patients (6.1%). Thirty-one percent of these patients received anthracycline-based chemotherapy: 70% of these received four courses of epidoxorubicin (100 mg/m^2) followed by four courses of intravenous CMF chemotherapy (cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, and 5-fluorouracil 600 mg/m^2) and 30% were treated with six courses of FEC chemotherapy (5-fluorouracil 500 mg/m^2, epidoxorubicin 75 mg/m^2, cyclophosphamide 500 mg/m^2). Fifty-four percent were treated with six courses of intravenous CMF (cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, and 5-fluorouracil 600 mg/m^2) and 15% with other types of chemotherapy. Tamoxifen was prescribed in 818 patients (54.5%), whereas 682 patients (45.5%) did not receive any hormonal treatment.

We defined a local relapse as any relapse that occurred in the breast, supraclavicular nodes, axillary nodes, or internal mammary nodes without occurrence of distant relapse for at least 6 months.

Statistical Analysis

Information collected for each patient during the hospital admission was retrieved and checked before linkage to vital status information. For the survival analysis, the date of surgery was used as the start of observation. Survival time was calculated from the date of surgery to the date of last follow-up or death. Only deaths from breast cancer were considered as events in our analyses, while the subjects deceased for other causes were censored at the date of death. LDFS was calculated from the date of surgery to the date of relapse occurrence.

The crude probability of survival (or relapse occurrence) was estimated by using the Kaplan–Meier method (5) and differences between patient groups were assessed by the log rank test (6). Survival comparisons were carried out using Cox proportional hazard regression models (7). Estimated relative risks of dying were expressed as adjusted hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). First, univariate models were used to evaluate the effect of each specific parameter. Finally, a regression model with stepwise selection was performed to identify the major significant death predictors. Further statistical analyses were carried out by type of surgery and pN status. Similar statistical analyses were carried out according to the disease-free survival. Statistical results were considered significant at a p-value less than 0.05. All statistical tests were performed using SAS software (SAS, Cary, NC).

RESULTS

At the time of analysis, the DSS was 83.1% (1246/1500); 16.9% (254/1500) of patients died from cancer. Actuarial cause-specific survival was 89.2% (±0.8% SE) and 78.2% (±1.3% SE) at 5 and 10 years.

Table 2. Disease-Specific Survival Analysis of 1500 Elderly Breast Cancer Cases According to Selected Individual Characteristics[a]

Variable	No. of subjects at start	No. of subjects deceased	Percent survival (95% CI)	Log rank test	HR (95% CI)
Age group (years)					
65.1–69.9	793	143	71.3 (65.8–76.1)		1[b]
70.0–74.9	460	82	70.6 (63.7–76.5)		1.04 (0.79–1.36)
≥75	247	29	55.8 (19.9–81.0)		0.91 (0.61–1.35)
				0.82	
Surgery					
Conservative	800	52	86.0 (80.5–90.0)		1[b]
Mastectomy	700	202	62.0 (57.2–66.4)		3.52 (2.59–4.79)
				< 0.0001	
pT					
1	572	27	84.2 (71.2–91.6)		1[b]
2	678	153	69.0 (64.2–73.3)		3.62 (2.40–5.46)
3	83	26	56.8 (40.2–70.4)		5.49 (3.20–9.41)
4b	158	48	48.3 (31.5–63.2)		6.10 (3.81–9.79)
				< 0.0001	
pN					
Negative	874	85	81.8 (76.9–85.7)		1[b]
1–3 positive	348	74	67.0 (59.0–73.9)		2.10 (1.53–2.86)
>3 positive	216	88	41.9 (32.5–51.0)		5.26 (3.90–7.09)
Not available	62	7	40.8 (14.1–82.8)		1.50 (0.69–2.23)
				< 0.0001	
Histotype					
Ductal NOS	1058	194	70.1 (65.3–74.3)		
Lobular	124	13	76.1 (56.8–87.6)		
NOS + lobular	190	17	67.3 (55.4–76.7)		
Other types	128	10	73.4 (46.3–88.4)		
				0.01	
Tamoxifen use					
No	682	128	72.5 (67.0–77.1)		1[b]
Yes	818	126	67.1 (59.7–73.4)		1.08 (0.84–1.39)
				0.54	
Radiotherapy					
No	583	154	65.4 (60.4–69.9)		1[b]
Yes	917	100	72.4 (57.2–83.0)		0.55 (0.42–0.71)
				0.0001	
Chemotherapy					
No	1408	241	71.3 (67.0–75.1)		1[b]
Yes	92	13	42.4 (15.6–67.3)		1.90 (1.08–3.33)
				0.02	
Local relapse					
No	1355	144	82.5 (79.3–85.3)		1[b]
Yes	145	100	12.5 (6.2–21.1)		8.04 (6.27–10.3)
				< 0.0001	
Total			1500		254

[a]Number of patients at risk, number of deaths, survival, log rank test at the last follow-up, and hazard risk (HR) from separate Cox regression models including each specific parameter.
[b]Reference category.
NOS, not otherwise specified.

Disease-Specific Survival

The univariate analysis for DSS showed a significant statistical association between survival and the type of surgery ($p < 0.0001$), pT ($p < 0.0001$), pN ($p < 0.0001$), histotype ($p = 0.01$), radiotherapy ($p = 0.0001$), chemotherapy ($p = 0.02$), and occurrence of local relapse ($p < 0.0001$), as reported in Table 2.

At the multivariate analysis, the prognostic factors associated with a poorer outcome were the occurrence of a local relapse ($p < 0.0001$), pN ($p < 0.0001$), the type of surgery ($p < 0.0001$), and the use of radiotherapy ($p < 0.0006$) and chemotherapy ($p = 0.01$) (Table 3). Mastectomy was associated with a poorer prognosis because it was associated with a more advanced pT.

To understand why radiotherapy was associated with a poorer outcome, we performed a multivariate analysis stratifying patients for the type of surgery. We found that radiotherapy was associated with a poorer DSS only in patients who underwent mastectomy (Table 4); this is due

Table 3. Multivariate Analysis by Cox Regression Model With Stepwise Selection Carried Out to Identify Major Significant Death Predictors[a]

Death predictor	p	HR	95% CI
Local-regional relapse occurrence	< 0.0001	5.74	4.40–7.48
pN	< 0.0001	1.38	1.21–1.57
Mastectomy	< 0.0001	3.34	2.21–5.04
Radiotherapy	0.0006	1.77	1.28–2.45
Chemotherapy	0.01	2.05	1.16–3.60

[a]Overall survival analysis (*n*:1500).

to the policy which has been followed at our institution where radiotherapy has been prescribed only to patients who had more than one negative prognostic factor (pN+, pT3–pT4b, presence of angiovascular invasion).

In patients who underwent conservative surgery, chemotherapy was a negative prognostic factor. We believe, as shown at univariate analysis, that this is due to the type of chemotherapy: in fact most of the patients of this series who underwent chemotherapy were offered CMF, which was associated to a poorer prognosis, and now would not be accepted as the standard of care in most patients. In our series, the use of CMF was correlated with a higher risk of death (HR 2.19; 95% CI 1.12–4.28) compared to the use of anthracycline (HR 1.10; 95% CI 0.27–4.46).

When we performed a multivariate analysis stratifying patients for the number of positive axillary nodes (Table 5), we found that chemotherapy was associated with a poorer prognosis only for patients with one to three positive nodes. CMF was an unsatisfactory treatment in patients with positive axillary nodes.

Age at presentation was not statistically associated with DSS, neither at the univariate nor the multivariate analysis.

Local-regional relapse was an independent prognostic factor in all groups of patients.

Table 4. Multivariate Analyses by Cox Regression Model With Stepwise Selection Stratified by Type of Surgery[a]

Death predictor	p	HR	95% CI
Conservative surgery (*n*:800)			
Local-regional relapse occurrence	< 0.0001	9.93	5.26–18.74
pN	< 0.0001	1.72	1.31–2.26
Chemotherapy	0.01	4.11	1.40–12.06
Mastectomy (*n*:700)			
Local-regional relapse occurrence	< 0.0001	5.15	3.88–6.85
pN	< 0.0001	1.33	1.15–1.53
Radiotherapy	0.0005	1.77	1.28–2.45

[a]Stratified survival analysis.

Local-Regional Recurrence

With a median time of 3.4 years (SD ± 3.2; range 0.3–19.9 years), we observed 145 local-regional (breast, supraclavicular, axillary and internal mammary nodes) relapses (9.7%).

Univariate analysis for LDFS is reported in Table 6. We noted that age at presentation was again not associated with a higher rate of local relapse.

At the multivariate analysis, we found that mastectomy ($p < 0.0001$), histotype ($p < 0.0001$), pN status ($p < 0.0001$), and pT status ($p = 0.001$) were the only independent prognostic factors associated with local relapse. When we performed multivariate analysis stratifying patients for the type of surgery, we noted that, irrespective of age at presentation, in patients who underwent conservative surgery, tamoxifen improved LDFS.

DISCUSSION

An estimated 203,500 women were diagnosed with breast cancer in 2002, with almost half of the cases occurring in women 65 years of age or older (8). Specific clinical trials data demonstrate that treatment efficacy is not modified by age (9–11). This efficacy evidence is limited by the lack of inclusion of substantial numbers of older women, particularly those of advanced age and those with comorbidities.

In 1998 the British Association of Surgical Oncology Breast Specialty Group (12) stated that there is a significant difference in the extent of treatment offered to the elderly (13,14). August et al. (15) found that, in the United States, while 98% of patients less than 65 years of age receive standard treatment, only 81% of those more than 65 years of age were treated according to protocol.

Table 5. Multivariate Analysis by Cox Regression Model With Stepwise Selection Stratified by pN Status[a]

Death predictor	p	HR	95% CI
pN = 0 (*n*:874)			
Local-regional relapse occurrence	< 0.0001	11.50	7.4–17.71
pT	0.02	1.32	1.04–1.69
pN + (1–3) (*n*:348)			
Local-regional relapse occurrence	< 0.0001	5.21	3.26–8.34
Chemotherapy	0.0005	2.80	1.30–6.04
Tamoxifen	0.004	0.54	0.34–0.87
pT	0.02	1.32	1.04–1.68
pN + (>3) (*n*:216)			
Local-regional relapse occurrence	< 0.0001	3.43	2.20–5.37
pT	0.03	1.28	1.02–1.60

[a]Stratified survival analysis.

Table 6. Local Disease-Free Survival Analysis of 1500 Elderly Breast Cancer Cases According to Selected Individual Characteristics[a]

Variable	No. of subjects at start	No. of relapses	Cumulative incidence	Log rank test	HR (95% CI)
Age group (years)					
65.1–69.9	793	77	0.135		1[b]
70.0–74.9	460	48	0.179		1.11 (0.77–1.59)
≥75	247	20	0.111		1.00 (0.62–2.64)
				0.84	
Surgery					
Conservative	800	23	0.058		1[b]
Mastectomy	700	122	0.223		5.72 (3.66–8.95)
				< 0.0001	
pT					
1	572	12	0.052		1[b]
2	678	88	0.171		5.49 (3.0–10.04)
3	83	16	0.221		8.98 (4.25–18.99)
4b	158	29	0.313		9.50 (4.86–18.62)
				< 0.0001	
pN					
Negative	874	54	0.096		1[b]
1–3 positive	348	37	0.191		1.70 (1.12–2.59)
>3 positive	216	46	0.265		4.25 (2.87–6.31)
Not available	62	8	0.195		2.54 (1.21–5.35)
				< 0.0001	
Histotype					
Ductal NOS	1058	102	0.128		
Lobular	124	8	0.114		
NOS + lobular	190	32	0.293		
Other types	128	3	0.086		
				< 0.0001	
Tamoxifen use					
No	682	76	0.149		1[b]
Yes	818	69	0.165		0.87 (0.63–1.21)
				0.41	
Radiotherapy					
No	583	100	0.222		1[b]
Yes	917	45	0.077		0.32 (0.22–0.45)
				< 0.0001	
Chemotherapy					
No	1408	142	0.151		1[b]
Yes	92	3	0.091		0.47 (0.15–1.47)
				0.18	
Total				1500	145

[a]Number of patients at risk, number of relapses, cumulative incidence, log rank test and hazard risk (HR) from separate Cox regression models including each specific parameter.
[b]Reference category.
NOS, not otherwise specified.

In our series, at the multivariate analysis for DSS, local relapse, pN, mastectomy, radiotherapy and chemotherapy were independent prognostic factors. Radiotherapy was a negative prognostic factor only for patients who underwent mastectomy: this is because of the association with other negative prognostic factors for patients who received radiation therapy.

We also observed an improvement in patients treated recently compared with patients treated in previous decades. We believe that these results are due to a screening program that started in Florence at the beginning of 1980 (16) and also to a more rational use of adjuvant treatment.

The most recent American Cancer Society guidelines include a recommendation that screening decisions in older women should consider their current health status and estimated life expectancy, and that women should continue to receive screening mammography as long as they are in reasonably good health and are candidates for treatment (17). Screening programs permit early identification of lesion in the breast and consequently treatment at an early stage of breast cancer. Kemeny et al. (18) found that surgery in healthy elderly women is safe and without additional risk compared with their younger counterparts. Vlastos et al. (19) obtained the same results.

Table 7. Overall and Stratified DFS Analyses by Separate Cox Regression Models With Stepwise Selection to Identify Significant Relapse Predictors

Relapse predictor	p	HR	95% CI
Overall DFS analysis			
Mastectomy	< 0.0001	4.26	2.64–6.89
Histology (NOS + lobular)	< 0.0001	2.49	1.67–3.72
pN	< 0.0001	1.44	1.21–1.71
pT	0.001	1.35	1.12–1.61
Death predictor	**p**	**HR**	**95% CI**
Stratified survival analysis			
Conservative surgery (*n* = 800)			
Tamoxifen	0.01	0.23	0.11–0.67
pN	0.04	1.56	1.01–2.43
Mastectomy (*n* = 700)			
Histology (NOS + lobular)	< 0.0001	2.48	1.58–3.88
pN	< 0.0001	1.47	1.21–1.78
pT	0.003	1.34	1.10–1.64

DFS, disease-free survival; NOS, not otherwise specified.

Warren et al. (20) showed no substantial increase in the cost for breast-conserving surgery and radiation therapy compared with modified radical mastectomy in elderly women. Wyckoff et al. (21) and Zachariah et al. (22) reported that the elderly are able to tolerate radiotherapy as well as younger patients, with similar incidences of skin reaction and failure to complete treatment.

The Early Breast Cancer Trialists' Collaborative Group showed that the principal benefit of adjuvant radiotherapy is a significant reduction in isolated local recurrence rates (23). We found this to be the case in our series, although only in univariate analysis.

In our study, local relapse was an independent prognostic factor for DSS in differently stratified multivariate analysis. Therefore we believe that adjuvant radiotherapy should be offered independently from the age at presentation.

In our department, adjuvant systemic therapy was also driven by age at presentation. This was due to the fact that it was believed that in elder patients the toxicity of an anthracycline-based chemotherapy would have been too high and that the biology of tumors in older patients was somehow less aggressive. This led to a more cautious approach.

We found that the use of chemotherapy was associated with a poorer DSS. This was due to the fact that only patients with negative prognostic factors received chemotherapy. We also found a trend in favor of anthracycline-based chemotherapy.

In our study, the age at presentation was never an independent prognostic factor for DSS and LDFS. Therefore we see no reason to recommend a different approach than for younger patients.

The Breast Cancer Trialists' Collaborative Group in a meta-analysis showed that adjuvant chemotherapy resulted in a 10% reduction in death from breast cancer in the 60–69 year age group (24). Ibrahim et al. (25) compared adjuvant doxorubicin-based chemotherapy in patients 50–64 years of age and in those more than 65 years of age and found similar tolerance to treatment and similar disease-free survival rates.

However, although meta-analysis data support a decrease in mortality for all subsets of postmenopausal women given chemotherapy, the administration of chemotherapy to all postmenopausal and elderly women remains controversial. De Michele et al. (26) found that age was associated with physician recommendation for adjuvant chemotherapy. The decrease in recommendation was not simply a matter of greater comorbidity in the elderly; in fact adjustment for comorbidity did not impact the relation between age and recommendation, despite the fact that adjusting for age eliminated the significant association between comorbidity score and an adjuvant chemotherapy recommendation. Moreover, increasing age was not associated with the rate of patient acceptance of adjuvant chemotherapy, and when adjuvant chemotherapy was recommended, age did not have a significant influence on the treatment regimen selected. We believe research is needed targeting older patients with breast cancer to enable development of specific treatment guidelines (27) for chemotherapy (28–31).

CONCLUSION

Women more than 65 years of age are a prominent cohort in the breast cancer population. Often elderly patients do not receive treatment according to prognostic factors. We suggest treating patients based not on their age, but their prognostic factors.

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