

The Natural History of Breast Carcinoma in the Elderly

Implications for Screening and Treatment

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BACKGROUND. The authors evaluated the two indicators of metastatic proclivity (namely, virulence [V ; the rate of appearance of distant metastases] and metastagenicity [M ; the ultimate likelihood of developing distant metastases]) of breast carcinoma in elderly women. The authors then compared these characteristics with the corresponding characteristics in a cohort of younger women to determine whether breast carcinoma was more indolent in women age > 70 years, as is commonly believed in the medical community.

METHODS. The authors examined 2136 women who underwent mastectomy without adjuvant systemic therapy at The University of Chicago Hospitals (Chicago, IL) between 1927 and 1987. The median follow-up period was 12.3 years. Distant disease-free survival (DDFS) was determined for women who did not receive systemic therapy. V and M were obtained from log-linear plots of DDFS.

RESULTS. No significant difference in tumor size at presentation was observed among women age < 40 years, women ages 40–70 years, and women age > 70 years ($P = 0.86$), whereas significantly fewer women age > 70 years presented with positive lymph nodes compared with younger women ($P = 0.05$). In women with negative lymph node status, there was a higher DDFS rate among patients ages 40–70 years (81% at 10 years) compared with patients age > 70 years (65% at 10 years; $P = 0.018$). There was no significant age-related difference among women with lymph node-positive disease ($P = 0.2$). For example, the 10-year DDFS rate for women ages 40–70 years was 33%, compared with 38% for women age > 70 years. Among those with lymph node-negative disease, V was 3% per year for women ages 40–70 years as well as women age > 70 years. Among women with lymph node-negative disease, M was 0.20 for patients ages 40–70 years and 0.35 for patients age > 70 years. In women with positive lymph node status, both V (11% per year vs. 10% per year) and M (0.70 vs. 0.65) were similar in both age groups.

CONCLUSIONS. Fewer women age > 70 years had lymph node involvement at presentation. However, when this finding was taken into account, the authors found no evidence that breast carcinoma was more indolent in women age > 70 years. These results support the use of similar diagnostic and therapeutic efforts for elderly women and younger women, with modification for elderly women based only on comorbidity. *Cancer* 2004;100:1807–13. © 2004 American Cancer Society.

KEYWORDS: breast carcinoma, elderly, outcome.

The American population is aging, and forecasts predict that by 2030, 20% of the U.S. population will be > 65 years old.¹ Moreover, the elderly are aging, with an estimated 8.8 million individuals age > 85 years expected to be living in the United States in 2030.¹ The incidence of breast carcinoma increases with age; whereas only 1 in 225 women age < 40 years develops breast carcinoma, this increases

to 1 in 24 for women ages 40–59 years and to 1 in 14 for women ages 60–79 years.² As the population ages and survival of chronic disease improves, the number of elderly women with breast carcinoma will increase.

Despite some evidence to the contrary,³ there is a perception that breast carcinoma in the elderly is less aggressive than breast carcinoma in younger women.^{4,5} For this reason, along with the higher incidence of comorbidities, breast carcinoma management in the elderly often differs from the management of younger women.⁶ For example, elderly women are more likely to undergo wide local excision alone or wide local excision followed by tamoxifen, with other radiotherapy and chemotherapy omitted.^{6,7} Women age > 70 years also are less commonly included in randomized clinical trials, making the therapeutic impact of new approaches difficult to assess in this population.¹

With the increasing acceptance of screening mammography and more effective therapies, mortality secondary to breast carcinoma has been decreasing.^{8,9} Screening guidelines for the elderly are inconsistent, resulting in a smaller percentage of older women receiving screening mammograms compared with younger women.^{10–15} The majority of screening mammography trials did not include women age > 70 years. Therefore, the benefit of mammography is not well defined in these women.

Our goal in the current study is to compare the natural history of breast carcinoma in the elderly with the natural history of this malignancy in younger patients. The current patient population had undergone definitive locoregional therapy and had been followed for a sufficiently long period of time to observe the metastatic potential of the disease. In the current study, the two components of metastatic proclivity (namely, virulence [V ; the rate of appearance of distant metastases] and metastagenicity [M ; the ultimate likelihood of developing distant disease]) were compared between age groups.

MATERIALS AND METHODS

The medical records of 2136 patients diagnosed with locoregional breast carcinoma who underwent mastectomy at the University of Chicago Hospitals (Chicago, IL) between 1927 and 1987 were reviewed. Five hundred fifty-one (25.8%) patients received adjuvant systemic therapy consisting of chemotherapy, hormonal therapy, or ovarian ablation. One hundred fifty-five (7.3%) patients were age < 40 years at diagnosis. These patients were excluded from the analysis of V and M . The majority of patients were followed at 3-month intervals during the first year after diagnosis and yearly thereafter. The median follow-up for sur-

living patients was 12.3 years. Pathologic information was obtained from original pathology reports. Information on tumor grade was not available for many patients because their diagnoses predated the development of standardized grading criteria. Lymph node status data were not available for 99 patients. Tumor size was determined by macroscopic measurement of the excised mass or the greatest tumor diameter on histologic section. Information on tumor size was not available for eight patients. Additional details of the overall patient population in this database have been described elsewhere.^{11,12,16–19}

Distant disease-free survival (DDFS) was defined as the elapsed time from mastectomy to distant disease. Both distant disease recurrence and breast carcinoma-related death were considered to be events for the purposes of DDFS calculations. Patients were censored for death due to intercurrent disease if they were without known metastatic disease. The cause of death was not known for 60 patients (2.8%). Actuarial DDFS curves were obtained using Kaplan–Meier calculations.²⁰

To study the effects of patient age on the rate of metastatic expression, the DDFS is presented using a log-linear plot. As previously described, we define the initial rate of metastatic expression as V , whereas the plateau is used to determine M , the ultimate likelihood of metastatic disease ($[100 - \text{plateau}]/100$). A straight-line plot approximating the first 4 yearly points was used for determination of the initial slope. The plateau was defined by the presence of at least three consecutive identical points.²¹

RESULTS

Patient and Tumor Characteristics

Patient and tumor characteristics for the entire group and for women who did not receive systemic therapy are shown in Table 1. The median age of the entire population was 54 years (range, 21–91 years). Two hundred fifty-one patients (12%) were age > 70 years. The median age of the patients who did not receive chemotherapy was also 54 years (range, 23–91 years), and 182 patients (12%) were age > 70 years. Patient and treatment characteristics by age group are shown in Table 2. The distribution of tumor size at presentation was not significantly different among women age < 40 years, women ages 40–70 years, and women age > 70 years ($P = 0.86$). The proportion of women with lymph node-positive disease decreased with age. For example, 45% of patients age > 70 years had positive lymph node status, compared with 55% of patients age 40–70 years ($P = 0.05$). Among patients with lymph node-positive disease, there was no significant difference across age groups in the proportion of women

TABLE 1
Patient Characteristics

Characteristic	All patients (%)	No systemic therapy (%)
Age (yrs)		
< 40	268 (13)	155 (10)
40–50	581 (27)	417 (26)
51–60	605 (28)	467 (29)
61–70	427 (20)	364 (23)
> 70	251 (12)	182 (12)
Unknown	4 (< 1)	0 (0)
Tumor size (cm)		
≤ 2	697 (33)	490 (34)
2.1–5	1028 (48)	682 (48)
> 5	403 (19)	256 (18)
Unknown	8 (< 1)	2 (< 1)
No. of positive lymph nodes		
0	900 (44)	715 (50)
1–3	590 (29)	384 (27)
≥ 4	547 (27)	331 (23)
Unknown	99 (5)	0 (0)
Histology		
Infiltrating ductal carcinoma	1868 (88)	1261 (88)
Infiltrating lobular carcinoma	46 (2)	28 (2)
Other	211 (10)	136 (10)
Unknown	11 (< 1)	5 (< 1)

TABLE 2
Patient and Treatment Characteristics by Age

Characteristic	Age (yrs)			P
	< 40 (%)	41–70 (%)	> 70 (%)	
Tumor size				
Median size (cm)	3.0	3.0	3.0	NS
Size (cm)				
< 2	85 (32)	521 (32)	89 (36)	0.86
2–5	130 (49)	781 (49)	114 (46)	
> 5	51 (19)	307 (19)	45 (18)	
Unknown	2 (< 1)	4 (< 1)	2 (< 1)	
Axillary lymph nodes				
Median no. removed	19	16	14	
Positive lymph nodes				
0	106 (40)	683 (42)	110 (44)	0.05
1–3	85 (32)	447 (28)	54 (28)	
≥ 4	73 (28)	434 (27)	43 (17)	
Unknown	4 (< 1)	52 (3)	43 (17)	
Chemotherapy administered				
Yes	47 (18)	165 (10)	15 (6)	< 0.001
No	210 (78)	1392 (86)	214 (86)	
Unknown	11 (4)	56 (4)	21 (8)	
Hormonal therapy administered				
Yes	70 (26)	191 (11)	18 (7)	< 0.001
No	179 (67)	1333 (83)	212 (85)	
Unknown	19 (7)	89 (6)	20 (8)	

NS: not significant.

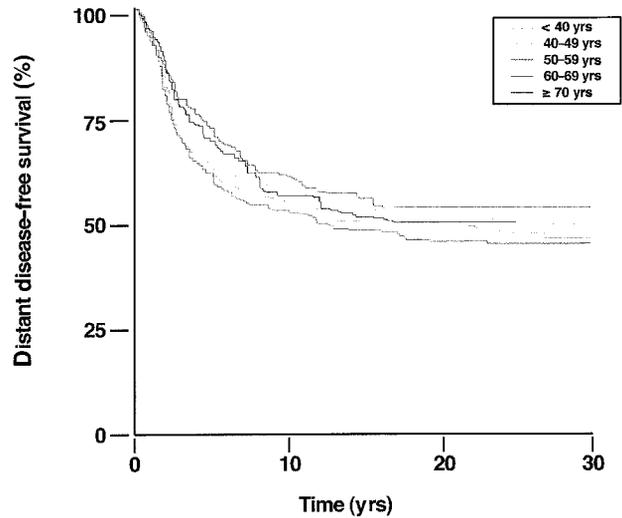


FIGURE 1. Distant disease-free survival as a function of time for women ages < 40 years, 40–49 years, 50–59 years, 60–69 years, and ≥ 70 years who underwent mastectomy without systemic therapy. Time is calculated from the date of mastectomy.

with 1–3 positive lymph nodes (52% of patients with lymph node-positive disease) relative to women with at least 4 positive lymph nodes (48% of women with lymph node-positive disease) ($P = 0.16$). Logistic regression analyses of the relations between age and tumor size and age and lymph node status confirmed these results (data not shown). Significantly more women age < 40 years received systemic therapy compared with older patients ($P < 0.001$).

Outcome

The majority of women in the current study received no systemic therapy. Because the goal of the current study was to examine the natural history of breast carcinoma in women age > 70 years without the confounding effects of systemic therapy, women who received systemic therapy were excluded from further outcome analysis. DDFS rates among women ages < 40 years, 40–49 years, 50–59 years, 60–69 years, and ≥ 70 years are shown in Figure 1. Only 6% of women experienced local disease recurrence. To determine whether age was an independent risk factor in determining DDFS, a Cox multivariate analysis was performed. As shown in Table 3, age was not an independent determinant of DDFS in the current patient cohort. Tumor size, positive lymph nodes, and systemic therapy significantly impacted DDFS. Figure 1 shows no significant difference in DDFS by age group. Because breast carcinoma has been shown to be more aggressive in women age < 40 years,¹⁶ we compared women age < 40 years with a combined cohort that

TABLE 3
Cox Multivariate Analysis for Factors Influencing Distant Disease-Free Survival

Variable	Hazard ratio (95% CI)	P
Size	1.02 (1.01-1.02)	< 0.001
Positive lymph nodes	1.03 (1.03-1.03)	< 0.001
Age (> 70 yrs vs. ≤ 70 yrs)	0.97 (0.74-1.20)	0.59
Chemotherapy	0.72 (0.57-0.91)	0.008
Hormonal therapy	0.80 (0.66-0.97)	0.026

CI: confidence interval.

included women ages 40–70 years and women age > 70 years.

We analyzed patients with lymph node–negative disease and patients with lymph node–positive disease separately. Log-linear plots of DDFS are shown in Figure 2. The DDFS rates for women ages < 40 years, 40–70 years, and > 70 years with lymph node–negative disease are shown in Figure 2A–C. The 5- and 10-year DDFS rates for women age < 40 years who had lymph node–negative disease were 83% and 78%, respectively. The 5 and 10-year DDFS rates for women ages 40–70 years who had lymph node–negative disease were 87% and 81%, respectively, compared with 84% and 65%, respectively, for women age > 70 years who had lymph node–negative disease ($P = 0.018$). However the rate of distant disease development (V) was similar for women age < 40 years (4%) and women age 40–70 and ≥ 70 (both 3%). The rate of ultimate appearance of distant disease after locoregional treatment only (M) was higher in women age > 70 years compared with younger women. The DDFS rate for women age > 70 years reached a plateau at 65%, compared with 80% for women ages 40–70 years, yielding M values of 0.35 for women age > 70 years and 0.20 for younger women. The DDFS rate for women age < 40 years reached a plateau at 73%, corresponding to an M value of 0.27.

In women age < 40 years who had lymph node–positive disease, the 5- and 10-year DDFS rates were 47% and 40%, respectively. The 5- and 10-year DDFS rates were 45% and 33%, respectively, for women ages 40–70 years who had lymph node–positive disease, whereas the DDFS rates were 52% and 38%, respectively, for women age > 70 years (Fig. 2D–F). The log-linear plots of DDFS for women ages 40–70 years and women age > 70 years are comparable, indicating no significant differences between these patient populations ($P = 0.2$). V was similar across age groups (11% per year for women age < 40 years and women ages 40–70 years and 10% for women age > 70 years), as was M (0.64 for women age < 40 years, 0.70 for

women ages 40–70 years, and 0.65 for women age > 70 years).

DISCUSSION

Controversy surrounds the management of breast carcinoma in elderly patients. Often, screening is underutilized in this group of women, despite the fact that the number of women in this group is increasing.^{22–24} This underutilization exists despite retrospective data that demonstrate a benefit for women age > 70 years who have limited comorbidities and who receive mammography, a cohort similar to the one analyzed in the current report.^{25–27} It is often assumed that extensive local therapy may not be well tolerated in this population, although limited data exist to support this belief.^{15,27–30} Extensive or multiple comorbidities often may preclude aggressive surgical management and systemic therapy that may otherwise be considered standard in a younger cohort of women with similar disease characteristics. In addition, the commonly held perception by physicians that the disease is more indolent in older women compared with younger women serves to perpetuate a heterogeneous approach to curative management.

In a population treated with locoregional therapy, we explored whether the natural history of breast carcinoma in elderly patients was different from the natural history of this malignancy in younger women. Our database offers a unique opportunity to evaluate the natural history of the disease, because the majority of women in it did not receive systemic therapy. To analyze whether breast carcinoma was more indolent in elderly women compared with younger patients and whether different screening and treatment guidelines therefore would apply, we evaluated outcomes in the current population of patients treated with mastectomy between 1927 and 1987. The series was collected and monitored by a single surgeon at the Uni-

FIGURE 2. (A–C) Distant disease-free survival (DDFS) for patients with lymph node–negative disease. The probability of DDFS is plotted logarithmically as a function of time for patients ages (A) < 40 years, (B) 40–70 years, and (C) > 70 years. $P = 0.018$ for patients ages 40–70 years versus patients age > 70 years. The initial slope of the survival curve is indicated. Time is calculated from the date of mastectomy. After 10 years, fewer than 20 patients age > 70 years were at risk for distant disease. (D–F) DDFS for patients with lymph node–positive disease. The probability of DDFS is plotted logarithmically as a function of time for patients ages (D) < 40 years, (E) 40–70 years, and (F) > 70 years. $P = 0.20$ for patients ages 40–70 years versus patients age > 70 years. The initial slope of the survival curve is indicated. Time is calculated from the date of mastectomy. After 9 years, fewer than 20 patients were at risk for distant disease.

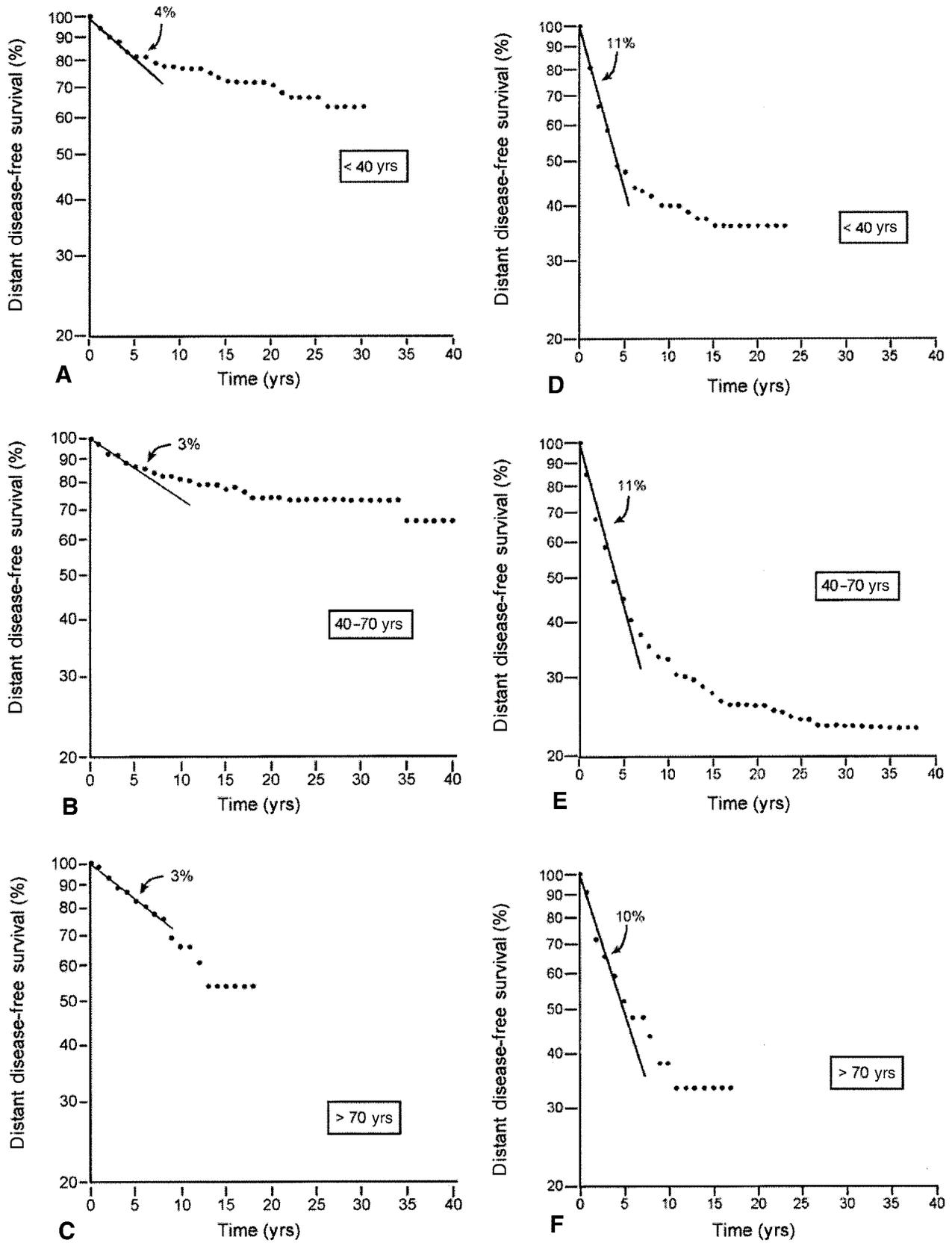


FIGURE 2.

versity of Chicago Hospitals, and meticulous long-term follow-up was performed. Because this population was considered to be healthy enough to undergo curative surgery, natural bias regarding comorbidity and life expectancy was present. However, because this group was screened by a single surgical service with consistent screening criteria, the bias can be considered constant within the population.

The current patient population was diagnosed before the widespread use of mammography. Therefore, these patients had clinically detected disease. The majority of women were diagnosed after a physical examination, which adds to the uniformity of this cohort and eliminates the possible confounding effects of mammography. This consideration is particularly important when drawing conclusions regarding women age > 70 years, many of whom are diagnosed clinically because of the decreased frequency of screening mammography in this population.

The majority of these women were diagnosed and treated before the publication of randomized trials that spurred the acceptance of adjuvant systemic therapy as a major component of breast carcinoma management.^{31,32} In the current series, only a few patients received systemic therapy (227 women who received chemotherapy and 279 women who received endocrine therapy), and these women were excluded from the analysis.

The long follow-up duration and lack of systemic therapy use in the current study population offer us the opportunity to analyze the kinetics of the natural history of breast carcinoma. Studying the rate of appearance of distant disease after locoregional therapy and the ultimate occurrence of distant disease in this uniform population provides insight into the natural history of the disease in this population.

We found that women age > 70 years presented with tumors that were similar in size those of younger women, but these women were more likely than younger women to have negative lymph node status. There were no significant differences in axillary lymph node involvement between women age > 70 years and younger women when compared according to tumor size. Although fewer elderly patients had lymph node-positive disease, the proportion of women with < 4, 4–9, and \geq 10 positive lymph nodes was similar in women age \leq 70 years compared with older women.

Cox multivariate analysis was performed on the entire patient population, including women age < 40 years and women receiving adjuvant systemic therapy, to identify factors impacting DDFS. Although tumor size, lymph node status, and the administration of systemic therapy were significant independent determinants of DDFS, age was not a significant variable.

We analyzed the expression of metastatic proclivity by studying DDFS, V , and M . V is an expression of the rate of clinical manifestation of metastases and is quite important in elderly patients, for whom comorbidity and competing mortality are significant. Among patients with lymph node-negative disease, V was similar for women age \leq 70 years and women age > 70 years. However, it is noteworthy that the value of M was significantly higher among elderly women compared with younger patients. No differences in V and M were found among patients with lymph node-positive disease.

These data indicate that in the current surgical cohort, breast carcinoma is no more indolent in the elderly than it is in younger patients and that the metastatic potential of breast carcinoma in the elderly does not differ significantly from the metastatic potential in younger patients. In fact, in the subgroup of elderly patients with lymph node-negative disease, breast carcinoma appeared to be more aggressive than was expected. With this in mind, the approach to management of breast carcinoma in the elderly must be reassessed. In the United States, women who reach age 80 years have a 5-year survival rate of > 70%, with an average life expectancy of 9.1 years.³³ Elderly individuals represent the most rapidly accruing segment of the U.S. population as life expectancies continue to increase. Breast carcinoma among the elderly will be an increasingly significant healthcare consideration in the future and should be managed optimally using mammography and appropriate locoregional therapy, as has been established in younger women. Systemic treatment decisions should consider comorbidities rather than chronologic age. In this manner, elderly women with breast carcinoma, like their younger counterparts, will enjoy the benefits of early detection and appropriate therapy.

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