Breast Carcinoma in Elderly Women

Features of Disease Presentation, Choice of Local and Systemic Treatments Compared with Younger Postmenopausal Patients

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BACKGROUND. Aging remains one of the single greatest risk factors for the development of new breast carcinoma. The aim of the study was to evaluate the relation between biologic features at first diagnosis of breast carcinoma and treatment choice for postmenopausal women ≥ 50 years to optimize treatment in the elderly.

METHODS. The sample included 2999 consecutive postmenopausal patients referred for surgery at the European Institute of Oncology (Milan, Italy) from April 1997 to February 2002. The patients were grouped according to age: young postmenopausal (YPM; 50–64 years, $n = 2052$), older postmenopausal (OPM; 65–74, $n = 801$), and elderly postmenopausal (EPM; ≥ 75, $n = 146$).

RESULTS. EPM patients referred to surgery had larger tumors compared with YPM patients (pT4: 6.7% vs. 2.4%) as well as greater lymph node involvement (lymph node positive: 62.5% vs. 51.3%). EPM patients showed a higher degree of estrogen and progesterone receptor expression ($P < 0.01$), less peritumoral vascular invasion ($P < 0.01$), and less HER-2/*neu* expression ($P < 0.01$) than YPM patients. Comorbidities were more often recorded for elderly patients (72% EPM vs. 45% YPM; $P < 0.001$), did not influence surgical choices, and were similar across groups (breast conservation: 73.9%, 76.9%, and 72.9%, respectively). No systemic therapy (either chemotherapy or endocrine therapy) was recommended for 19.1% of the EPM compared with 5.4% and 4.7% of the two other groups.

CONCLUSIONS. In spite of larger tumor size at presentation, older patients had tumors with more favorable biologic characteristics, when compared with younger postmenopausal patients. Reluctance to prescribe systemic treatments was due to the complexity of evaluation for these patients. Taking into account the data from the current study and given the climate of uncertainty regarding optimal treatment, the authors decided to individualize care on the basis of biologic characteristics, comorbidity, social support, functional status, and patient preferences. Trials of tailored adjuvant therapy should be a health care priority. ***Cancer* 2004; 101:1302–10.** © *2004 American Cancer Society.*

KEYWORDS: breast carcinoma, elderly patients, postmenopausal, treatment, breast-conserving surgery.

Breast carcinoma is the most common form of malignant disease among women in most of the developed world, and aging remains one of the single greatest risk factors for the development of new breast carcinoma. Approximately 50% of breast carcinomas occur in women ≥ 65 years, and > 30% of breast carcinomas occur among women > 70 years.[1] Older women represent the fastest growing segment of the population in the United States and in Europe.[2] Therefore, during the coming decades, older women will represent an increased cohort of both patients with newly diagnosed disease and survivors.[3,4] These older survivors of breast carcinoma are likely to be a somewhat heterogeneous group, especially with respect to multiple comorbid conditions.[5,6] Currently, treatment for elderly women with breast carcinoma is largely extrapolated from data derived from trials

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comprising younger patients, which is thus variable and represents evolving paradigms.[7–11] Decisions about optimal treatment patterns will ultimately depend on trial data regarding efficacy and women's treatment preferences.[12] There are scant data on the long-term sequelae of different breast carcinoma treatments to guide older women who are facing these important decisions.[13] Improvements in life expectancy increase the incentive to allow older women with breast carcinoma to be treated without major barriers related to age, functional status, and social support. One way to assess such features is provided by grouping the older cohorts according to the need for rehabilitative intervention.[14] A formal geriatric assessment is used only rarely to aid the decision-making process for cancer treatment. Subjective evaluation and personal prejudices of the physician often guide the therapeutic approach for older women.[15–17]

Objective assessments and a standardized approach are usually available in large cancer institutes, rather than in smaller centers. Larger institutes usually benefit from a geriatric service. It is important to acknowledge the pioneering work of geriatric oncologists who endeavored to bridge the gap. In the prognostic assessment of breast carcinoma in elderly women, two aspects need to be considered, i.e., "seed" and "ground" effects.[18] The seed reflects the tumor itself and its biology, which includes factors such as the increased prevalence of endocrine responsiveness, low proliferation rate, and the prevalence of well differentiated tumors. Less is known about the ground or "soil" effects. The ground effects refer to immune senescence, neoangiogenesis, and to the availability of growth hormones.

Immunohistochemical determination of HER-2/*neu*, steroid hormone receptors, proliferation fraction, and vascular invasion have not been studied systematically and specifically for the upper age groups.

The aims of the current study were to describe the characteristics and treatment of women $>$ 50 years diagnosed with breast carcinoma and to compare women who are young postmenopausal (50–64 years) with those who are old postmenopausal (65–74 years) and elderly postmenopausal ($>$ 75 years). Understanding breast carcinoma in these age groups is significant because of the relative lack of research on breast carcinoma treatment in the elderly women. The current report describes such features in an attempt to plan future studies and, thereby, improve treatments for elderly patients.

MATERIALS AND METHODS

We evaluated 2999 consecutive postmenopausal patients with breast carcinoma referred for surgery at the European Institute of Oncology in Milan between April 1997 and February 2002. Data on patient medical history, concurrent diseases, surgery, pathology, and results of staging procedures (e.g., bone scan, chest X-ray, abdominal ultrasound) were recorded. Pathology investigations included evaluation of the primary tumor and lymph node and/or sentinel lymph node when applicable.[19] Tumor grade was evaluated according to Elston and Ellis[20] and peritumoral vascular invasion (PVI) was assessed according to Rosen and Oberman.[21] Estrogen receptor (ER) level, progesterone receptor (PgR) level, and Ki-67 labeling index (determined with the MIB-1 monoclonal antibody) were evaluated immunocytochemically as previously reported.[22] HER-2/*neu* overexpression was evaluated immunocytochemically using a 1:100 dilution of a polyclonal antiserum (Dako, Glostrup, Denmark). Overexpression was considered to have occurred if $>$ 10% of neoplastic cells had complete membrane staining. For evaluation of ER, PgR, and the Ki-67 labeling index, the percentage of cells exhibiting definite nuclear staining over $\geq$ 2000 neoplastic cells examined at $\times$ 400 magnification was recorded. The slides were evaluated independently by two of the authors. The threshold values for HER-2/*neu* overexpression and for overexpression of ER and PgR were 10% and 20% for MIB-1, respectively, as previously reported.[22] Grading was not provided by pathologists for the group of patients who underwent preoperative chemotherapy due to the interference of the treatment with architectural and cytologic features of the tumor. Staining for HER-2/*neu* overexpression was only performed routinely after September 1999. All the data were stored in a Microsoft Access database and constantly checked for consistency on a weekly basis, by comparing it with the original data from the patient clinical chart. The database was used for interdisciplinary discussion (i.e., among surgeons, pathologists, medical oncologists, and radiation oncologists) and resulted in a proposal for postoperative adjuvant treatments.

Surgical Procedures

Patients underwent surgery either by quadrantectomy with sentinel lymph node biopsy and/or complete axillary lymph node dissection (ALND) or by modified radical mastectomy for breast carcinoma. Wide breast resection or quadrantectomy was performed using a radial skin incision centered on the palpable tumor or a periareolar incision for tumors close to the areola. For patients with nonpalpable lesions, we performed radio-guided surgery by a radioisotopic localization with ^{99m}Tc as previously described.[23] Patients with infiltrating single tumors $<$ 3 cm in diameter and with clinically negative axillary lymph nodes underwent breast-conserving surgery and sentinel lymph node

biopsy. Otherwise, a complete ALND was performed. Sentinel lymph node biopsy or ALND was performed through the same incision in patients who received upper outer breast resection or through a counter incision for other tumor sites.

Primary Chemotherapy

Patients with large or locally advanced breast carcinoma (cT2–4) were treated with several chemotherapy regimens for a treatment duration of up to six courses. All patients had biopsies performed through Tru-cut (C.R. Bard, Inc., Covington, GA) and were evaluated after standard fixation before treatment. The treatment was based on tumor characteristics.

Statistical Analysis

The aim of the current analysis was to compare tumor characteristics, biologic markers, and multidisciplinary treatments among three groups of patients: young postmenopausal (YPM; 50–64 years), older postmenopausal (OPM; 65–74 years), and elderly postmenopausal (EPM; women $\geq$ 75 years). ER, PgR, and KI-67 were categorized into their clinically accepted groups. There are no clinically relevant categories for HER-2/*neu*, which was split into two groups at the 10% level. The associations between categorical variables and age group were measured in contingency tables using two-sided chi-square tests of associations. The Kruskal–Wallis test was used to measure quantitative biologic markers. We performed a binary logistic and multinomial regression analyses to estimate the interdependence of tumor characteristics, biologic features (both as categorical and continuous variables), and age on treatment. The final model contained the characteristics and features that were significant at the 5% level. Interaction tests were used to investigate the homogeneity of effects over the three age groups.

RESULTS

A total of 2999 postmenopausal patients with breast carcinoma who underwent surgery were referred for a multidisciplinary evaluation. Of these, 2052 patients (68.4%) were classified as YPM, 801 (26.7%) were classified as OPM, and 146 (4.9%) were classified as EPM. Table 1 summarizes the tumor characteristics according to age. Patients in the EPM group had larger tumors at diagnosis than younger patients (Table 1). Lymph node involvement was greater among EPM women compared with YPM women (62.5% vs. 51.3%; Table 1). Histology was the same in all age groups, although mucinous carcinoma was slightly increased in the EPM group compared with the YPM and OPM patients (Table 1). In spite of the larger tumors at presentation, older patients had tumors with more favorable biologic characteristics compared with younger patients (i.e., a higher degree of ER and PgR receptor expression, less PVI, and less HER-2/*neu* expression; Table 1). Receptor expression was similar among the three groups (80.8% vs. 83.7% vs. 81.9%, respectively, for the YPM, OPM, and EPM patients), although a larger percecntage of OPM patients had a higher degree of ER and PgR expression in the tumor ($>$ 10% of cells: 39.7–48.4% and 54.9%, respectively; $P < 0.01$). HER-2/*neu* positive was associated with age ($P < 0.01$), and the percentage of women who were HER-2/*neu* was negatively associated with age. PVI decreased with age from 31% in the YPM group to 25% in the EPM group (Table 1; $P = 0.02$). However, neither grade ($P = 0.89$) nor Ki-67 labeling index ($P = 0.56$) was associated with age (Table 1).

As expected, the incidence of comorbidities was greater among EPM patients—24% reported no comorbidities compared with 54.8% and 35.7% of the other groups. In the EPM group, the most common condition with a high impact of comorbidity was hypertension under active treatment (22.6%). Cardiovascular diseases were observed in 20.5% of the patients. Diabetes occurred in 0.7% of EPM patients. Two or more comorbid conditions occurred in 21.2% of EPM patients.

One hundred and ninety-five patients (6.5%) received preoperative chemotherapy—195 in the YPM group (9.5%), 31 in the OPM group (3.9%), and 1 patient in the EPM group (0.7%). Surgical approaches were similar in the 3 groups of patients ($P = 0.47$; Table 2). For women who underwent breast-conserving surgery, radiotherapy was recommended to only 54.7% of elderly patients ($>$ 75 years), compared with 84.5% of older women (65–75 years) and 86.6% of younger patients (50–64; $P< 0.01$). For clarity, the younger patients received a standard radiotherapy regimen when indicated, with the exception of women who were treated with intraoperative radiotherapy as participants in an institutional trial or women who received confirmation during postsurgical follow-up and/or workup for a suspicious metastatic lesion. Chemotherapy was recommended to 6.4% of women in the EPM group compared with 35.4% of women in the other two groups. For ER-positive patients, endocrine treatment was recommended to 74.4% of the EPM women compared with 72.5% of YPM women and 82.0% of OPM women. Decision-making was oriented to recommend no systemic therapy (either chemotherapy or endocrine therapy) to 19.1% of EPM patients compared with 5.4% and 4.7% of YPM and OPM patients (Table 2).

The choice of adjuvant therapies depended on medical decisions influenced by grade, stage, ER status, lymph node status, and comorbid condition.

TABLE 1
Description of Biologic Characteristics, Histology, Pathologic Stage of Breast Tumors and Comorbid Illness in Postmenopausal Women Diagnosed with Breast Carcinoma at the Europe Institute of Oncology in Milan April 1997–February 2002 (n = 2999)

Factors	YPM	OPM	EPM	Two-sided P value[b]
No. of patients evaluable for ER/PgR	1913	773	144	
Percentage ER < 10%	21.4	17.5	18.8	0.07
ER ≥ 10%	78.6	82.5	81.3	
Percentage PgR < 10%	47.5	40.1	38.2	< 0.01
PgR > 0 10%	52.5	59.9	61.8	
ER and PgR negative	19.1	16.3	18.1	
ER or PgR < 10%	41.2	35.3	27.1	
ER and PgR ≥ 10%	39.7	48.4	54.9	< 0.01
No. of patients evaluable for Ki-67 proliferative index	1851	758	138	
Ki-67 < 20%	51.3	53.3	54.3	
Ki-67 ≥ 20%	48.7	46.7	45.7	0.56
No. of patients evaluable for PVI	1845	749	130	
Percentage PVI present	30.6	25.5	24.6	< 0.02
No. of patients evaluable for grade	1576	678	116	
1	18.8	17.7	16.4	
2	47.6	49.3	50.9	
3	33.6	33.0	32.8	0.89
No. of patients evaluable for HER-2/*neu*	1105	422	107	
HER-2/*neu* = 0	57.3	66.1	64.6	
HER-2/*neu* < 10%[a]	1.9	0.7	2.8	
HER-2/*neu* ≥ 10%	40.8	33.2	32.7	< 0.01
Histology				
No. of patients evaluable	1966	783	146	
Infiltrating ductal (%)	74.2	72.3	71.9	
Infiltrating lobular (%)	10.1	11.2	10.3	
Cribriform (%)	2.4	1.6	2.4	
Mucinous (%)	1.1	2.8	4.1	
Tubular (%)	1.1	1.1	0	
Other (mixed tumors and rare subtypes)	11.1	10.0	12.3	0.81
Pathologic stage (pTNM)				
No. of patients evaluable for pT	1864	748	134	
pT0	2.4	1.5	0.7	
pT1	62.8	56.6	45.5	
pT2	28.9	35.6	44.8	
pT3	3.6	3.9	2.2	
pT4	2.4	2.5	6.7	< 0.01
No. of patients evaluable for pN	1806	741	96	
pN0/sentinel node negative	48.9	47.1	37.5	
pN1	48.3	49.9	52.1	
pN2	2.8	3.0	10.4	< 0.01
No. of patients evaluable for positive lymph nodes				
No. of positive lymph nodes	1814	742	95	
0	48.9	47.1	37.5	
1–3	28.6	34.1	26.7	
4–9	10.7	8.5	13.7	
≥ 10	11.8	10.3	22.1	< 0.01
No. of patients evaluable for comorbid illness	2052	801	146	
Percentage with hypertension (%)	12.7	21.5	22.6	
Percentage with cardiovascular disease (%)	4.1	12.9	20.5	
Percentage with diabetes (%)	0.9	1.4	0.7	
Two or more comorbid conditions	10.5	13.4	21.9	< 0.01

PVI: peritumoral vascular invasion; YPM: young postmenopausal women; OPM: older postmenopausal women; EPM: elderly postmenopausal women; ER: estrogen receptor; PgR: progesterone receptor.

[a] refers to complete staining of the membrane.

[b] The P values are taken from a chi-square test for association or equality of proportions.

TABLE 2
Local and Systemic Treatment in Percentage of Patients in Relation to Age Groups

Type of treatment	YPM	OPM	EPM	Two-sided *P* value
Surgery				
No. of patients evaluable	2051	801	146	
BCS (%)	73.9	76.9	72.6	
mastectomy (%)	22.3	20.2	23.3	
other (%)	3.8	2.9	4.1	0.47
Radiotherapy in BCS				
No. of patients evaluable	1506	613	104	
receiving RT (%)	86.6	84.5	54.7	< 0.01
Systemic therapy				
No. of patients evaluable	2032	795	141	
no treatment (%)	4.7	5.4	19.1	
CT only	22.8	12.6	6.4	
HT only	37.3	58.4	71.6	
CT + HT	35.2	23.6	2.8	< 0.01

YPM, OPM, EPM: younger, older, elderly pastmenopausal patients; BCS: breast-conserving surgery; RT: radiotherapy; CT: chemotherapy; HT: hormone therapy.

Many of these variables were themselves related to age. Consequently, the association with age may just be a reflection of the tumor characteristic associations, and this is investigated in the multinomial logistic regression models (Table 3). Adjusting for ER status, PgR status, comorbidity, Ki-67 labeling index, and PVI, there was still a significant association between age group and the propensity to receive systemic therapy. All variables in the multinomial regression model were independently associated with receiving systemic therapy ($P < 0.05$) with the sole exception of comorbidities ($P = 0.08$).This is expected as these variables are part of the clinical decision-making process. Adjusting for these variables, women in the EPM group are less likely to receive any systemic therapy, ($P < 0.01$). Compared with a woman in the EPM group, a woman in the YPM has an odds ratio (OR) of 0.008 (95% confidence interval [CI], 0.002, 0.039) of receiving no systemic therapy and a woman in the OPM group has an OR of 0.020 (0.004, 0.106) of receiving no systemic therapy.

Similar multinomial models revealed that the type of surgery received was not influenced by the age of the patient but was dictated by tumor characteristics.

Women in the EPM group are less likely to receive radiotherapy ($P = 0.01$). Compared with a woman in the EPM group, a woman in the YPM group has an OR of 0.47 (95% CI 0.27, 0.75) of not receiving radiotherapy and a woman in the OPM group has an OR of 0.50 (0.29, 0.85) of receiving no radiotherapy.

DISCUSSION

The study described the characteristics and treatment of women > 50 years diagnosed with breast carcinoma and compared YPM women (50–64 years) with OPM women (65–74 years) and EPM women (> 75 years). We observed that even if elderly patients referred to surgery had larger tumors and greater lymph node involvement compared with younger women with smaller tumors and less lymph node involvement, they have a more favorable biologic tumor profile overall. Comorbidities were more often recorded in elderly patients compared with younger patients, but these did not influence surgical treatment but affected adjuvant treatments. Moreover, the subjects include a large sample from a recent period , reducing bias related to changes in incidence and treatment over time.

Although available age-specific clinical data demonstrate that treatment efficacy is not modified by age, elderly patients are underrepresented in cancer clinical trials.[24,25] Older patients are more likely to have conditions that make them ineligible for clinical trials because of protocol exclusions mainly related to comorbidities or ageist trial designing.[26] The results of a recent analysis[27] showed that 32% of participants in Phase II and III clinical trials were elderly, compared with 61% of patients with incident cancers in the United States who are elderly. The degree of underrepresentation was more pronounced in trials for early-stage rather than for late-stage cancers. Protocol exclusion criteria on the basis of organ system abnormalities and functional status limitations were associated with lower elderly participation. An analysis of 16,396 patients consecutively enrolled in 164 clinical trials under the auspices of the Southwest Oncology Group during the years 1993–1996 demonstrated that elderly patients were generally underrepresented in treatment protocols compared with the general cancer population (25% vs. 63%). This was mainly evident for patients with breast carcinoma.[28] Indeed, despite the finding that patients with breast carcinoma ≥ 65 years accounted for 49% of the entire breast carcinoma population cohort in trials, only 9% of them were included in treatment protocols. This finding was due to the attitude of clinicians who proposed participation in clinical trials to only a few elderly patients and excluded them from treatment for comorbid conditions, and to the risk of excessive toxicity of systemic treatment. This attitude is also related to the widespread, although controversial, impression among clinicians, that breast carcinoma in younger women is an aggressive disease, whereas it is indolent among older women. Against such prejudices, several reports[29,30] illustrated a significant benefit of disease-free survival after treatment with tamoxifen.[31,32] The opportunity to be able to tailor treatments according to several biologic features (e.g., hormone receptors, c-erb-B2 overexpression, multicentricity) leads to an increasing

TABLE 3
Multinomial Regression Model[a]

	No CT or HT			CT only			HT Only		
Systemic therapy	**OR**	**LCL**	**UCL**	**OR**	**LCL**	**UCL**	**OR**	**LCL**	**UCL**
YPM	0.0077	0.0015	0.0392	0.487	0.007	3.391	0.0394	0.0094	0.165
OPM	0.0201	0.0038	0.106	0.16	0.022	1.116	0.104	0.0244	0.444
EPM	1			1			1		
ER and PgR negative	250.023	49.069	1273.943	1569.886	343.496	7174.875	0.393	0.0539	2.869
ER or PgR < 10%	1.317	0.643	2.738	2.945	1.645	5.283	0.594	0.448	0.789
ER and PgR > 10%	1			1			1		
No comorbidities	0.575	0.236	1.4	1.751	0.755	4.063	0.73	0.472	1.128
CV comorbidities	0.459	0.177	1.195	1.335	0.518	3.438	0.659	0.408	1.064
Non CV comorbidities	0.995	0.351	2.821	1.256	0.456	3.435	1.046	0.619	1.77
2+ comorbidities	1			1			1		
C-erb-B2 absent	1.316	0.697	2.484	1.164	0.71	1.907	1.687	1.261	2.257
C-erb-B2 < 10%	1.86	0.179	19.317	4.329	1.093	17.143	1.546	0.526	4.543
C-erb-B2 ≥ 10%	1			1			1		
Ki-67 < 20%	3.245	1.604	6.565	0.93	0.568	1.524	1.732	1.307	2.295
Ki-67 ≥ 20%	1			1			1		
PVI absent	8.637	3.249	22.958	0.786	0.475	1.301	4.118	3.034	5.591
PVI present	1			1			1		
Radiotherapy	No radiotherapy								
	OR	LCL	UCL						
YPM	0.45	0.27	0.75						
OPM	0.5	0.293	0.854						
EPM	1								
0 positive lymph nodes	3.36	2.297	4.916						
1–3 positive lymph nodes	3.686	2.49	5.456						
4–9 positive lymph nodes	2.134	1.372	3.319						
10+ positive lymph nodes	1								
Surgery—conservative	0.361	0.184	0.706						
Surgery—mastectomy	9.056	4.54	18.064						
Surgery—other	1								
Surgery	Conservative surgery			Mastectomy					
	OR	LCL	UCL	OR	LCL	UCL			
YPM	1.114	0.475	2.617	1.05	0.426	2.584			
OPM	1.516	0.603	3.811	1.243	0.47	3.284			
EPM	1			1					

YPM, OPM, EPM: Younger, older, elderly postmenopausal women; CT: chemotherapy; HT: hormone therapy; OR: odds ratio; ER/PgR: estrogen/progesterone receptor; CV: cardiovascular; PVI: peritumoral vascular invasion; LCL: lower confidence limit; UCL: upper confidence limit.

[a] The estimates were derived from a multinomial regression model using SPSS. They are all to be interpreted relative to the baseline category in the multinomial model. For systemic therapy, the baseline reference category is systemic therapy—both CT and HT; for radiotherapy, it is radiotherapy yes and for surgery, it is surgery—Other (see text). For radiotherapy, the OR/ are interpreted as from a logistic regression. So Compared with the EPM group, a woman in the YPM group has an OR of not receiving radiotherapy of 0.45. The OR associated with lymph nodes and surgery reflect treatment practice. Relative to someone with 10+ positive lymph nodes, the OR of receiving no radiotherapy is 3.67 for a woman with 1–3 positive lymph nodes. Compared with a women receiving other surgery, the OR of receiving no radiotherapy is high (9.06) for a woman who had a mastectomy but low (0.36) for a woman receiving conservative surgery. Some of the OR/ are very large; or very small, reflecting the systematic structures in the use of systemic therapy. Patients who are ER and PgR negative do not normally receive hormonal therapy. Compared with the EPM group, women in the YPM and OPM groups are much less likely (OR = 0.007 and 0.020, respectively) of receiving no systemic therapy relative to both CT and HT. For the other parameters, women with Ki-67 < 20 are much more likely to receive no CT or HT than women with Ki-67. > 20 relative to receiving both CT and HT.

need for an accurate biologic characterization of breast carcinoma, even for elderly women. Patients in the EPM group had larger tumors (pT4) compared with patients in the YPM group (6.7% vs. 2.4%) as well as greater lymph node involvement (62.5% vs. 51.3%). Information in the literature either confirms[33] or rejects[34] this observation, indicating the controversy related to lymph node involvement. Our cohort was collected over a period of time in which accuracy in evaluating lymph node involvement increased due to sentinel lymph node staging.[35] This might account for the heterogeneity of reporting on lymph node involvement across series. Other hypotheses related to delay in diagnosis should also be considered.[36] This may reflect reduced breast awareness among older women, who are less likely to self-examine[37] and may also be due to lack of mammographic screening.

Surgical approaches to elderly and to younger patients were similar in our institution, in keeping with the principle of ensuring that each individual is of-

fered an equal opportunity to receive appropriate treatment.[38] Elderly patients, suitable for breast conservation, are offered this type of treatment and investigational approaches are being developed to decrease the distress of 6 weeks of daily radiotherapy by implementing innovative, intraoperative, one-shot radiotherapy.[39] This time-saving treatment can have a significant impact on a patient and on the decision of the physician to employ radiotherapy. All three groups of patients were treated similarly, unless there was significant comorbidity to limit their overall likely survival. If older patients were suitable for breast conservation, they were offered this mode of treatment, and treatments administered did not differ from those administered to their younger counterparts (Table 2). Axillary surgery plays an established role in the staging and treatment of breast carcinoma. The surgical management of the axilla in elderly patients has to be determined on a case-by-case basis, which also takes the patient's wishes into consideration. The decision will depend on the patient, on tumor characteristics, on available technologies, and on local expertise. To all patients with tumors $\leq$ 3 cm with a clinically negative axilla, we offer sentinel lymph node biopsy. Our overall results with this technique indicate that sentinel lymph node biopsy can accurately predict the status of the axilla, thus avoiding unnecessary ALND.[35] In patients with tumors $>$ 3 cm with clinically negative axilla and in patients with any cT with clinically involved axilla, we offer ALND Level I–III. These data are noteworthy because other studies suggest that elderly women are less likely to be offered or receive breast conservation surgery.[40,41] The most recent data favor mastectomy as the most common choice for older women,[41] both for reasons related to the tumor itself and to patient preference.

Elderly patients referred to surgery present with a higher risk of disease recurrence (i.e., they have more positive lymph nodes) and are likely to have an endocrine- responsive disease. Endocrine receptor positivity was similar among the three groups (78.6% vs. 82.5% vs. 81.3%, respectively, for the YPM, OPM, and EPM groups), with a trend for EPM patients to have a higher degree of ER and PgR expression in the tumor. The proliferation index (Ki-67) did not differ among the three groups, although PVI and overexpression of HER-2/*neu* were different among the groups. Steroid receptors, tumor proliferation, c-erb-B2 overexpression, and PVI are prognostic indicators and predictors of treatment outcome, and thus might aid in decision-making regarding the choice of adjuvant treatment.[12] As expected, comorbid conditions were more often recorded for EPM patients compared with YPM patients (Table 1; 65.7% vs. 49.2% and 32.7 respectively; $P < 0.01$). In the EPM group, the most common condition with high impact of comorbidity was hypertension under active treatment (22.6%). Cardiovascular disease was observed in 20.5% of the patients. Two or more comorbid conditions occurred in 21.2% of EPM patients. The presence of comorbidity in our study influenced the choice of adjuvant treatment. Even if several studies have shown that older patients received less extensive treatment (e.g., adjuvant radiotherapy and chemotherapy),[42–44] little data exist on treatment for older patients with breast carcinoma with serious comorbid conditions because these patients generally are not eligible for clinical trials.[28,44]

Chemotherapy was recommended to 6.4% of EPM patients compared with 35.4% of patients in the other two groups. It is, however, typically indicated for patients with endocrine-nonresponsive disease, especially when axillary lymph nodes are involved. For patients with endocrine-responsive tumors, endocrine treatment was recommended to 74.4% of EPM patients, to 72.5% of YPM patients, and to 82.0% of OPM patients. Conversely, no systemic therapy (either chemotherapy or endocrine therapy) was recommended to 19.1% of EPM patients compared with 5.4% and 4.7 % of patients in the two other groups (Table 2).

A differentiated approach to local and systemic treatments in elderly patients with breast carcinoma has been well documented.[45–49] Even if several reports showed that breast carcinoma prognosis is poor for older women,[48] this difference seems to be related to failure to treat older patients in a similar manner to their younger counterparts. A recent study showed that both older and younger patients with locoregional breast carcinoma fare equally well.[49] Our data suggest that age per se should not be the only factor in the decision-making process for patients with cancer patients. In the elderly, the overall status of the patient, more than the age itself, should be addressed when treatment options are being considered. Acute and chronic medical conditions, nutritional status, level of activity, and disease-specific symptoms all need to be considered. Only these concomitant factors, together with the patient's opinion, should influence the type and extent of therapy. The goals of treatment in elderly patients should be the same as those in younger patients. Studies of comprehensive treatments in patients $\geq$ 75 years, as well as in sick patients, should probably be considered for the future. Finding reliable and effective ways to include elderly patients with comorbidities in clinical trials is a major challenge that will need to be addressed in the years to come.[50]

REFERENCES

1. Kimmick GG, Balducci L. Breast cancer and aging: clinical interactions. *Hematol Oncol Clin North Am.* 2000;14:213–234.

2. Ries LAG, Kosary CL, Hankey BF, et al. National Cancer Institute SEER cancer statistics review 1973–1995 (specific data from NCHS public use tape). Bethesda, MD: National Cancer Institute, 1998.
3. Lash TL, Silliman RA. Prevalence of cancer. *J Natl Cancer Inst.* 1998;90:399–400.
4. Parkin DM, Bray FI, Devesa SS. Cancer burden in the year 2000. The global picture. *Eur J Cancer.* 2001;37:S4–S66.
5. Guralnik JM. Assessing the impact of comorbidity in the older population. *Ann Epidemiol.* 1996;6:376–380.
6. Mandelblatt JS, Bierman AS, Gold K, et al. Constructs of burden of illness in older patients with breast cancer: a comparison of measurement methods. *Health Serv Res.* 2001;36:1085–1107.
7. National Institutes of Health. NIH consensus conference. Treatment of early breast cancer. *JAMA.* 1991;265:391–395.
8. Nattinger AB, Gottlieb MS, Veum J, Walker AP, Goodwin JS. Geographic variation in the use of breast-conserving treatment for breast cancer. *N Engl J Med.* 1992;326:1147–1149.
9. Cancer and Leukemia Group B. Protocol no. 9343: tamoxifen vs. radiotherapy and tamoxifen after breast conservation in the elderly with local disease. Chicago, IL: Cancer and Leukemia Group B, 1999.
10. Hughes K, Schnaper L, Berry D, et al. Comparison of lumpectomy plus tamoxifen with and without radiotherapy (RT) in women 70 years of age and older who have clinical state I, estrogen receptor positive (ER+) breast carcinoma [abstract 24a]. *Proc Am Soc Clin Oncol.* 2001;20:93.
11. Turner RR, Ollila DW, Krasne DL, Giuliano AE. Histopathologic validation of the sentinel lymph node hypothesis for breast carcinoma. *Ann Surg.* 1997;226:271–276.
12. Goldhirsch A, Wood WC, Gelber RD, Coates AS, Thurlimann B, Senn HJ. Meeting highlights: updated international expert consensus on the primary therapy of early breast cancer. *J Clin Oncol.* 2003;21:3357–3365.
13. Ashing-Giwa K, Ganz PA, Petersen L. Quality of life of African-American and white long term breast carcinoma survivors. *Cancer.* 1999;85:418–426.
14. Hamerman D. Toward an understanding of frailty. *Ann Intern Med.* 1999;130:945–950.
15. Fentiman IS, Tirelli U, Monfardini S, et al. Cancer in the elderly: why so badly treated? *Lancet.* 1990;335:1020–1022.
16. Repetto L, Fratino L, Audisio RA, et al. Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients: an Italian Group for Geriatric Oncology Study. *J Clin Oncol.* 2002;20:494–502.
17. Audisio RA, Gennari R, Sunouchi K, et al. Preoperative assessment of cancer in elderly patients: a pilot study. *Supportive Cancer Ther.* 2003;1:55–60.
18. Balducci L, Beghe C. Cancer and age in the USA. *Critical Rev Oncol Hematol.* 2001;37:137–145.
19. Viale G, Bosari S, Mazzarol G, et al. Intraoperative examination of axillary sentinel nodes in breast carcinoma patients. *Cancer.* 1999;85:2433–2438.
20. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with a long-term follow-up. *Histopathology.* 1991;19:403–410.
21. Rosen PP, Oberman HA. Tumors of the mammary gland. Washington, DC: Armed Forces Institute of Pathology, 1993.
22. Colleoni M, Orvieto E, Nolè F, et al. Prediction of response to primary chemotherapy for operable breast cancer. *Eur J Cancer.*1999;35:574–579.
23. Gennari R, Galimberti V, De Cicco C, et al. Use of Technetium-99m-labeled colloid albumin for preoperative and intraoperative localization of nonpalpable breast lesions. *J Am Coll Surg.* 2000;190:692–699.
24. Muss A. Older age: not a barrier to cancer treatment. *N Engl J Med.* 2001;345:1128–1129.
25. Mitka M. Too few older patients in cancer trials. *JAMA.* 2003;290:27–28.
26. Holmes CE, Muss HB. Diagnosis and treatment of breast cancer in the elderly. *CA Cancer J Clin.* 2003;53:227–244.
27. Lewis JH, Kilgore ML, Goldman DP, et al. Participation of patients 65 years of age or older in cancer clinical trials. *J Clin Oncol.* 2003;21:1383–1389.
28. Hutchins LF, Unger JM, Crowley JJ, Coltman CA Jr., Albain KS. Underrepresentation of 65 years of age or older in cancer-treatment trials. *N Engl J Med.* 1999;30:2061–2067.
29. Fentiman IS, van Zijl J, Karydas I, et al. Treatment of operable breast cancer in the elderly: a randomised clinical trial EORTC 10850 comparing modified radical mastectomy with tumorectomy plus tamoxifen. *Eur J Cancer.* 2003;39:300–308.
30. Fentiman IS, Christiaens MR, Paridaens R, et al. Treatment of operable breast cancer in the elderly: a randomised clinical trial EORTC 10851 comparing tamoxifen alone with modified radical mastectomy. *Eur J Cancer.* 2003;39:309–316.
31. Yanick R, Ries LG, Yates JW. Breast cancer in aging women. A population-based study of contrasts in stage, surgery, and survival. *Cancer.* 1989;63:976–981.
32. Crivellari D. Results of adjuvant treatments in breast cancer patients over 70 years old: the IBCSG experience. International Breast Cancer Study Group. *Tumori.* 2002;88:S81–82.
33. Diab SG, Elledge RM, Clark GM. Tumor characteristics and clinical outcome of elderly women with breast cancer. *J Natl Cancer Inst.* 2000;92:550–556.
34. Fisher CJ, Egan MK, Smith P, Wicks K, Millis RR, Fentiman IS. Histopathology of breast cancer in relation to age. *Br J Cancer.* 1997;75:593–596.
35. Veronesi U, Paganelli G, Viale G, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. *N Engl J Med.* 2003;349:546–553.
36. Coates AS. Breast cancer: delays, dilemmas, and delusions. *Lancet.* 1999;353:1112–1113.
37. Siahpush M, Singh GK. Sociodemographic variations in breast cancer screening behaviour among Australian women: results from the 1995 National Health Survey. *Prevent Med.* 2002;35:174–180.
38. Tejeda HA, Green SB, Trimble EL, et al. Representation of African-Americans, Hispanics, and withes in National Cancer Institute cancer treatment trials. *J Natl Cancer Inst.* 1996;88:812–816.
39. Veronesi U, Orecchia R, Luini A, et al. A preliminary report of intraoperative radiotherapy (IORT) in limited-stage breast cancer that are conservatively treated. *Eur J Cancer.* 2001;37:2178–2183.
40. Monypenny I. UK symptomatic breast audit 1.4.2001–31.3.2002. London: British Association of Surgical Oncology, 2003.
41. Lazovich DA, Whithe E, Thomas DB, Moe RE Underutilization of breast-conserving surgery and radiation therapy among women with stage I or II breast cancer. *JAMA.* 1991; 266:3433–3438.
42. Bouchardy C, Rapiti E, Fioretta G, et al. Undertreatment strongly decreases prognosis of breast cancer in elderly women. *J Clin Oncol.* 2003;21:3580–3587.

43. Yanick R, Wesely MN, Ries LA, et al. Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older *JAMA*. 2001;285:885–892.
44. Kemey MM, Peterson BL, Kornablith AB, et al. Barriers to clinical trial participation by older women women with breast cancer. *J Clin Oncol*. 2003;21:2268–2275.
45. 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:1475–1480.
46. de Rijke JM, Schouten LJ, Schouten HC, Jager JJ, Koppejan AG, van den Brandt PA. Age-specific differences in the diagnostics and treatment of cancer aged 50 years and older in the province of Limburg, The Netherlands. *Ann Oncol*. 1996; 7:677–685.
47. Yancik R, Ries LA. Aging and cancer in America: demographic and epidemiologic perspectives. *Hematol Oncol Clin North Am*. 2000;14:17–23.
48. Lipschitz DA, Goldstein S, Reis R, Weksler ME, Bressler R, Neilan BA. Cancer in the elderly: basic science and clinical aspects. *Ann Intern Med*. 1985;102:218–228.
49. Coebergh JWW. Significant trends in cancer in the elderly. *Eur J Cancer*. 1996:32A:569–571.
50. Wild L, Reed WR. The need for targeted research into breast cancer in the elderly. *Br J Surg*. 2003;90:388–399.