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Early-Stage Breast Cancer in the Octogenarian: Tumor Characteristics, Treatment Choices, and Clinical Outcomes

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Abstract

Background—Nodal staging with sentinel node biopsy (SLNB), post-lumpectomy radiotherapy (RT), and endocrine therapy (ET) for estrogen receptor-positive (ER+) tumors is valuable in the treatment of early-stage (stages 1 or 2) breast cancer but used less often for elderly women.

Methods—This retrospective study investigated women referred for surgical evaluation of biopsy-proven primary early-stage invasive breast cancer from January 2001 to December 2010. Clinicopathologic features, treatment course, and outcomes for women ages 80–89 years and 50–59 years were compared.

Results—The study identified 178 eligible women ages 80–89 years and 169 women ages 50–59 years. The elderly women more often had grade 1 or 2 disease ($p = 0.003$) and ER+ tumors ($p = 0.007$) and less frequently had undergone adjuvant therapies (all $p < 0.001$). Lumpectomy was performed more commonly for the elderly (92 vs. 83 %, $p = 0.02$), and axillary surgery was less commonly performed (46 vs. 96 %; $p < 0.001$). Fewer elderly women had undergone post-lumpectomy RT (42 vs. 89 %; $p < 0.001$) and ET for ER+ tumors (72 vs. 95 %; $p < 0.001$). During the median follow-up period of 56 months for the 80- to 89-year old group and 98 months for the 50- to 59-year-old group, death from breast cancer was similar (4 vs. 5 %; $p = 0.5$). The two

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groups respectively experienced 7 versus 6 locoregional recurrences and 11 versus 13 distant recurrences.

Conclusions—The octogenarians had disease survivorship similar to that of the younger women despite less frequent use of adjuvant therapies, likely reflecting lower-risk disease features. Whether increased use of axillary surgery, post-lumpectomy RT, and/or ET for ER+ tumors would further improve outcomes is an important area for further study, but treatment should not be deferred solely on the basis of age.

Breast cancer is known to affect older women disproportionately. It is estimated that by 2050, approximately 20 % of adults in the United States will be 65 years of age or older and 20 % of those will be at least 85 years old.¹ As the population continues to age, the number of elderly women with invasive cancer will continue to increase, particularly among octogenarians.² Prospective data to guide treatment in this group are lacking. Patients in this age group are consistently underrepresented in clinical trials, comprising only 7–10 % of the participants in cooperative group trials.^{1,3,4}

Age is suggested to be an independent risk factor for not receiving effective cancer therapies.^{1,5–7} In many practice settings, the literature indicates that older women with breast cancer are undertreated, with a corresponding increase in mortality.^{6,8–11} The reasons for this pattern are complex, attributable to a multifaceted interplay of patient, physician, and medical system factors.

We performed a retrospective cohort study of treatment patterns among this understudied group during the past decade. We sought to compare clinical and pathologic disease characteristics, therapies recommended and received, and subsequent outcomes between women 80–89 years of age with early-stage breast cancer and a younger cohort of women ages 50–59 years.

METHODS

Patient Cohort

After institutional review board approval, we conducted a retrospective cohort study of women ages 80–89 years and 50–59 years who were referred for surgical evaluation of biopsy-proven early-stage (stage 1 or 2) invasive breast cancer from January 2001 to December 2010 at our institution. We included all women ages 80–89 years who met our inclusion criteria and selected every fifth woman from the larger cohort of younger women obtained from our Tumor Registry database. We excluded women with incomplete medical records, those who received neoadjuvant chemotherapy, those presenting with bilateral breast cancers, and those with a personal history of breast cancer.

Variables Studied

From the medical record, we abstracted standard clinicopathologic data, comorbidities, treatment offered (surgery, radiotherapy, chemotherapy, and endocrine therapy) and treatment received, patient and physician preferences, and Eastern Cooperative Oncology Group (ECOG) functional status affecting clinical decision making. The primary outcomes

of interest were the incidence of locoregional and distant recurrence and disease-free survival. The secondary outcomes were treatment offered, treatment received, and whether women received the standard of care with nodal staging, post-lumpectomy radiotherapy, and endocrine therapy for estrogen receptor-positive (ER+) disease.

Statistical Analysis

Descriptive data are presented as median (interquartile range) or proportion. We compared the elderly and younger groups with the Wilcoxon rank-sum, Fisher's exact, or Chi square tests. We used the Kaplan–Meier estimator to compute the survival function for disease-free survival, defined as no locoregional recurrence, no distant metastasis, and no death from breast cancer, and compared survival curves for the elderly and younger groups using the log-rank test. The same approach was used for overall survival. We also used a competing risk regression model¹² to compare disease-free survival between the two groups, considering death from a cause other than breast cancer as a competing risk. The Pepe-Mori test was used to compare these curves between the elderly and younger women. All tests were two-sided, and *p* values lower than 0.05 were considered statistically significant. Statistical analysis was performed with SAS 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

From January 2001 to December 2010, we identified 257 potentially eligible women ages 80–89 years and 281 potentially eligible women ages 50–59 years. After applying the exclusion criteria, we had 178 women (69.3 %) in the elderly group and 169 women (60.1 %) in the younger group. The ECOG status differed between the groups. A higher proportion of the elderly women had an ECOG status of 2 or more at diagnosis, and the majority of the younger women had an ECOG status of 0 (*p* < 0.01).

The frequency of palpable tumors was similar in the two groups (*p* = 0.41), but disease was discovered more frequently on the screening mammogram of the elderly women, although this difference was not statistically significant (*p* = 0.29). All the women underwent a mammogram at the time of diagnosis, and nearly all the women had an ultrasound. Although used infrequently overall, magnetic resonance imaging was less often used for the elderly women (2.8 %) than for the younger women (14.2 %; *p* < 0.001). Although the groups had a similar majority of patients with invasive ductal carcinoma, the elderly had a higher prevalence of lobular histology, and the younger women had a more mixed histology.

Tumors were similar in size between the two groups, but the elderly women more often had grade 1 or 2 disease (*p* = 0.003), were more likely to have ER+ status (*p* = 0.007), and less frequently displayed lymphovascular invasion (*p* = 0.03). Table 1 summarizes the clinicopathologic disease features in the elderly and younger cohorts of women.

In all cases, both patient preference and physician recommendation were documented in the medical record. All adjuvant therapies were recommended less frequently to the elderly patients (all *p* < 0.005) and consequently were received less frequently (all *p* < 0.001). Surgery was offered and received by all young patients, and nearly all the elderly patients. Lumpectomy was performed more frequently for the elderly, whereas mastectomy was more

commonly performed for the younger women ($p = 0.02$). Among those who had a mastectomy, only one elderly woman (7.1 %) had reconstruction compared with half of the younger women ($p = 0.006$). The need to perform reexcision for positive or close margins was similar between the two groups ($p = 0.14$). Although axillary surgery was performed less frequently for the elderly (46.3 %) than for the younger women (95.9 %; $p < 0.001$), when performed, use of sentinel lymph node biopsy was similar ($p = 0.85$). Among the women who underwent lumpectomy, significantly fewer elderly women received radiotherapy (42.2 %) than younger women (89.4 %; $p < 0.001$). The elderly women with ER+ tumors were less likely to receive endocrine therapy (72 %) than the younger women (95 %; $p < 0.001$). Overall, the elderly women were less likely to receive all the applicable standard-of-care treatments (39.9 %) than the younger women (60.1 %; $p < 0.001$). Table 2 summarizes the treatment methods recommended and received, as well as the operative details.

The median follow-up period for the full cohort was 73.1 months (range 49.0–107.8 months), with a significantly shorter follow-up period for the elderly than for the younger group ($p < 0.001$). The incidence of locoregional recurrence was similar among the elderly (3.9 %) and younger (3.6 %) groups ($p = 0.85$), as was the incidence of distant metastasis (6.2 and 7.7 %, respectively; $p = 0.58$). Likewise, the time to locoregional recurrence and distant metastasis did not differ between the two groups. In the comparison of the elderly women with the younger women, the rates of locoregional recurrence varied respectively by local therapies received as follows: 3 % for both age groups receiving lumpectomy with radiotherapy, 4 versus 13 % for the patients receiving lumpectomy alone, 0 % for both age groups receiving mastectomy with radiotherapy, and 10 versus 0 % for the women receiving mastectomy alone. Concerning the 14 recurrences in the elderly group, 1 patient (7.1 %) did not have axillary staging surgery, 7 patients (50 %) did not have post-lumpectomy radiotherapy, and 4 patients (28.6 %) did not have endocrine therapy for ER+ tumors. The outcomes are shown in Table 3.

Disease-free survival did not differ between the elderly and younger groups ($p = 0.36$, log-rank; Fig. 1). Although more elderly women died of causes other than breast cancer (31.5 % vs. 7.1 %), the competing risk analysis for disease-free survival did not demonstrate a difference (figure not shown; $p = 0.65$). However, overall survival differed between the two groups ($p < 0.001$, log-rank), with worse survival in the elderly group (Fig. 2).

DISCUSSION

This study found similar breast cancer survivorship among octogenarians and younger women, despite the fact that elderly women less frequently undergo nodal staging surgery or receive all adjuvant therapies, including standard post-lumpectomy radiotherapy and endocrine therapy for ER+ tumors. The similarity in outcomes likely was a consequence of the observed favorable tumor biology in the elderly. Interestingly, the majority of the elderly women also were in a relatively independent and functional state of health, as estimated by ECOG status at diagnosis, with potential to have tolerated and further benefited from standard adjuvant therapies.

As the population of elderly women with breast cancer continues to grow, the application of an unbiased treatment algorithm is becoming increasingly important. Elderly patients are more likely to be undertreated based on the assumption that the toxicities of treatment will be poorly tolerated. This perceived age-related increase in frailty also may account for the underrepresentation of elderly patients in clinical trials and may be worth reevaluating.^{4,8} Although individual patient comorbidities certainly must be considered, with the risks and benefits of certain therapies weighed carefully, the ever-increasing life expectancy in this age group may be underestimated by providers. According to recent U.S. life tables, an 80-year-old woman is expected to live a median of 8.6 years, with a wide interquartile range of 4.6–13 years.¹³

In our study, 60 % of the elderly women had an ECOG status of 0 or 1 at diagnosis, reflecting an independent and ambulatory functional status. Yet, adjuvant therapies were received by a smaller fraction of this cohort. In the majority of cases, the patient choices for adjuvant therapies were consistent with the documented physician preference, emphasizing the significant impact of physician recommendation on patient decisions. The elderly women in our study had lower-risk disease features than the younger women, with a higher frequency of low-grade and ER + disease and a lower frequency of lymphovascular invasion. These features are consistent with the favorable tumor biology reported for patients older than 65 years.^{14–16} Similar findings of less frequent nodal evaluation, chemotherapy, post-lumpectomy radiotherapy, and endocrine therapy for ER+ tumors also have been observed in multiple retrospective studies investigating patients 70 years of age or older¹⁷ as well as comparable cohorts 80 years of age or older with early-stage disease.^{15,16,18}

Although nearly all the women in this study underwent a breast operation, less than half of the elderly women had nodal staging, typically a standard element of surgical therapy. The presence of axillary metastases is a key prognostic factor, and in the contemporary era, landmark trials have established sentinel lymph node biopsy as the accepted standard for initial nodal staging.^{19–22} Sentinel lymph node biopsy allows identification of patients with axillary metastases who may specifically benefit from adjuvant radiotherapy and systemic therapies. However, our data corroborate previous observations that this step is omitted for the majority of elderly patients,^{15,16,18} resulting in potential withholding of adjuvant therapies for patients who would have met the indications. Only 2 % of the elderly patients in our study received chemotherapy, consistent with the reported underuse or use of non-guideline chemotherapy for older patients.^{8,23} Although a lack of nodal staging information contributes to this underuse, the aforementioned perception of poor tolerance of chemotherapy-associated toxicities and the assumed low benefit also may be significant reasons for omission of chemotherapy.^{1,4} Pooled data suggest that reasonably healthy elderly patients may in fact benefit from chemotherapy as much as younger patients.¹ In a large study of 23,110 node-positive and 31,572 node-negative women ages 65–74 years with stages 1–3 cancer, significantly lower mortality in both the node-positive and node-negative women was observed with the use of chemotherapy.²⁴

Although the toxicities of chemotherapy may certainly require this particular method to be omitted for less healthy patients, post-lumpectomy radiotherapy and endocrine therapy are generally well tolerated. As expected, these methods were used more frequently than

chemotherapy in our study, with 42 % of the elderly patients receiving post-lumpectomy radiotherapy and 72 % receiving endocrine therapy in cases of ER + disease. However, these proportions remained low despite being the standard of care, and were significantly lower than the observed rates in the younger cohort of patients.

Two randomized controlled trials have shown significantly lower rates of locoregional recurrence among elderly women with the use of post-lumpectomy radiotherapy.^{25–27} Notably, the patients in these trials were receiving concurrent endocrine therapy. The CALBG 9343 study of patients 70 years of age or older with stage 1 and ER + disease treated with tamoxifen showed that post-lumpectomy radiotherapy reduced both the rate of locoregional recurrence and the time to recurrence but had no overall survival benefit.²⁶ A recent prospective trial of an analogous population found a similar reduction in locoregional recurrence with post-lumpectomy radiotherapy among patients with tumor 2–5 cm in size (pathologic T2).²⁸

Given the propensity of elderly women to have ER+ tumors, the value of endocrine therapy for this cohort should be recognized and optimized. A consensus from prospective trials demonstrates that elderly women with hormone receptor-positive cancers benefit from endocrine therapy.¹ Data from the Early Breast Cancer Trialists' Collaborative Group demonstrated significant benefits in terms of survival and recurrence with the use of tamoxifen, showing that among women older than 70 years, the ratio of annual events for treated patients versus control subjects was 0.49.²⁹ In a study of 504 women ages 65 years or older with early-stage ER+ disease undergoing lumpectomy and radiotherapy, Murphy et al.³⁰ found that endocrine therapy nonadherence was predictive of distant metastasis and lower disease-free survival.

This study provided long-term follow-up evaluation of patients treated during a decade and offers insight into decision making by both the patients and the physicians.

The limitations of our study included the retrospective nature of review and the relatively small sample sizes. However, the reported trends continue to raise the possibility that the use of applicable adjuvant therapies may yet further improve outcomes for elderly women, and this remains an important area for further study.

During a median follow-up period of 6 years, the incidence of recurrence and the time to recurrence among the elderly women in our study were similar to those for the younger women, despite more favorable disease features and undertreatment by all methods among the elderly. Although consideration of individual patient comorbidities is important in making optimal treatment choices, it also is important to recognize that many elderly patients in good health may tolerate surgery and adjuvant therapies well and that standard treatments should not be deferred solely on the basis of age. Individual assessment of patient comorbidities, discussion of risks and benefits of standard adjuvant therapies, and a clear dialogue between patients and physicians are essential in formulating optimal breast cancer treatment plans for the elderly.

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FIG. 1.
Disease-free survival stratified by age

FIG. 2.
Overall survival stratified by age

TABLE 1

Clinicopathologic characteristics

	Ages 80–89 years (<i>n</i> = 178) <i>n</i> (%)	Ages 50–59 years (<i>n</i> = 169) <i>n</i> (%)	<i>P</i> Value
Median age at diagnosis: years (IQR)	83 (81–85)	55 (52–57)	<0.001
ECOG status at diagnosis			<0.001
0	29 (16.3)	131 (77.5)	
1	78 (43.8)	33 (19.5)	
2	54 (30.3)	4 (2.4)	
3	13 (7.3)	0 (0)	
4	4 (2.2)	0 (0)	
Missing	0 (0.0)	1 (0.6)	
Palpable tumor			0.41
Yes	63 (35.4)	67 (39.6)	
No	115 (64.6)	102 (60.4)	
Mammogram performed			–
Yes	178 (100.0)	169 (100.0)	
No	0 (0.0)	0 (0.0)	
Tumor found on screening mammogram			0.29
Yes	111 (62.4)	96 (56.8)	
No	67 (37.6)	73 (43.2)	
Ultrasound performed			0.16
Yes	176 (98.9)	133 (96.4)	
No	3 (1.1)	6 (3.6)	
MRI performed			<0.001
Yes	5 (2.8)	24 (14.2)	
No	173 (97.2)	145 (85.8)	
Core biopsy performed			<0.001
Yes	170 (95.5)	137 (81.1)	
No	8 (4.5)	32 (18.9)	
Tumor characteristics ^a	(<i>n</i> = 175)	(<i>n</i> = 169)	
Histology			0.01
Ductal	137 (77.0)	132 (78.1)	
Lobular	29 (16.3)	16 (9.5)	
Mixed/other	3 (5.1)	21 (12.4)	
Missing	3 (1.7)	0 (0.0)	
Grade			0.003
1 and 2	147 (84.0)	118 (69.8)	
3	27 (15.4)	51 (31.2)	
Missing	1 (0.6)	0 (0.0)	
Receptor status			0.002
ER+/HER2+	10 (5.7)	23 (13.6)	
ER+/HER2–	150 (85.7)	116 (68.6)	

	Ages 80–89 years (<i>n</i> = 178) <i>n</i> (%)	Ages 50–59 years (<i>n</i> = 169) <i>n</i> (%)	<i>P</i> Value
ER–/HER2+	6 (3.4)	10 (5.9)	0.007
ER–/HER2–	8 (4.6)	20 (11.8)	
Missing	1 (0.6)	0 (0.0)	
ER tumors			0.007
Positive	161 (92.0)	139 (82.2)	
Negative	14 (8.0)	30 (17.8)	
Median pathologic tumor size: mm (IQR) ^a	14.0 (9.0–23.0)	14.0 (9.0–20.0)	0.58
Lymphovascular invasion			0.03
Positive	24 (13.7)	41 (24.3)	
Negative	150 (85.7)	128 (75.7)	
Missing	1 (0.6)	0 (0.0)	

IQR interquartile range, *ECOG* Eastern Cooperative Oncology Group, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2

^aSurgery was not performed for 3 women ages 80–89 years

TABLE 2

Treatment methods offered and received

	Ages 80–89 years (n = 178) n (%)	Ages 50–59 years (n = 169) n (%)	p Value
<i>Treatment offered</i>			
Surgery	176 (98.9)	169 (100.0)	0.50
Radiotherapy	91 (51.1)	136 (80.5)	<0.001
Chemotherapy	9 (5.1)	111 (65.7)	<0.001
Endocrine	122 (68.5)	138 (81.7)	0.005
Combination therapy	140 (78.7)	166 (98.2)	<0.001
<i>Treatment received</i>			
Surgery	175 (98.3)	169 (100.0)	0.25
Radiotherapy	72 (40.4)	131 (77.5)	<0.001
Chemotherapy	4 (2.2)	102 (60.4)	<0.001
Endocrine	105 (59.0)	132 (78.1)	<0.001
Combination Therapy	129 (72.5)	165 (97.6)	<0.001
<i>Surgical treatment</i>			
	(n = 175)	(n = 169)	
Type of breast surgery performed			0.02
Lumpectomy	161 (92.0)	141 (83.4)	
Mastectomy	14 (8.0)	28 (16.6)	
Reconstruction after mastectomy	1 (7.1)	14 (50.0)	0.006
Reexcision for positive margins	56 (32.0)	67 (39.6)	0.14
Axillary surgery performed			<0.001
Yes	81 (46.3)	162 (95.9)	
Sentinel lymph node biopsy	47 (58.0)	92 (56.8)	0.85
Axillary lymph node dissection	34 (42.0)	70 (43.2)	
No	94 (53.7)	7 (4.1)	
<i>Standard of care provided^a</i>			
	(n = 178)	(n = 169)	
Yes	71 (39.9)	161 (95.3)	<0.001
No	107 (60.1)	8 (4.7)	

^aDefined as nodal staging and receipt of post-lumpectomy radiotherapy and/or endocrine therapy for estrogen receptor-positive (ER+) tumors, as applicable

TABLE 3**Outcomes**

	Ages 80–89 years (<i>n</i> = 178) <i>n</i> (%)	Ages 50–59 years (<i>n</i> = 169) <i>n</i> (%)	<i>p</i> Value
Median follow-up period: months (IQR)	55.6 (38.9–75.3)	98.2 (71.9–123.1)	<0.001
Locoregional recurrence	7 (3.9)	6 (3.6)	0.85
Median time to locoregional recurrence: months (IQR)	24.6 (21.3–60.0)	125.4 (16.1–145.5)	0.25
Distant metastasis	11 (6.2)	13 (7.7)	0.58
Median time to distant metastasis: months (IQR)	40.4 (11.6–47.5)	41.2 (24.1–56.0)	0.36
Vital status			
Alive without evidence of disease	111 (62.4)	140 (82.8)	<0.001
Alive with disease	4 (2.2)	8 (4.7)	0.21
Died of breast cancer	7 (3.9)	9 (5.3)	0.54
Died of other/unknown cause	56 (31.5)	12 (7.1)	<0.001

IQR interquartile range