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Treatment Strategies in Octogenarians with Early-Stage, High-Risk Breast Cancer

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Abstract

Background—Octogenarians with early-stage breast cancer often have low-risk tumor biology. However, optimal treatment strategies for those with high-risk biology remain unclear.

Methods—We reviewed the records of women ages 80–89 years with biopsy-proven, Stage I–II invasive breast cancer who were referred for surgical evaluation from January 2001 through December 2010. High-risk was defined as human epidermal growth factor receptor-positive (HER2+), triple-negative (TN), or histologic grade 3 disease.

Results—Among 178 patients, 40 (22%) were high-risk: 12 were grade 1–2 (10 HER2+, 2 TN); 28 were grade 3 (7 HER2+, 6 TN, 15 estrogen receptor-positive (ER+)/HER2–). The high-risk group had larger tumors and more often had ductal histology and lymphovascular invasion than the low-risk group and was more likely to undergo mastectomy (18 vs. 5%, $p = 0.02$), radiotherapy (55 vs. 36%, $p = 0.03$), and chemotherapy (10 vs. 0%, $p = 0.002$). Endocrine therapy use was similar among ER+ patients in both groups. The four patients in the high-risk group given chemotherapy were HER2+ and received trastuzumab-based regimens, without any reported toxicities. At median follow-up of 67 months, 10% of the high-risk group had a recurrence (3 distant-only, 1 simultaneous locoregional and distant in a patient treated with mastectomy without radiotherapy).

Conclusions—Tailored locoregional and systemic therapy resulted in low incidence of failure in these octogenarians with high-risk cancers with low morbidity. Modern adjuvant therapies should

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be considered for elderly women with high-risk cancers in the absence of significant comorbidities.

As the population ages, the number of elderly women with invasive breast cancer will continue to rise, particularly among octogenarians.¹ The majority of cancers in the elderly are low-grade and estrogen receptor (ER)-positive, consistent with relatively favorable tumor biology.^{2–5} This phenomenon likely accounts for the non-inferior disease survivorship that has been observed among octogenarians, despite less frequent use of standard adjuvant therapies.⁴

Elderly patients are underrepresented in clinical trials, comprising fewer than 10% of the participants in cooperative group trials.⁶ Prospective data to guide their treatment are limited, particularly in the high-risk subset. Thus, optimal treatment strategies among the minority of octogenarians with high-risk disease remain unclear.

We therefore performed a retrospective cohort study of treatment patterns and outcomes to evaluate clinicopathologic disease characteristics, therapies recommended and received, and outcomes among octogenarians with high-risk disease features, compared with those with lower-risk disease. Our results may help improve results for these patients.

METHODS

Patient Cohort

This study analyzed a subset of patients from a previously published study from this institution.⁴ We conducted a retrospective cohort study of women ages 80–89 years who were referred for surgical evaluation of biopsy-proven early stage (stage I or II) invasive breast cancer from January 2001 to December 2010. We excluded women with incomplete medical records, those who received neoadjuvant therapy, those presenting with bilateral breast cancers, and those with a personal history of breast cancer. Our institutional review board approved this study.

Variables Studied

We reviewed medical records and 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 scores. High-risk disease was defined as having a tumor that was human epidermal growth factor receptor 2-positive (HER2+), had a triple-negative (TN) receptor phenotype, or was histologic grade 3 disease. The primary outcomes of interest were the incidence of locoregional and distant recurrence. Secondary outcomes of interest were treatments received and complications from these therapies.

Statistical Analysis

Descriptive data are presented as median (interquartile range) or proportion. We compared the high-risk and low-risk 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. We compared survival curves for the high-risk and low-risk groups using the log-rank test. All tests were two-sided, and p values less than 0.05 were considered statistically significant. Statistical analysis was performed with SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

We identified 178 women who met eligibility criteria. Of these patients, 40 (22.5%) had high-risk disease features: 12 had grade 1–2 cancers (10 HER2+, 2 TN), whereas 28 had grade 3 cancers (7 HER2+, 6 TN, 15 ER+/HER2–). Table 1 summarizes the clinicopathologic characteristics of the high-risk and low-risk groups. Patients with high-risk disease had larger tumors and more frequently had lymphovascular invasion than patients with low-risk disease (both $p < 0.002$). The frequency of palpable tumors was similar in the two groups ($p = 0.49$); the disease was discovered more frequently on screening mammograms among the low-risk group, though this difference was not statistically significant ($p = 0.28$). All women underwent mammograms at diagnosis, and nearly all women (98.9%) had an ultrasound.

Surgery was deferred in three patients, all of whom were in the low-risk group. All of these patients had significant cardiopulmonary comorbidities rendering them poor surgical candidates. Women in the high-risk group were more likely to have a mastectomy (17.5 vs. 5.0%, $p = 0.02$) and more frequently had radiotherapy (55.0%) compared with the low-risk group (36.2%, $p = 0.03$). Axillary management was similar between the two groups; 50% of high-risk versus 45% of low risk women ($p = 0.36$) underwent axillary surgery (Table 2). Nodal burden was low among high-risk patients who had axillary surgery; positive lymph nodes were found in only 5 of 20 (25%) patients with a median of 1 positive node (range 1–8). Among the 22 high-risk patients who had radiotherapy, 5 (22.7%) had comprehensive nodal irradiation in addition to breast or chest wall irradiation. The high-risk group also was more likely to receive chemotherapy (10.0%) than the low-risk group (0%; $p = 0.002$). Among patients with ER + tumors, the proportion that received endocrine therapy was similar in the low-risk (62.2%) and high-risk (70.4%) groups ($p = 0.42$). All of the four high-risk patients who received chemotherapy were HER2+ and were treated after 2007 with a trastuzumab-based regimen. All of these patients had an ECOG status of 1, with no major preexisting cardiopulmonary or other comorbidities. Two (50.0%) had T1 tumors, whereas the remaining two (50.0%) had T2 tumors. There were no reported early (within 1 month) or late (after 1 month) complications related to chemotherapy. Details of complications from surgery, radiotherapy, or endocrine therapy were not consistently available for analysis. Details of locoregional and systemic therapy received are summarized in Table 2.

The median follow-up period for the entire cohort was 69.2 (interquartile range 45.7–89.8) months and was similar between the groups ($p = 0.12$). There was no statistically significant difference in the incidence of disease recurrence between high-risk and low-risk patients ($p = 0.86$) or in the time to recurrence ($p = 0.50$). The incidence of locoregional recurrence was 2.5% in the high-risk group and 4.3% in the low-risk group, while the incidence of distant metastasis was 10.0 and 7.2%, respectively. Among the four patients in the high-risk group with any disease recurrence, three were distant-only, and one was simultaneous (within 1

month) locoregional (chest wall) and distant in a patient treated with mastectomy without radiotherapy; none of these four patients had received chemotherapy. The median time to recurrence was 17.3 (interquartile range 7.8–62.4) months: three recurrences occurred within the first 2 years (1 TN, 1 HER2+, and 1 ER + HER2–/grade 3, respectively), and one recurrence (ER + HER2–/grade 3) was more than 9 years after initial diagnosis. Conversely, among the 12 patients in the low-risk group with disease recurrence, the median time to recurrence was 44.8 (interquartile range 23.0–69.0) months. When comparing high-risk and low-risk groups, there was no difference in disease free-survival ($p = 1.0$; Fig. 1a) or overall survival ($p = 0.66$; Fig. 1b). Outcomes are shown in Table 3.

DISCUSSION

In this contemporary population of octogenarians with early-stage breast cancers, women with high-risk disease features more frequently received more aggressive locoregional and systemic treatments compared with those with low-risk biology, but the overall utilization of these therapies was low. Tailored therapy was well tolerated with a low incidence of failure. Disease-specific outcomes were similar in both groups, with 10% of high-risk and 8.6% of low-risk patients experiencing disease recurrence, and 5% of patients in both groups experiencing death from breast cancer. Most women (90%) were in a relatively functional state of health (ECOG status 2 or lower at diagnosis) and therefore could arguably tolerate and derive benefit from standard adjuvant therapies.

Elderly women are known to be undertreated based on the perception of risk of treatment-related toxicities.⁴ It also is likely that providers underestimate life expectancy, with recent U.S. data indicating that an 80-year-old woman is expected to live a median of 8.6 years, with a wide interquartile range (4.6–13 years).⁶ This study provides insight into a growing population that is underrepresented in most clinical trials, with data being even further limited among the small minority of elderly women with high-risk disease biology.⁶

Surgery and adjuvant radiotherapy, when indicated, comprise the cornerstones of achieving locoregional control in early-stage breast cancer. Although nearly all of the women in this study underwent a breast operation, only half of high-risk patients had nodal staging. These findings corroborate previous observations that nodal surgery is frequently omitted in elderly patients.⁴ This may result in decreased regional control and potential withholding of adjuvant therapies in patients who might benefit from them if they were known to have axillary nodal involvement.

Omitting radiotherapy is considered appropriate for elderly women with stage I ER-positive tumors receiving endocrine therapy due to the absence of differences in distant metastasis or cancer-specific survival rates from the addition of radiotherapy in multiple randomized control trials, as long as patients consider the slightly higher local recurrence rates acceptable.^{7–12} However, the effects of omitting radiotherapy in elderly patients with ER-negative tumors are less well documented. In a study of patients older than age 70 years in Nottingham, England, 5 of 26 patients (20%) with ER-negative tumors had a local recurrence, with a median follow-up of 37 months in the entire series.¹³ In the randomized Ontario-British Columbia trial for women aged 50 years or older, the 35 patients with

luminal HER2, HER2-enriched, basal-like, and TN non-basal cancers treated with tamoxifen alone had a 10-year ipsilateral breast recurrence rate of 38% compared with 6% for the 36 patients receiving tamoxifen and radiation therapy.¹⁴ Even the degree of ER expression may be important. Local recurrence occurred in 6 of 65 unirradiated patients (9%) with “ER poor” tumors in the PRIME II trial compared with no recurrence in the 55 irradiated patients, with median follow-up of 5 years.¹² Such tumors were defined as having an Allred score of 6 or less, less than 20 fmol/mg protein, less than 50% cells staining, or less than “++” staining. Comparable results in patients with “ER-rich” tumors were 3% (20/593) and 1% (5/601), respectively.¹² In our study, it is notable that overall only 55.0% of high-risk patients received radiotherapy. A recent study of Surveillance, Epidemiology and End Results registry data which included 3432 women aged 70 or older with T1-T2N0 ER-negative cancers found that the use of adjuvant radiotherapy after breast-conserving surgery was associated with a reduced incidence of future mastectomy (analyzed as a surrogate for local recurrence), as well as breast cancer death.⁷

Reasons for omission of standard adjuvant chemotherapies for elderly patients include a presumption that it will be poorly tolerated and an assumption it will have little benefit.⁶ However, a retrospective review of 2640 patients who received anthracycline-containing adjuvant chemotherapy in three clinical trials from 1997 to 2008 found that women > 65 years of age derived a significant benefit in disease-free survival at a median follow-up of 10 years, comparable to that seen in younger patients, albeit with a somewhat increased risk of hematologic toxicity (32 vs. 21%, $p < 0.01$).¹⁵ Similar results were seen in a CALBG study including 633 women > 65 years, which randomized patients to CMF (cyclophosphamide, methotrexate and 5-fluorouracil) or cyclophosphamide plus doxorubicin versus capecitabine. This trial found a benefit from combination therapy.¹⁶ Although the toxicities of chemotherapy may certainly require omission of this modality for less healthy patients, the value of these treatments in appropriately selected patients without significant comorbidities must be acknowledged. The optimal chemotherapeutic regimen for this population remains unclear. Recent studies investigating chemotherapy regimens in patients > 65 years include the ICE (Ibandronate with or without Capecitabine in Elderly Patients with Early Breast Cancer) trial, which showed no difference in disease-free or overall survival between arms, and the ELDA (Elderly Docetaxel Adjuvant) trial, which found no difference in disease-free or overall survival comparing CMF to weekly docetaxel but more toxicities in the docetaxel arm.^{17,18}

A number of landmark trials have demonstrated a clear improvement in both disease-free and overall survival in patients with early-stage HER2+ breast cancer receiving chemotherapy including trastuzumab, compared to chemotherapy alone, with a systematic review finding a 47% relative risk reduction for recurrence in participants older than age 60 years, a similar magnitude as for younger participants.^{19,20} Multiple studies having shown advanced age and preexisting heart disease to be risk factors for cardiotoxicity.^{19,21} However, increasing age was not associated with cardiotoxicity in the HERA trial, potentially attributable to individual tailoring of chemotherapy to age and comorbidities.²² In our study, all patients who received chemotherapy were HER2+ and received either trastuzumab alone or paclitaxel and trastuzumab. Although limited by a small sample size, we observed no chemotherapy-related toxicities in these patients, who all remain without

recurrence to date. Other limitations of this study include inability to analyze the impact of pre-operative clinical nodal staging on decision-making for axillary management, radiotherapy, and systemic therapy, due to variable documentation. Additionally, this study excluded patients who received neoadjuvant therapy, as the number of patients treated was exceedingly small. However, particularly with the growth of modern targeted systemic therapies, outcomes among high-risk patients treated with this approach are an important area of further investigation.

Further research is required to better define the overall tolerability and outcomes of various treatment regimens in elderly patients, particularly among the subset with more aggressive biology. Awaited ongoing studies include the ASTER 70s multicenter trial, which is evaluating the impact of adjuvant chemotherapy on survival in women > 70 years with high risk of relapse and the Japanese RESPECT trial, which is comparing monotherapy trastuzumab with trastuzumab given in combination with chemotherapy in patients > 70 years with HER2+ early-stage cancer.

CONCLUSIONS

Treatment strategies for the minority of octogenarian patients with high-risk (TN, HER2-positive, and high-grade) cancers are understudied. Although we observed more frequent use of adjuvant therapies in high-risk compared to low-risk patients, the overall utilization of these therapies was low. We found a low morbidity and low incidence of failure in octogenarians with high-risk cancers who received tailored locoregional and systemic therapies. Modern adjuvant therapies should be used to reduce the risk of relapse and cancer death for elderly women with high-risk breast cancer when not limited by significant comorbidities.

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FIG. 1.
a Disease-free survival.
b Overall survival

TABLE 1

Clinicopathologic characteristics

Characteristic	High-risk <i>n</i> = 40	Low-risk <i>n</i> = 138	<i>p</i>
<i>Patient characteristics</i>			
Age at diagnosis, year	83.0 (80.0–86.0)	83.0 (81.0–85.0)	0.88
ECOG status at diagnosis			0.40
0	4 (10.0)	25 (18.1)	
1	19 (47.5)	59 (42.8)	
2	15 (37.5)	39 (28.3)	
3	1 (2.5)	12 (8.7)	
4	1 (2.5)	3 (2.2)	
Ethnicity			0.006
Caucasian	34 (85.0)	130 (94.2)	
Hispanic	3 (7.5)	1 (0.7)	
African American	0 (0)	6 (4.3)	
Asian	3 (7.5)	1 (0.7)	
Palpable tumor	16 (40.0)	47 (34.1)	0.49
Mammogram performed	40 (100.0)	138 (100.0)	–
Tumor found on screening mammogram	22 (55.0)	89 (64.5)	0.28
Ultrasound performed	40 (100.0)	136 (98.6)	1.0
Magnetic resonance imaging performed	2 (5.0)	3 (2.2)	0.31
Core biopsy performed	40 (100.0)	130 (94.2)	0.20
<i>Tumor characteristics</i>			
Pathologic tumor size, mm	19.0 (13.5–26.0)	13.0 (8.0–22.0)	0.002
Histology			0.09
Ductal	37 (92.5)	106 (76.8)	
Lobular	3 (7.5)	26 (18.8)	
Other	0 (0)	6 (4.3)	
Histologic grade ^a			< 0.0001
1	0 (0)	61 (45.5)	
2	12 (30.0)	73 (54.5)	
3	28 (70.0)	0 (0)	
Lymphovascular invasion ^a	12 (30.0)	12 (8.9)	0.0007

Data presented as median (interquartile range) and *n* (%)

ECOG Eastern Cooperative Oncology Group

^aGrade unavailable for four cases in the low-risk group, and lymphovascular invasion unavailable for three cases in the low-risk group

TABLE 2

Locoregional and systemic medical treatments received

Characteristic	High-risk <i>n</i> = 40	Low-risk <i>n</i> = 138	<i>p</i>
<i>Locoregional treatment</i>			
Local treatment			0.009
None	0 (0)	3 (2.2)	
Lumpectomy alone	13 (32.5)	80 (58.0)	
Lumpectomy + radiotherapy	20 (50.0)	48 (34.8)	
Mastectomy alone	5 (12.5)	5 (3.6)	
Mastectomy + radiotherapy	2 (5.0)	2 (1.4)	
Axillary treatment			0.36
None	17 (42.5)	53 (38.4)	
SLNB (± radiotherapy)	10 (25.0)	39 (28.3)	
ALND (± radiotherapy)	10 (25.0)	23 (16.7)	
Nodal radiotherapy, no surgery	3 (7.5)	23 (16.7)	
<i>Adjuvant medical treatment</i>			
Chemotherapy and endocrine therapy	1 (2.5)	0 (0)	0.002
Chemotherapy only	3 (7.5)	0 (0)	
Endocrine therapy only	18 (45.0)	86 (62.3)	
None	18 (45.0)	52 (37.7)	

Data are presented as n (%)

SLNB sentinel lymph node biopsy; *ALND* axillary lymph node dissection

TABLE 3**Outcomes**

	High-risk <i>n</i> = 40	Low-risk <i>n</i> = 138	<i>p</i>
Follow-up, months	67.1 (35.2–82.2)	69.4 (46.5–95.7)	0.12
Time to recurrence, months	17.3 (7.8–62.4)	44.8 (23.0–69.0)	0.50
Disease recurrence			0.86
None	36 (90.0)	126 (91.3)	
Locoregional only	0 (0.0)	2 (1.4)	
Distant only	3 (7.5)	6 (4.3)	
Locoregional and distant	1 (2.5)	4 (2.9)	
Vital status			0.27
Alive without evidence of disease	28 (70.0)	86 (62.3)	
Alive with disease	2 (5.0)	2 (1.4)	
Died of breast cancer	2 (5.0)	7 (5.1)	
Died of other/unknown cause	8 (20.0)	43 (31.2)	

Data presented as median (interquartile range) and *n* (%)