Breast cancer treatment in the elderly: Do treatment plans that do not conform to NCCN recommendations lead to worse outcomes?

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ABSTRACT

Background: Aging remains one of the greatest risk factors for development of new breast cancer with more than 30% of breast cancers occurring after the age of 75. Elderly women have been found to not conform with all aspects of treatment recommendations. Our study compared outcomes of elderly breast cancer patients whose treatment did or did not conform to NCCN guidelines.
Methods: A retrospective review was conducted of breast cancer patients over the age of 70. Comparisons were made between patients whose treatment did or did not conform to NCCN guidelines for recurrence, metastatic disease, and breast cancer related deaths.
Results: Patients whose treatment did not conform to NCCN guidelines were older (80.5 vs. 77.7 years, $P = 0.001$). No significant difference was seen between groups for tumor size, breast cancer type, or nodal status; however, more nonconforming women were ER/PR positive (90.3% vs. 76.6%, $P = 0.020$). There was no significant difference in local recurrence, metastatic disease, or breast cancer related deaths.
Conclusions: Women whose treatment did not conform to NCCN guidelines were not associated with worse outcomes.

Introduction

Aging remains one of the single greatest risk factors for the development of new onset breast cancer, with approximately one-half of all cases of new onset breast cancer occurring in women older than 65 years of age, and more than 30% occurring after the age of 75.[1,2] Elderly patients with breast cancer often present with similar disease characteristics as their younger counterparts. In addition, the cancer stage at diagnosis is typically comparable to those in younger women, although some studies have shown elderly women to have advanced disease at the time of presentation.[2] Breast cancer research in the elderly has generally been lacking, and until recently, women over the age of 70 have largely been excluded from breast cancer trials. It was assumed in the past that older cancer patients were unlikely to survive for a sufficient length of time to allow for local or systemic recurrence. However,

research has since shown that most breast cancer octogenarians survive greater than six years following their cancer diagnosis with the 5-year survival rate for women 70–79 years of age noted to be 82.4%, and those 80 years and older noted to be 74%.[3,4]

Studies have also shown that in spite of favorable prognostic factors such as low-grade tumor types, lower incidence of axillary lymph node involvement and vascular invasion, estrogen receptor-positive disease, and less aggressive tumor biology, elderly breast cancer patients often receive less than the standard-of-care when compared to their younger counterparts.[1,5] Reasons for under treatment of elderly women may be multifactorial, with physicians limiting treatment for elderly patients secondary to comorbidities and life expectancy. According to Hamaker et al.,[6] physicians did not recommend therapy because of older age in 14% and comorbidities in 11%, but 31% of treatment omissions were as a result of patient preference.

Recent research has shown that elderly women who underwent lumpectomies were noncompliant with radiation and hormonal therapy, with noncompliance being even higher in women aged 80 years and older.[7]

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There is a paucity of research evaluating how nonconformity to National Comprehensive Cancer Network (NCCN guidelines) affects outcomes in elderly breast cancer patients. The purpose of this study was to assess whether nonconformity to NCCN treatment guidelines in elderly patients has a negative impact with regards to local recurrence, metastatic disease, and disease-specific survival, compared to patients whose treatment conformed to NCCN guidelines.

Methods

This study was approved for implementation by the Institutional Review Board of Ascension Via Christi Hospitals Wichita, Inc. A retrospective chart review was conducted on women 70 years and older, who underwent treatment for newly diagnosed breast cancer between September 1, 2006 and July 31, 2013. The data was obtained from a single surgeon's practice and included: age at diagnosis, comorbidities, tumor characteristics, nodal status, treatment received (surgery, hormonal therapy, and/or radiation therapy), and whether treatment received conformed to NCCN treatment guidelines.

Patients were stratified into 2 groups; those whose treatment conformed to NCCN treatment guidelines (conforming) and those whose treatment did not conform to NCCN treatment guidelines (nonconforming). The NCCN guidelines were used to determine whether patients met the standard-of-care. According to the NCCN guidelines,[8] it is considered standard-of-care to radiate patients undergoing mastectomy who have greater than 5-cm tumors or who have four or more involved lymph nodes, although there are options to radiate smaller tumors with one to three positive lymph nodes. It is also considered standard-of-care that elderly patients receive hormonal therapy (either trastuzumab or an aromatase inhibitor) if they undergo a lumpectomy but can forego radiation. If elderly patients undergo a mastectomy, or lumpectomy with radiation, then the medical oncologist assesses risk versus benefits to decide whether the patient would receive hormonal therapy. Overall, the guidelines are straightforward, but have some flexibility so that the clinician may use patient characteristics to make appropriate decisions. Patients who did not meet NCCN guidelines were considered nonconforming, irrespective of whether the decision not to proceed with NCCN recommendations was patient or medical/radiation oncologist driven. The retrospective nature of data collection made it impossible to correctly determine whether treatment decisions were based on patient choices, physician recommendations, co-morbid conditions or a combination of these factors.

Conformity with NCCN treatment guidelines was determined overall, as well as for each treatment modality separately (surgery, radiation therapy, and hormonal therapy). Comparisons were then made between the conforming and nonconforming groups. Both groups were evaluated over several years (with a minimum of 5-year follow-up) for recurrence, metastatic disease, and breast cancer related deaths.

For patients who were deceased, we were able to obtain date and cause of death by utilizing the death database of the Kansas Department of Health and Environment (KDHE). This database provided death records for patients in the state of Kansas only.

Statistical analysis

Continuous data are reported as the mean ± standard deviation of the mean, and frequencies are reported for categorical data. Primary comparisons were made between the conforming and nonconforming groups. For analyses, comparisons of continuous and categorical data were conducted using t tests and Chi-square analysis, respectively. All statistical tests were two-sided, and analyses were considered significant when the resultant P value was ≤0.05. All analyses were conducted using SPSS release 19.0 (IBM Corp., Armonk, New York).

Results

Initial records review yielded a total of 186 women older than 70 years of age that were treated for breast cancer. Of those, 7 were excluded due to the presence of metastatic disease at the time of diagnosis, leaving 179 patients for study inclusion (conforming n = 107, and nonconforming n = 72). Nonconforming patients were older than their conforming counterparts by 2.6 years (80.5 vs. 77.7 years, P = 0.001; Table 1). No differences were observed with regard to comorbidities between study groups (Table 1). No significant difference was seen between conforming and nonconforming women with regards to tumor size, breast cancer type (DCIS or invasive), HER2 status, or nodal status; however, more nonconforming women were ER/PR positive (90.3% vs. 76.6%, P = 0.020; Table 2).

Both groups were examined with regards to nonconformity with surgery, radiation, hormonal, and chemo therapy recommendations (Table 3). In the conforming group, as per protocol, there was 100% conformity with NCCN treatment guidelines with regards to surgery, chemotherapy, and hormonal therapy. With regards to radiation therapy, 2 patients decided to forego treatment despite recommendations from the medical oncologist. However, they were considered conformant based on the NCCN guidelines. For the nonconforming group, patients were all nonconforming with chemotherapy, with none of the 6 patients undergoing treatment per recommendations. Similarly, nonconforming patients only conformed with radiation therapy guidelines 25.0% of the time, hormonal treatment guidelines 30.6% of the time, and surgical guidelines 81.7% of the time. A subset analysis of HER2 positive patients showed that only 11 of the 179 included patients were HER2 positive (6.1%). Of the 11 HER2 positive patients, 7 were also ER/PR positive and 4 were ER/PR negative. Three of the HER2 positive patients were nonconforming (ages 70, 77, and 88) to recommendations and the other 7 (ages 71, 75, 76, 77, 79, 80, and 86) conformed with NCCN guidelines receiving the recommended chemotherapy/trastuzumab regimen. As would be expected per protocol, nonconformity was statistically significant in all areas of treatment (Table 3) even though treatment recommendations were equivalent between groups for all adjuvant therapies except hormonal therapy.

In comparing outcomes, there was no significant difference in breast cancer local recurrence (2.8% vs. 1.4%, P = 0.650), metastatic disease (2.8% vs. 2.8%, P = 1.000), or breast cancer-related deaths (7.8% vs 10.1%, P = 0.595; Table 4) between conforming and nonconforming patients. All-cause mortality rates were significantly higher in the nonconforming patients (46.4% vs. 27.5%, P = 0.011). While all-cause mortality was significantly higher in the nonconforming group, significantly more of the women in the nonconforming group who died were also over the age of 80 as compared to the conforming group (84.4% vs. 60.7%, P = 0.039). This finding is also consistent with the fact that more women in the nonconforming group were over the age of 80, as was shown in Table 1. Some of the causes of death unrelated to breast cancer were respiratory failure due to end stage COPD, heart failure, failure to thrive due to dementia, and a more aggressive form of malignancy, which the patients had during the time of breast cancer diagnosis.

Comments

The incidence of breast cancer significantly increases with age,

Table 1
Comparison of age and comorbidities between patients who did or did not conform with NCCN breast cancer treatment guidelines.

Parameter	Conforming Number (%)	Nonconforming Number (%)	P-value
Number of subjects	107 (59.8%)	72 (40.2%)	–
Age (yrs)*	77.7 ± 5.4	80.5 ± 6.1	0.001
Age group			
70–79 yrs	68 (63.6%)	32 (44.4%)	0.012
≥ 80 yrs	39 (36.4%)	40 (55.6%)	
Comorbidities			
Hypertension	62 (57.9%)	39 (54.2%)	0.617
Hyperlipidemia	34 (31.8%)	23 (31.9%)	0.981
Thyroid Disease	18 (16.8%)	12 (16.7%)	0.978
Diabetes mellitus	16 (15.0%)	17 (23.6%)	0.143
Arrhythmias including atrial fibrillation	16 (15.0%)	10 (13.9%)	0.843
Depression	10 (9.3%)	7 (9.7%)	0.993
Coronary artery disease	8 (7.5%)	10 (13.9%)	0.162
COPD	7 (6.5%)	7 (9.7%)	0.437
Peptic ulcer disease	6 (5.6%)	2 (2.8%)	0.478
Dementia	5 (4.7%)	1 (1.4%)	0.404
Congestive heart failure	4 (3.7%)	5 (6.9%)	0.336
Anemia	4 (3.7%)	4 (5.6%)	0.716

Data presented as the mean ± SD.

and in recent years the average age of a woman with newly diagnosed breast cancer has risen to 62 years.[9] This data also shows that over 40% of breast cancers occur in women over the age of 65. While the average age at diagnosis has increased, survival is improving. According to SEER, the 5-year survival rate for breast cancer from 2009-2015[9] was 89.9%, compared to a 5-year survival rate of 87% from 2000 to 2013.[4] Despite an improvement in overall survival rates, elderly patients continue to have lower 5-year survival rates than their younger counterparts; 82.4% for women 70–79 years of age and 74% for those 80 years and older.[4] The difference in survival rates for the elderly is of importance. According to Tang et al.,[10] there is an overall increase in life expectancy due to improvements in medicine, and as a result of this, a 30% increase in the number of breast cancer cases is expected for the elderly in the next decade. Research concerning the best treatment for these women is essential.

The question in our study was to determine if lack of conformity to NCCN treatment guidelines in women over the age of 70 contributes to their lower survival rates. Nonconformity has been

Table 2
Comparison of disease characteristics between patients who did or did not conform with NCCS breast cancer treatment guidelines.

Parameter	Conforming Number (%)	Nonconforming Number (%)	P-value
Number of subjects	107 (59.8%)	72 (40.2%)	–
Tumor size (mm)[a]	11.0 (8–25)	13.0 (8–20)	0.796
Cancer type			0.079
DCIS	18 (16.8%)	20 (27.8%)	
Invasive cancer	89 (83.2%)	52 (72.2%)	
Receptor status			0.022
ER/PR +	82 (76.6%)	65 (90.3%)	
ER/PR -	25 (23.4%)	7 (9.7%)	
HER2[b]			0.558
Positive	7 (7.9%)	4 (7.7%)	
Negative	81 (91.0%)	46 (88.5%)	
Unknown/patient refused	1 (1.1%)	2 (3.8%)	
Nodal status			0.522
Node +	19/92 (20.7%)	6/38 (15.8%)	
Node -	73/92 (79.3%)	32/38 (84.2%)	

[a] Data presented as the median (IQR).
[b] Only patients with invasive cancer included.

Table 3
Comparison of recommended treatments and treatment conformity between patients who did or did not conform with NCCN breast cancer treatment guidelines.

Parameter	Conforming Number (%)	Nonconforming Number (%)	P-value
Number of subjects	107 (59.8%)	72 (40.2%)	–
Surgery recommended	107 (100%)	71 (98.6%)	0.402
Received surgery	107 (100%)	58 (81.7%)	<0.001
Surgery type			<0.001
None	0 (0%)	13 (18.3%)	
Lumpectomy	56 (52.3%)	35 (49.3%)	
Mastectomy	51 (47.7%)	23 (32.4%)	
Radiation recommended	44 (41.1%)	28 (38.9%)	0.765
Radiation received	42 (95.5%)	7 (25.0%)	<0.001
Chemo recommended	18 (16.8%)	6 (8.3%)	0.102
Chemo received	18 (100%)	0 (0.0%)	<0.001
Hormone Tx recommended	62 (56.4%)	62 (86.1%)	<0.001
Hormone Tx received	62 (100%)	19 (30.6%)	<0.001

attributed to fear of treatment side effects, higher rate of patient comorbidities, poorer performance status, transportation difficulties, limited social support, patient or family preference, concerns about quality of life, and lower life expectancy.[5] According to Tesarova et al.,[5] elderly patients with breast cancer are frequently undertreated, even after adjustment for confounding factors, such as comorbidities, need for social support, and functional status.

According to Hamaker et al.,[6] elderly patients with breast cancer who were not treated according to the Netherland national guidelines were significantly older (83.0 vs 76.9 years, $P < 0.001$) and had more comorbidities (1.7 vs 1.2 comorbidities) than those treated according to the guidelines. Also, 7% of patients that were not treated in accordance with the guidelines did not receive radiotherapy and 5% did not receive hormonal therapy despite the availability of clear guidelines. Our study similarly showed nonconforming patients to be older than their conforming counterparts by 2.8 years (80.5 vs. 77.7 years, $P = 0.001$). Nonconformity rates were exponentially higher in our study, with rates of nonconformity with radiation and hormonal therapy noted to be 75.0% and 69.4%, respectively. Similarly, Strader et al.[7] found that patients 80 years and older were significantly more nonconforming than patients between 70 and 79 (52.0% vs. 25.5%; $P = 0.008$), with the patients being significantly less likely to conform to NCCN guidelines in all 3 areas of treatment (surgery, radiation, and hormonal therapy). However, both studies by Hamaker et al.[6] and Strader et al.[7] did not provide outcomes for these patients to determine whether nonconformity resulted in higher rates of local recurrence, metastatic disease or disease-specific mortality. Soyder et al.[11] did evaluate outcomes of 35 elderly patients over 69 years of age who had been treated for T1N0M0 (stage 1) and T2N0M0 (stage 2) cancers. Their patients underwent breast conserving surgery (BCS) and hormonal therapy (HT); BCS, HT, and radiation therapy (RT); or BCS, chemotherapy (CT), HT and RT. No cancer-specific mortality or local recurrence was seen during the follow-up in any of the groups. This study showed that BCS and HT regimen is an effective treatment option for early breast cancer in appropriate 70 years or older patients. Additionally, this small study shows that less treatment may give an equal survival rate.

Our study, which is a follow-up to the study by Strader et al.,[7] evaluated outcomes as a result of nonconformity. We compared patient outcomes with regards to local recurrence, metastatic disease, breast cancer related death, and all-cause death in patients that were conforming vs nonconforming with NCCN treatment guidelines. The study showed no difference between both groups with regards to local recurrence, metastatic disease, and breast cancer related death. The nonconforming group had a higher rate of

Table 4
Comparison of rates of local recurrence, metastatic disease and mortality between patients who did or did not conform with NCCN breast cancer treatment guidelines.

Parameter	Conforming	Nonconforming	*P*-value
	Number (%)	Number (%)	
Number of subjects	107 (59.8%)	72 (40.2%)	−
Local recurrence	3 (2.8%)	1 (1.4%)	0.650
Metastatic disease	3 (2.8%)	2 (2.8%)	1.000
Deaths: All-cause	28/102 (27.5%)	32/69 (46.4%)	0.011
All-cause mortality 70–79 years	11 (39.3%)	5 (15.6%)	0.039
All-cause mortality ≥80 years	17 (60.7%)	27 (84.4%)	
Deaths: Breast cancer related	8/102 (7.8%)	7/69 (10.1%)	0.602
Deaths: Non-breast cancer related	20/102 (19.6%)	25/69 (36.2%)	0.015
Non-breast cancer causes of death			
Pulmonary	4 (20.0%)	7 (28.0%)	
Cardiac	4 (20.0%)	4 (16.0%)	
Dementia/failure to thrive	4 (20.0%)	4 (16.0%)	
Other cancer	1 (5.0%)	2 (8.0%)	
Cerebrovascular accident	1 (5.0%)	0 (0.0%)	
Trauma	1 (5.0%)	0 (0.0%)	
Unknown/other	5 (25.0%)	8 (32.0%)	

all-cause death, compared to the conforming group (46.4% vs. 27.5%; *P* = 0.011). Unlike Hamaker et al.[6] who found nonconforming patients to have more co-morbidities, our populations did not differ with regards to measured comorbidities with the notable exception of age, which was greater in the nonconforming group. It is probable that the patients' age in addition to their other co-morbid medical conditions and/or perceived life-expectancy/quality of life influenced their decision to be nonconforming with treatment recommendations. Tesarova et al.[5] stated that under diagnosis and undertreatment in elderly patients adversely affects their overall survival. Conversely our study, like that of Soyder et al.,[11] showed patient outcomes to not be dependent on their treatment choices.

Limitations

The retrospective nature of the study, along with its small sample size comes with inherent design limitations. Furthermore, we were not able to gather data with regards to whether nonconformity was patient, surgeon, or oncologist driven. We also were not able to specifically look at the number of patients who stopped taking hormonal therapy due to the side-effect profile.

Conclusions

Data from our study showed that nonconformity to NCCN guidelines in elderly patients with breast cancer did not significantly affect their outcome (local recurrence, metastatic disease, and breast cancer related deaths). Nonconformity with hormonal therapy also did not significantly affect patient outcomes. Larger studies are required to confirm these findings. In addition, more research may be required to verify whether hormonal therapy is required in elderly patients, as this could affect/change future treatment guidelines/recommendations.

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