OUTCOMES AFTER MASTECTOMY AND LUMPECTOMY IN OCTOGENARIANS AND
NONAGENARIANS WITH EARLY-STAGE BREAST CANCER

by

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Abstract

Prospective studies have shown equal outcomes after mastectomy or breast conservation in patients with invasive breast cancer; however, many of these studies excluded elderly patients. We identified patients in their eighties and nineties with clinical stage 0 to II breast cancer undergoing mastectomy or lumpectomy with or without radiation from the prospective sentinel lymph node (SLN) database at Wake Forest Baptist Health and analyzed their treatment and survival. Of 92 patients, 24 (26.1%) underwent mastectomy, 22 (23.9%) lumpectomy with radiation, and 46 (50.0%) lumpectomy alone. Significant differences were noted in tumor size ($p=0.018$), nodal status ($p=0.013$), and stage ($p=0.011$) across the groups. Only 7.6% of patients had chemotherapy, while 65.3% took anti-estrogen therapy. Recurrence occurred in 11 (12.0%) patients. In univariate analysis, overall survival did not differ by surgery. Age was the only factor that increased risk of death ($HR=1.19$, $p=0.028$). Neither tumor factors nor type of local treatment significantly influenced overall survival. Octogenarians and nonagenarians with early-stage breast cancer undergoing breast-conserving surgery with or without radiation have equivalent survival to patients having a mastectomy.

Breast cancer disproportionately affects older women with regards to incidence and rate of mortality.¹ This is important as the US population is aging and living longer.² While women age 80 years and older account for only 4% of the US population, they made up over 12% of the 230,000 new breast cancer diagnoses and 25% of the 40,000 breast cancer-related deaths in 2015.²⁻³

Prospective studies have shown equal survival outcomes after mastectomy and breast-conserving therapy in patients with invasive breast cancer, however, many of these studies excluded women 80 years and older.⁴⁻⁶ Breast cancers in these elderly patients tend to be less aggressive, as they are more likely to be hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2/neu)-negative, and low grade.⁷⁻¹¹ Despite favorable tumor biology, elderly women 80 years and older often present with more advanced disease, larger tumors with nodal spread, and have a higher risk of dying from breast cancer.^{7-8, 10-13} This may be related to decreased screening in this age group.¹³

Historically, treatment of breast cancer in elderly patients tends to be less aggressive than for younger patients.^{8, 14} The elderly are less likely to receive surgical resection, axillary nodal staging, adjuvant radiation therapy, hormone therapy, chemotherapy, or they are given non-guideline chemotherapy.^{7-10, 12, 15-17} Age, comorbid

conditions, lack of evidence-based treatment of breast cancer in the elderly population, less aggressive biological nature of breast cancer, patient and provider bias, psychosocial issues, and diminished functional status are all cited as reasons for undertreatment in this population, however, studies vary on the degree of impact this undertreatment plays on recurrence and survival.^{10, 14-15, 18-22}

Prior analysis of a large national contemporary population-based dataset performed at our institution demonstrated that survival in women 70 years and older with early-stage invasive breast cancer is not dependent on type of local treatment but rather on tumor-specific variables and nodal disease, making assessment of lymph node status important in this age group.¹⁸ The purpose of the current study was to review the local treatment and outcomes of octogenarians and nonagenarians treated for early-stage breast cancer at our institution. We also looked at the use and adherence to adjuvant anti-estrogen therapy in these elderly patients.

Materials and Methods

Patient Cohort

After Institutional Review Board approval, we conducted a retrospective cohort study of the prospectively maintained sentinel lymph node (SLN) database at Wake Forest Baptist Health. This database captures all patients who undergo SLN mapping in the operating room. We also reviewed our individual breast surgeon's databases to capture additional patients who met inclusion criteria but may not have undergone SLN mapping. We identified all patients 80 years of age and older who underwent surgical treatment of breast cancer at Wake Forest Baptist Health between January 1, 2005 and December 31, 2015. We included only patients with clinical stage 0 to II node-negative breast cancer. We excluded patients with benign, stage III, and stage IV disease.

Study Variables and Definitions

From the medical record, we collected the following data: age, race, tumor size, nodal status, method of diagnosis, hormone receptor status, local treatment (lumpectomy or mastectomy), SLN biopsy, axillary lymph node dissection (ALND), radiation therapy (XRT), receipt of anti-estrogen therapy, chemotherapy, and trastuzumab administration. Tumor size and nodal status were evaluated by pathologic examination of the final surgical specimen. The method of diagnosis included a palpable mass on physical exam, mammogram, ultrasound, and computed tomography (CT) scan. Estrogen and progesterone receptors were considered positive if greater than 1% of nuclei were involved. Her2/neu receptor was considered positive if greater than 1% of the membrane was involved. The primary outcomes of interest were the incidence of locoregional recurrence, distant metastasis, and

breast cancer-specific survival. The secondary outcomes were adherence to anti-estrogen therapy, reasons for nonadherence, and SLN positivity. Adherence was defined as completion of five years of anti-estrogen therapy (tamoxifen, aromatase inhibitor, or combination of the two) as recommended by the National Comprehensive Cancer Network or continued use of anti-estrogen therapy at the time of study completion.²³ Patients who did not start anti-estrogen therapy were excluded from analysis of adherence to recommended treatment.

Statistical Analysis

Demographic and tumor characteristics were summarized overall and by stage and treatment type. Descriptive data are presented as median and frequency. Differences in medians and frequencies were assessed using Chi square and Fisher's exact tests. Univariate Cox regression models were used to predict factors associated with breast cancer-specific death. All statistical analyses were conducted using SPSS software, Version 19.0 (IBM Corp., Somers, NY) and SAS, Version 9.4 (SAS Institute, Inc., Cary, NC), and a 0.05 significance level was used throughout the analysis.

Results

Patient and Tumor Characteristics

We identified 92 eligible women with clinical stage 0 to II node-negative breast cancer who underwent surgical resection at Wake Forest Baptist Health during the eleven-year study period. Median age was 82 years (range 80 to 94 years) (Table 1). After final histology from the surgical specimen and evaluation of axillary lymph nodes, 10 patients (10.9%) had stage 0 disease, 53 (57.6%) stage I, 19 (20.7%) stage II, and 10 (10.9%) stage III invasive breast cancer (Figure 1). Eighty-one patients (88.0%) were white, ten (10.9%) black, and one (1.1%) other (Hispanic ethnicity). Thirty-four cancers (37.0%) were diagnosed after a palpable mass was detected by the patient or provider, but the majority were diagnosed via imaging, with 54 (58.7%) by mammogram, three (3.3%) by ultrasound, and one (1.1%) by CT scan.

Twenty-four patients (26.1%) underwent mastectomy, 22 (23.9%) lumpectomy with radiation, and 46 (50.0%) lumpectomy alone (Table 2, Figure 2). There was a significant difference in the type of surgery by stage ($p = 0.011$), with the vast majority of lumpectomy alone performed for stage I disease (Table 2). The majority of patients had ER-positive (78.3%) and Her2/neu-negative (82.6%) tumors. SLN biopsies were performed in 78 patients (84.8%). Fourteen patients (15.2%) did not undergo SLN mapping. The use of SLN mapping did not differ

significantly by type of surgery ($p = 0.265$). Of those who underwent SLN biopsy, the SLN was positive in 19 patients (24.4%). ALND was performed in 15 patients (16.3%).

Of the 72 patients who had ER-positive tumors, 47 patients (65.3%) received anti-estrogen therapy; 15 received tamoxifen, 37 received an aromatase inhibitor (AI), and 5 patients received both. None of the 20 patients (21.7%) with an ER-negative tumor received tamoxifen or an AI. Of the 47 patients who received tamoxifen or an AI, only 21 patients (44.7%) adhered to a five-year course or were still taking anti-estrogen therapy at the time of study completion. Reasons for nonadherence were adverse side effects (84.6%), disease progression or development of endometrial thickening or a second malignancy (11.5%), and financial constraints (3.9%) (Table 3). Sixteen patients (17.4%) were Her2/neu receptor-positive. Of these, five (31.3%) received trastuzumab. Chemotherapy was given to seven patients in the overall cohort (7.6%). Eleven patients (12.0%) had a recurrence of their breast cancer, of which five developed locoregional recurrence and six developed distant metastasis (Figure 3). There was no difference in locoregional recurrence ($p=0.414$) or distant metastasis ($p=0.697$) between the three local treatment groups (mastectomy, lumpectomy with radiation, or lumpectomy alone). There was also no difference in locoregional recurrence ($p=0.221$) or distant metastasis ($p=0.437$) when looking only at patients who underwent lumpectomy with radiation versus lumpectomy alone. Three patients (3.3%) in the cohort died a breast cancer-related death. Of those who died, two had undergone a mastectomy and one a lumpectomy with radiation. There was no significant difference in death due to breast cancer between the three groups ($p=0.163$) (Table 2).

Survival Analyses

In univariate analysis, increased age was the only significant risk factor for death (HR 1.19, 95% CI 1.02-1.38, $P=0.028$). Black race, mastectomy, higher stage, a positive SLN, and having an ALND were all risks for worse survival, but none of these reached statistical significance (Table 4).

Discussion

Several prospective studies with long-term follow-up have demonstrated equivalent outcomes with mastectomy or breast conservation in women with breast cancer. As many of these studies excluded elderly women, retrospective population-based studies have been performed to assess the effect of treatment type and age on outcomes of patients undergoing treatment for breast cancer. In most of these studies, overall and disease-specific survival was noted to be improved in women undergoing breast conservation.²⁴⁻²⁵ We showed that octogenarians and nonagenarians with early-stage breast cancer undergoing breast-conserving surgery with or without radiation have

equivalent survival to patients having a mastectomy. Additionally, adjuvant radiation therapy adds no survival benefit over lumpectomy alone. In univariate analysis, age was the only factor that significantly decreased survival. Schonberg et al. proposed the identification of specific tumor factors and patient characteristics that may help identify elderly patients who may benefit from more aggressive treatment and those who may not as age was a stronger predictor than comorbidity in both survival and in determining the type of treatment a patient received.¹²

Our previous study of 1,784 women older than 70 years in the SEER database noted improved overall and breast cancer-specific survival in women undergoing lumpectomy with or without radiation in comparison to those undergoing mastectomy. However, when adjusting for age, tumor size, lymph node status, race, comorbidities, and performance status (ability to perform ADLs), we noted that the type of surgery was not an independent factor determining survival.¹⁸ In this older cohort treated at our institution, we also found that type of local treatment did not impact survival.

The question of whether lymph node status should be routinely assessed for elderly patients with early-stage breast cancer has been debated in the literature. In our cohort, 85% of patients underwent SLN mapping and 16.3% had an ALND. The International Breast Cancer Study Group Trial 10-93, which randomized women 60 years and older with clinically node-negative breast cancer to surgery with axillary clearance plus tamoxifen or surgery alone plus tamoxifen, found no difference in overall or disease-free survival. Additionally, the no axillary surgery arm group had an improvement in early quality of life.²⁶⁻²⁷ This has led to the argument that because nodal status is potentially less relevant in determining the need for adjuvant systemic chemotherapy for hormone receptor (HR)-positive early-stage breast cancer in older women, axillary dissection or sentinel node biopsy to determine nodal status could arguably be avoided. Conversely, Hieken, Nettnin, and Velasco found that the results of SLN biopsy at their institution changed nonsurgical adjuvant treatment plans in 38% of 104 patients over the age of 65.²⁸ We found that patients with a positive SLN for malignancy or who underwent an axillary dissection had no increased risk of death. The majority of our patients underwent axillary staging, however, the SLN was positive in less than a quarter. Of the 19 patients with positive SLN, 12 went on to have completion ALND, 7 of whom had a nodal status greater than N1 (metastases in 4 or more lymph nodes). This study did not specifically look at whether knowledge of nodal status changed adjuvant treatment. Based on these results and our current study, we cannot make a conclusion regarding the relativity of determining nodal status in the treatment of older women with early-stage breast cancer. Further studies should look at the influence of nodal staging on treatment decisions.

We found no difference in survival in octogenarians and nonagenarians with early-stage breast cancer who underwent lumpectomy with or without radiation therapy. This confirms Hughes' et al. Cancer and Leukemia Group B (CALGB) 9343 study which examined 636 women over the age of 70 with clinical T1N0M0 estrogen receptor (ER)-positive breast carcinoma treated by lumpectomy who were randomly assigned to receive tamoxifen plus radiation therapy or tamoxifen alone. At ten year follow-up, they found the previously observed small improvement in locoregional recurrence with the addition of radiation therapy remains; however, this did not translate into an advantage in overall survival, distant disease-free survival, or breast preservation.²⁹⁻³² An earlier study by Fyles et al. of 769 women age 50 years and older with T1-2N0M0 HR-positive breast cancers demonstrated that radiotherapy plus tamoxifen significantly reduces the risk of locoregional recurrence but has no impact on distant metastases or overall survival.³³ Similarly, the PRIME II trial examined 1,326 women over the age of 65 with pathologic T1-2N0M0 HR-positive breast cancer randomized to whole-breast radiotherapy plus endocrine therapy or endocrine therapy alone. The study found no differences between the two groups in terms of locoregional recurrence, distant metastases, contralateral breast cancers, new breast cancers, disease-free survival, or overall survival, and thus concluded that the addition of radiotherapy is not necessary for low-risk women.³⁴ Martelli et al. looked at tumor size and the addition of radiotherapy to lumpectomy to patients with pT1 versus pT2 tumors. They studied 1,451 patients with clinically node-negative breast cancer who all received hormone therapy despite hormone receptor status. They found that ipsilateral breast tumor recurrence (IBTR), distant metastasis, and breast cancer mortality were no different for pT1 patients whether or not they received radiation therapy, however, IBTR was significantly higher in the pT2 patients who did not receive radiation therapy while distant metastasis and breast cancer mortality were no different.³⁵ In our cohort, we saw no difference in locoregional recurrence or distant metastasis between the three groups or when radiation therapy was added to lumpectomy. Current NCCN guidelines state that adjuvant radiation therapy may be omitted in select older patients, however, careful attention should be paid to omitting it in patients with large tumors or those at risk for being nonadherent to anti-estrogen therapy.⁶

Elderly patients with HR-positive breast cancers may benefit from adjuvant anti-estrogen therapy. Both tamoxifen and AIs reduce the risk of recurrence and breast cancer-specific mortality.^{7, 30, 32, 36-37} AIs are slightly more effective than tamoxifen in terms of disease-free survival, however, the elderly are subject to their side effects of myalgias, arthralgias, bone pain, osteoporosis, and hot flashes.^{14, 30} Other adverse events of anti-estrogen therapy are increased risk of fracture, thrombotic events, and endometrial cancer.⁷ Treatment with anti-estrogen therapy can

reduce the risk of local recurrence whether or not a patient undergoes radiation therapy, however, the improvement in regional control and survival are dependent on treatment adherence.³⁸

Nonadherence to anti-estrogen therapy has been reported as high as 51% in the literature and shown to be related to worse outcomes.³⁶⁻³⁹ Most early discontinuation occurs within the first year of treatment.³⁷ Older age is associated with poor adherence to hormone therapy over time.^{7, 36, 38, 40} Frailty is associated with noninitiation of hormone therapy, however, it does not seem to be related to nonadherence.³⁶ Reasons cited for hormone therapy nonadherence are adverse side effects, financial constraints, and development of a second malignancy. We saw a 55.3% incidence of anti-estrogen therapy nonadherence in our cohort. The most common reasons for early discontinuation were bony in nature (arthralgias, bone pain, worsening osteoporosis, and fractures) followed by functional decline, fatigue, and weakness; neurologic side effects; and development of endometrial thickening, disease progression, or a second malignancy during treatment course. Less common were hot flashes, incontinence, and financial reasons. Despite the fact that two-thirds of our elderly patients took anti-estrogen therapy and less of half of these were compliant with a five-year treatment course, age was the only factor that increased a patient's risk of death.

Literature shows that chemotherapy improves survival in older breast cancer patients and that more aggressive chemotherapy improves disease-free survival and overall survival in node-positive disease regardless of age.^{7, 41-42} Despite this benefit, older patients experience higher rates of chemotherapy-related toxicity due to frailty, decreased functional status, decreased renal clearance, and diminished bone marrow reserve.⁷ Older age is associated with nonuse of chemotherapy or deviation from chemotherapy guidelines.^{7, 17} In our cohort, 7 patients (7.6%) received chemotherapy. Of the 16 patients who had Her2/neu receptor-positive tumors, 5 (31.3%) received trastuzumab.

There are several limitations of our retrospective cohort study. First, it is from a single tertiary academic institution, which limits its generalizability. Second, the relatively small sample size gives less statistical power, which limits the ability to detect differences between the groups.

Conclusion

Despite these limitations, our study is one of the few in the literature to examine the surgical outcomes in octogenarians and nonagenarians. Most elderly patients with early-stage breast cancer in this age group choose to undergo a lumpectomy without radiation. Octogenarians and nonagenarians with early-stage breast cancer

undergoing breast-conserving surgery with or without radiation have equivalent survival to patients having a mastectomy. In this age group, there is no difference in locoregional recurrence, distant metastasis, or breast-cancer related death between patients undergoing mastectomy or breast-conserving surgery without or without radiation. Despite the fact that less than half of patients are adherent to anti-estrogen therapy, survival is dependent on age rather than tumor factors, lymph node involvement, or local control. The addition of radiation therapy to lumpectomy adds no survival benefit and may be omitted in select patients.

TABLE 1. *Demographic and clinicopathologic characteristics of patients, stratified by stage*

Variable	Overall (n=92)		Stage 0 (n=10)		Stage I (n=53)		Stage II (n=19)		Stage III (n=10)		p value
	n/median	%/SD	n/median	%/SD	n/median	%/SD	n/median	%/SD	n/median	%/SD	
Age (years)*	82 (80-94)	2.96	82 (80-86)	2.01	82 (80-91)	2.77	84 (80-94)	3.68	81.5 (80-89)	3.13	0.865
Race											
White	81	88.0	7	70.0	7	88.7	17	89.5	10	100.0	0.442
Black	10	10.9	3	30.0	5	9.4	2	10.5	0	0.0	
Other	1	1.1	0	0.0	1	1.9	0	0.0	0	0.0	
Method of dx											
Palpable	34	37.0	4	40.0	14	26.4	9	47.4	7	70.0	0.017
Mammogram	54	58.7	5	50.0	38	71.7	9	47.4	2	20.0	
Ultrasound	3	3.3	1	10.0	1	1.9	1	5.3	0	0.0	
CT scan	1	1.1	0	0.0	0	0.0	0	0.0	1	10.0	

* Median (range)

Abbreviations: SD = standard deviation; dx = diagnosis

TABLE 2. *Demographic and clinicopathologic characteristics of patients, stratified by treatment type*

Variable	Overall (n=92)		Mastectomy (n=24)		Lumpectomy with radiation (n=22)		Lumpectomy alone (n=46)		p value
	n/median	%/SD	n/median	%/SD	n/median	%/SD	n/median	%/SD	
Age (years)*	82 (80-94)	2.96	82 (80-94)	3.64	81 (80-89)	2.70	82 (80-91)	3.71	0.159
Race									
White	81	88.0	21	87.5	21	95.8	39	84.8	0.688
Black	10	10.9	3	12.5	1	4.5	6	13.0	
Other	1	1.1	0	0.0	0	0.0	1	2.2	
Stage									
0	10	10.9	2	8.3	1	4.5	7	15.2	0.011
I	53	57.6	11	45.8	10	45.5	32	69.6	
II	19	20.7	5	20.8	7	31.8	7	15.2	
III	10	10.9	6	25.0	4	18.2	0	0.0	
T stage									
Tis	9	9.8	2	8.3	0	0.0	7	15.2	0.018
T1	64	69.6	14	58.3	17	77.3	33	71.7	
T2	13	14.1	3	12.5	4	18.2	6	13.0	
T3	6	6.5	5	20.8	1	4.5	0	0.0	
N stage									
N0	71	77.2	15	62.5	13	59.1	43	93.5	0.013
N1	13	14.1	5	20.8	5	22.7	3	6.5	
N2	5	5.4	3	12.5	2	9.1	0	0.0	
N3	3	3.3	1	4.2	2	9.1	0	0.0	
ER status									
Positive	72	78.3	16	66.7	17	77.3	39	84.8	0.217
Negative	20	21.7	8	33.3	5	22.7	7	15.2	
Her2/neu status									
Positive	16	17.4	4	16.7	4	18.2	8	17.4	0.991
Negative	76	82.6	20	83.3	18	81.8	38	82.6	
SLN bx performed									
Yes	78	84.8	20	83.3	21	95.5	37	80.4	0.265
No	14	15.2	4	16.7	1	4.5	9	19.6	
SLN positive									

Yes	19	24.4	6	30.0	8	38.1	5	13.5	0.088
No	59	75.6	14	70.0	13	61.9	32	86.5	
ALND performed									
Yes	15	16.3	7	29.2	6	27.3	2	4.3	0.008
No	77	83.7	17	70.8	16	72.7	44	95.7	
Recurrence									
Yes	11	12.0	4	16.6	2	9.1	5	10.8	0.657
Locoregional	5	5.4	2	8.3	0	0.0	3	6.5	
Distant	6	6.5	2	8.3	2	9.1	2	4.3	
No	81	88.0	20	83.3	20	90.9	41	89.1	
Death due to breast cancer									
Yes	3	3.3	2	8.3	1	4.5	0	0.0	0.163
No	89	96.7	22	91.7	21	95.5	46	100.0	

* Median (range)

Abbreviations: SD = standard deviation; ER = estrogen receptor; SLN = sentinel lymph node; bx = biopsy; ALND = axillary lymph node dissection

TABLE 3. *Reasons for nonadherence to anti-estrogen therapy (tamoxifen or aromatase inhibitor)*

	<i>n</i> =26
Reason for nonadherence	(<i>n</i> /%)
Bony (osteoporosis, arthralgias, bone pain, fractures)	11 (42.3)
Fatigue, weakness, functional decline	5 (19.2)
Neurologic side effects	3 (11.5)
Endometrial thickening, disease progression, second malignancy	3 (11.5)
Hot flashes	2 (7.7)
Financial	1 (3.9)
Incontinence	1 (3.9)

TABLE 4. *Univariate Cox models for overall survival*

Variables	Univariate Models		
	HR	95% CI	<i>p</i> value
Age	1.19	1.02 – 1.38	0.028
Race*			
White			
Black	1.43	0.41 – 5.00	0.527
Type of surgery			
Lumpectomy + XRT			
Lumpectomy alone	0.92	0.27 – 3.14	0.890
Mastectomy	1.95	0.64 – 5.94	0.240
Stage			
0			
I	0.97	0.20 – 4.75	0.969
II	1.61	0.32 – 7.99	0.563
III	1.49	0.27 – 8.22	0.649
SLN bx performed			
No			
Yes	0.36	0.10 – 1.32	0.123
SLN positive			
No			
Yes	1.93	0.77 – 4.81	0.160
ALND			
No			
Yes	1.36	0.51 – 3.59	0.539
Her2/neu status			
Negative			
Positive	1.32	0.27 – 6.55	0.737

* Latin American excluded due to low numbers

Abbreviations: HR = hazard ratio; CI = confidence interval; XRT = radiation therapy; SLN = sentinel lymph node; bx = biopsy; ALND = axillary lymph node dissection

FIG 1. *Distribution of patients by stage*

FIG 2. *Distribution of patients by stage, stratified by surgery type*

FIG 3. *Incidence of recurrence and breast cancer-related death, stratified by surgery*

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