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Surgical Management of the Axilla in Elderly Women with Node-Positive Breast Cancer

Caitlin E. Marks, BS^a, Yi Ren, MS^{b,c}, Laura H. Rosenberger, MD, MS^{a,b}, Samantha M. Thomas, MS^{b,c}, Rachel A. Greenup, MD, MPH^{a,b}, Oluwadamilola M. Fayanju, MD, MA, MPHS^{a,b,d}, Susan McDuff, MD, PhD^{b,e}, Gretchen Kimmick, MD, MS^{b,f}, E. Shelley Hwang, MD, MPH^{a,b}, Jennifer K. Plichta, MD, MS^{a,b}

^aDuke University Medical Center, Department of Surgery. Durham, NC.

^bDuke Cancer Institute. Durham, NC.

^cDuke University, Department of Biostatistics & Bioinformatics. Durham, NC.

^dDurham VA Medical Center, Department of Surgery. Durham, NC

^eDuke University Medical Center, Department of Radiation Oncology. Durham, NC.

^fDuke University Medical Center, Department of Medicine. Durham, NC.

Abstract

Background: Elderly women with clinically node-positive (cN+) breast cancer (BC) often have comorbidities that limit life expectancy and complicate treatment. We sought to determine whether the number of lymph nodes (LNs) retrieved among older women with node-positive breast cancer was associated with overall survival (OS).

Methods: Using the National Cancer Database (2010–2015), women 70–90y with cN+ BC and 1 LN removed were categorized by treatment sequence: upfront surgery or neoadjuvant

Corresponding Author: Jennifer Plichta, MD, MS, FACS, DUMC 3513, Durham, NC 27710, jennifer.plichta@duke.edu, Phone: 919-681-9156, Fax: 919-660-8608.

AUTHOR CONTRIBUTIONS

Marks: Study Design and Conception; Data Analysis/Interpretation; Manuscript Drafting; Critical Manuscript Review; Final Approval; Agreement to be Accountable for All Aspects

Ren: Study Design; Data Analysis/Interpretation; Critical Manuscript Review; Final Approval; Agreement to be Accountable for All Aspects

Rosenberger: Data Interpretation; Critical Manuscript Review; Final Approval; Agreement to be Accountable for All Aspects

Thomas: Study Design; Data Analysis/Interpretation; Critical Manuscript Review; Final Approval; Agreement to be Accountable for All Aspects

Greenup: Data Interpretation; Critical Manuscript Review; Final Approval; Agreement to be Accountable for All Aspects

Fayanju: Data Interpretation; Critical Manuscript Review; Final Approval; Agreement to be Accountable for All Aspects

McDuff: Data Interpretation; Critical Manuscript Review; Final Approval; Agreement to be Accountable for All Aspects

Kimmick: Data Interpretation; Critical Manuscript Review; Final Approval; Agreement to be Accountable for All Aspects

Hwang: Data Interpretation; Critical Manuscript Review; Final Approval; Agreement to be Accountable for All Aspects

Plichta: Study Design and Conception; Data Analysis/Interpretation; Manuscript Drafting; Critical Manuscript Review; Final Approval; Agreement to be Accountable for All Aspects

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chemotherapy (NAC). Multivariable Cox proportional hazards models with restricted cubic splines characterized the functional association of LN retrieval with OS; threshold values of LN retrieval were estimated. Cox proportional hazards models were used to estimate the association of LN retrieval groups with OS.

Results: In the upfront surgery cohort, a non-linear association was identified between LNs retrieved and OS. In the NAC cohort, no association was identified. For the upfront surgery cohort, the optimal threshold value of LN retrieval was 21 LN (90% CI 18–23). Based on this estimate, LN retrieval groups were created: <6, 6–11, 12–17, 18–23, and >23 LNs. After adjustment, retrieval of <12 LNs in the upfront surgery group was associated with a worse OS. No differences were observed in the NAC group.

Conclusions: For elderly women receiving upfront surgery, there is no survival benefit to removing more than 12 LN, and for those receiving NAC, there is no association between number of LNs removed and survival. In older women who present with cN+ BC, aggressive surgery to remove more than 12 LNs may not be necessary.

Keywords

elderly; breast cancer; node-positive; axillary lymph node dissection

INTRODUCTION

In 2017, women ≥70y made up a third of all new invasive breast cancer cases¹, and women ≥70y have a 6.7% probability of developing invasive breast cancer throughout the remainder of their lifetime². Despite the prevalence of breast cancer in this age group, and 11% of the population in the United States being ≥70y, elderly women with breast cancer are often under-represented or excluded from clinical trials^{3,4}. Furthermore, factors such as life expectancy, competing comorbidities, quality of life, and patient preference are often more relevant considerations when making treatment decisions in this elderly population⁵. Current guidelines are often the result of a multidisciplinary taskforce between providers in geriatrics and oncology⁵, and most are created by extrapolating research conducted on either the population as a whole or on younger cohorts⁶. Without well-studied standardized recommendations, the elderly population is less likely to receive guideline-concordant care and is at risk for being both undertreated and overtreated^{6–8}.

In general, breast cancer treatments are becoming more personalized than ever, and surgical management of the axilla continues to evolve as we strive to do what is necessary but nothing more. However, most research has focused on women with clinically negative nodes or limited axillary nodal involvement^{9–12}. Currently, the standard of care for women, including those ≥70y, with clinically node-positive (cN+) breast cancer is an axillary lymph node dissection (ALND)⁵. ALND is important for axillary staging and may offer some local-regional control. However, it is also associated with a variety of potential complications, including lymphedema, numbness, pain, reduced upper extremity range of motion, and reduced strength^{13–15}. To date, no studies have clearly elucidated whether less aggressive axillary management may be adequate in this elderly population with unique considerations. Therefore, we sought to determine if there exists a threshold for lymph node

(LN) removal that optimizes treatment planning and is associated with improved survival in an elderly population with cN+ breast cancer.

MATERIALS AND METHODS

Using the 2015 National Cancer Data Base (NCDB) Participant User File (PUF), we identified women (70–90y) diagnosed with cN+ invasive breast cancer from 2010–2015. Patients with metastatic disease, treated with neoadjuvant radiation, and/or with missing data regarding type of staging, surgery, treatment sequence, or survival were excluded. Given the potential selection bias in who may be offered neoadjuvant endocrine therapy and the variation in treatment response (compared to those receiving neoadjuvant chemotherapy [NAC]), patients receiving neoadjuvant endocrine therapy were excluded. Our study population was then divided into two cohorts based on treatment sequence: upfront surgery or NAC.

Patient and tumor characteristics were extracted from the NCDB, including the Charlson/Deyo Comorbidity Score, which is a numerical score reflecting the presence of comorbid conditions (e.g., diabetes, myocardial infarction, dementia, etc.)¹⁶. Patient characteristics were summarized with N (%) for categorical variables and median (interquartile range, IQR) for continuous variables for the entire study population and by treatment sequence. The two cohorts were compared using Chi-square or Fisher's exact tests for categorical variables, and t-tests or Wilcoxon Rank Sum tests for continuous variables. After stratifying each cohort by pN stage, subgroup analyses summarizing the number of LNs removed at the time of surgery, the number of pathologically positive nodes, and select treatment variables were conducted.

For each cohort (upfront surgery and NAC), separate multivariable Cox proportional hazards model with restricted cubic splines (RCS) were created to characterize the functional association of the number of LNs removed with OS, after adjustment for known covariates^{17,18}. The RCS method allows for a nonlinear relationship between the continuous dependent variable, LN retrieval, and OS, while restricting the two tails of the function to be linear to prevent instability^{17,18}. The number of knots used to fit the functional association with RCS was selected based on Akaike Information Criteria¹⁹ with 3-, 4-, and 5-knot models as candidate models. The 5-knot model (knots at 5th, 28th, 50th, 73rd, and 95th percentiles) and 3-knot model (knots at 10th, 50th, and 90th percentiles) were selected for the upfront surgery and NAC cohorts, respectively. If the RCS methodology revealed a non-linear association, a bootstrap simulation of that particular cohort with a Monte Carlo Markov Chain procedure was used to estimate the critical point that marked the directional change of the log-hazard ratio function across 1,000 iterations. The critical point, or the threshold value, and the 90% confidence intervals (CIs) were estimated from the 1,000 iterations as mean, 5th percentile, and 95th percentile. All RCS models were adjusted for known covariates, including pT, pN, age, race/ethnicity, grade, ER (estrogen receptor) status, PR (progesterone receptor) status, HER2 (human epidermal growth factor receptor 2) status, facility type, facility location, insurance, surgery type, chemotherapy, radiation, and endocrine therapy. Based on the thresholds and CIs identified, the study population was separated into LN retrieval groups defined by the number of LNs removed.

The potential association of the LN retrieval groups and OS were explored using Cox proportional hazards regression analyses, which were adjusted for covariates including patient age, pT stage, pN stage, tumor grade, ER status, PR status, HER2 status, facility type, facility location, insurance, receipt of surgery, chemotherapy, endocrine therapy, and/or radiation. To account for the correlation of patients treated at the same hospital, a robust sandwich covariance estimator was included in these models. A p-value <0.05 was considered statistically significant, and no adjustments were made for multiple comparisons. Statistical analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, NC). Due to use of de-identified data, our institutional review board granted the study exempt status.

RESULTS

Study Population and Tumor Characteristics

9,026 patients were identified: 941 (10.4%) received NAC, and 8,085 (89.6%) underwent upfront surgery (Figure 1). The median age of the entire study population was 76y (IQR 72–81). The median follow-up was 44.5 months (95% CI: 43.8–45.5), and the median survival was 83.8 months (95% CI 79.1 – non-estimable due to low number of events; Table 1). Compared to those who received NAC, women who underwent upfront surgery were significantly older (77y vs 73y, $p<0.001$) and more likely to have comorbidity scores > 0 (29% vs 21.5%, $p<0.001$). The NAC cohort had higher cT and cN stage, higher grade tumors, higher pT stage, lower pN stage, and more triple-negative tumors (Table 2, all $p<0.001$). Women in the NAC cohort were less likely to receive a mastectomy without radiation than the upfront surgery group (20% vs 35.8%, $p<0.001$), but were more likely to receive a lumpectomy plus radiation or mastectomy plus radiation (34.3% vs 31.3%, 39.9% vs 24.4%, both $p<0.001$; Table 2). At the time of axillary surgery, a median of 11–12 LNs were removed, and the median number of positive LNs was 2 for both cohorts (Table 2).

Lymph Node Retrieval and Adjuvant Treatment

After stratification based on pN stage, the median number of LNs retrieved was 3–19 LNs for the surgery upfront cohort and 7–18 LNs for the NAC cohort. In order to capture 90% of women within a specific pN stage, the minimum number of nodes retrieved ranged from 14–30 LNs in the upfront surgery cohort and from 21–26 LNs in the NAC cohort (Table 3). The percentage of women who received adjuvant therapy differed based on pN stage, and the largest differences between pN stages were noted between stages pN1 and pN2. In the upfront surgery cohort, 35.4% of women with pN1 disease received adjuvant chemotherapy, compared to 50.4% of those with pN2 disease (absolute difference of 15%). In this same cohort, 26.1% of women with pN1 disease received post mastectomy radiotherapy (PMRT), and 59.8% of those with pN2 disease received PMRT (absolute difference of 33.7%). In the NAC cohort, similar differences were observed: 61.2% of women with pN1 disease received PMRT, and 81% of those with pN2 disease received PMRT (absolute difference of 19.8%) (Table 3).

Lymph Node Retrieval and Overall Survival

In the upfront surgery cohort, the functional association between LN retrieval and OS was significant and non-linear (non-linearity $p<0.001$; Figure 2). However, in the NAC cohort,

there was no overall association between LN retrieval and OS (overall association $p=0.80$; Figure 3). The estimated threshold for LN retrieval associated with a marked change in OS was 21 LNs (90% CI 18–23). Based on this threshold and the associated 90% CI, 5 LN retrieval groups were created around this inflection point of 21 LNs: <6, 6–11, 12–17, 18–23, and >23 LNs. Notably, retrieval of <18 LNs was further divided into <6, 6–11, and 12–17 LNs to allow for more granularity in comparison to 18–23 LNs (the estimated 90% CI of the threshold).

In the unadjusted analysis, a significant difference in OS was noted between LN retrieval groups in both the upfront surgery and the NAC cohorts (Supplemental Figure 1). However, in the upfront surgery cohort, the unadjusted OS differed between the LN retrieval groups by only 0–2% at 1 year and 0–4% at 5 years (Table 4). In the NAC cohort, this difference ranged from 0–6% and 1–17% at 1 and 5 years, respectively (Table 4). After adjustment, in the upfront surgery cohort, retrieval of <6 LNs (HR 1.44, 95% CI 1.21–1.70) or 6–11 LNs (HR 1.30, 95% CI 1.11–1.51) were both associated with a higher risk of death as compared to retrieval of 18–23 LNs (both $p<0.001$), while removing 12–17 or >23 LNs were not associated with a significantly different risk of death (both $p>0.05$; Table 5). In the NAC cohort, there was no significant association with OS for any of the LN retrieval groups after adjustment (all $p>0.05$, Table 5).

DISCUSSION

For elderly women with cN+ breast cancer receiving upfront surgery in our study, removing more LNs resulted in identification of more positive LNs and thus higher pN stage. Furthermore, we demonstrated that receipt of adjuvant therapy was associated with higher nodal stage disease. The largest absolute differences in adjuvant therapy receipt were noted between stages pN1 and pN2, suggesting that establishing whether a patient is truly pN1 or pN2 may be the most relevant delineation in this elderly population. Our findings also suggest that many treatment decisions are likely influenced by the findings from the surgical evaluation of the axilla, and they are consistent with the National Comprehensive Cancer Network (NCCN) breast cancer guidelines, where pN stage is utilized for systemic adjuvant therapy decisions²⁰. When extrapolating these guidelines to the elderly population in particular, age is not a contraindication for PMRT nor adjuvant chemotherapy²¹. However, there is currently insufficient data to make global recommendations on systemic adjuvant therapy in the elderly, and decisions surrounding therapy are usually assessed on an individual level^{7,21}. Therefore, it is important to be mindful of the impact nodal information may have on adjuvant treatment decisions. If treatment decisions may be altered based on the identification of more positive nodes and the final pN stage, then performing a thorough ALND (clearly defining all true borders of the axilla during the dissection) may be an important consideration when determining the appropriate surgical and post-surgical management.

However, our data also suggest that regardless of the treatments received, removal of more LNs may not be associated with improved survival. This was most notably apparent for the NAC cohort, where no association was identified between number of LNs removed and survival. In the upfront surgery cohort, we demonstrated that removing <12 LNs was

associated with a worse OS, although removing more than 12 LNs did not improve survival, suggesting that the minimum cutoff for determining adequacy of axillary surgery in this elderly population with cN+ breast cancer may be 12 LNs. Currently, the NCCN defines an adequate ALND as removal of ≥ 10 LNs²⁰. However, this number is largely based on historic trials from the 1990s that sought to confirm that the axilla was truly node negative^{22,23}. More recently, Rosenberger *et al.* evaluated 129,685 patients with node-positive breast cancer in the NCDB and demonstrated that removal of approximately 20 LNs may result in more accurate nodal staging and subsequently impact adjuvant therapy decisions, which may improve survival²⁴. However, the median age of this population was 56y and excluded those >75y, which may account for some of the differences noted between our studies.

When considering the elderly population more specifically, Poodt *et al.*'s retrospective cohort study of women ≥ 75y with breast cancer demonstrated that the 10-year survival rate of women who received incomplete nodal staging did not statistically differ from women who received an ALND. Furthermore, only 14% of women who had incomplete axillary staging died of breast cancer or of complications from breast-cancer-related treatment. While most women in the incomplete nodal staging cohort had cN0 disease, a large proportion of the cohort had pN+ disease (44%), and yet, OS was not affected when compared to those receiving ALND²⁵. While elderly women with cN+ disease are not well studied, NCCN guidelines do recognize the uniqueness of this patient population. If information from an ALND will not contribute to adjuvant treatment decisions, then performing less aggressive axillary surgery in this population may be a reasonable option²⁰. Similar to the findings of Poodt *et al.*, our results suggest that performing less aggressive axillary surgery in select circumstances may not significantly impact OS in this elderly population with node-positive breast cancer.

There has been some research examining sentinel lymph node biopsy (SLNB) versus ALND in the general population of women with node-positive disease. Bonneau *et al.* evaluated 9,521 patients in the SEER (Surveillance, Epidemiology, and End Results) database with T1–2 tumors and ≥ 3 positive LNs who underwent upfront surgery (median age 56y). They noted no statistical difference in OS between those receiving SLNB vs ALND²⁶. On the other hand, Park *et al.* evaluated women with cT1–3, cN2–3 disease (median age 56y) and noted an association between ALND and improved OS for patients with cN2 and cN3 disease²⁷. This difference in the association between ALND and OS may be attributed to the size of the tumors in each study population: Bonneau *et al.* examined patients with relatively small tumors (T1–2) compared to the study population of Park *et al.*, which included T1–3 tumors. Our study population, like Bonneau *et al.*, consisted of women with relatively small tumors, cT1–2, which may explain the similarity to our findings.

Another important variable that has been shown to be associated with OS is patient age. Bonneau *et al.* and Park *et al.* both included women representative of the general population (median age 56y in both studies), while our study population focused on women ≥ 70y (median age 76y). Notably, the leading cause of death in people ≥ 65y is heart disease, suggesting that older women with a history of breast cancer may not actually die from breast cancer, but rather may be more likely to succumb to other conditions/diseases²⁸. Competing comorbidities in the elderly make “relative breast cancer survival” an important concept to

consider when selecting the appropriate breast cancer management^{5,29–31}. While multiple studies have assessed SLNB vs ALND in the general population with conflicting results, limiting our study to older women with smaller tumors may at least partially explain why our findings did not demonstrate a survival benefit to removing >12 LNs. However, further investigation of the axillary management in elderly women with breast cancer and various tumor sizes may be warranted.

Interestingly, we found no association between the number of LNs removed and OS in elderly women who received NAC. While previous studies have explored omission of ALND in patients who receive NAC if the SLNB is negative³², critics emphasize the high false negative rate of SLNB after NAC (12.6% in women with cN1)^{33,34}. In our NAC cohort, 85.7% had persistently positive nodes, and presumably many would have had a positive SLNB after NAC. Regardless, LN retrieval was not associated with a significant change in OS. One possible explanation is that adjuvant chemotherapy and radiation recommendations may be driven more by the presence of persistent nodal positivity after neoadjuvant chemotherapy (rather than an exact number of nodes involved after ALND)^{35–37}. Thus, despite a high false negative rate and a positive axilla after NAC, women >70y with T1–2 disease may not benefit from extensive axillary surgery if detailed nodal information will not impact adjuvant treatment decisions. While no published prospective trials have analyzed omission of ALND in women who receive NAC, the Alliance A11202 trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01901094) identifier: [NCT01901094](https://clinicaltrials.gov/ct2/show/study/NCT01901094)) is an ongoing trial randomizing women with a positive SLNB after NAC to receive ALND versus axillary radiotherapy. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-51/Radiation Therapy Oncology Group (RTOG) 1304 trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01872975) identifier: [NCT01872975](https://clinicaltrials.gov/ct2/show/study/NCT01872975)) is an ongoing trial of women with clinically node-positive breast cancer who convert to node negative after NAC, who are randomized to receive or not receive regional nodal radiation³⁸. The results of these studies will add further insight into how to best optimize axillary management in this elderly population with node-positive breast cancer who receive NAC.

When considering how our findings may impact patient care, it is important to note that a true ALND for breast cancer (the surgical procedure itself) is defined by the patient's anatomy and not the number of nodes removed, as surgeons typically remove the level I and II axillary tissue en bloc and do not dissect out individual LNs while in the operating room. However, surgeons do have some influence on how aggressively they clear this tissue from the axilla and potentially influence the number of nodes removed, particularly in the upfront surgery population. Similar to how level III nodes are no longer included in an ALND for breast cancer surgery, the dissection could be further limited to only level I nodes, and the medial border of the dissection would then be the pectoralis minor muscle. For patients receiving NAC where the number of nodes removed may be even less critical, one could alternatively consider a dual-tracer SLNB or targeted axillary dissection (TAD, retrieving a previously biopsied and clipped node and performing a SLNB)^{34,39}, which could still provide information for pathological nodal staging while minimizing the potential sequelae of axillary surgery. Furthermore, a combination of these strategies (level I dissection and tracer-based lymph node removal) could also be employed to help minimize the dissection.

There were a few limitations of our study, most of which are due to its retrospective design and the inherent limitations associated with the NCDB. However, utilizing a national database allows for larger sample sizes of elderly women with cN+ breast cancer and potentially increases diversity in multiple ways at the patient, facility, and disease-levels. One important limitation is the lack of data on the type of axillary surgery being performed (SLNB vs ALND). While the NCDB provides information on the number of nodes removed, the specific NCDB data set used for this study did not include information of the surgeon's intent. In addition, the NCDB only provides information related to OS and not breast cancer specific survival. However, in this population of women with competing comorbidities, OS is likely an appropriate outcome measure. It is also important to note that the NCDB only includes data from Commission on Cancer-accredited facilities, which may not be fully representative of the population, although numerous institutions are included in the NCDB. As with most retrospective analyses, there was likely some degree of selection bias that we could not account for in our analysis. For example, women who were healthier and able to withstand treatments like chemotherapy, were probably more likely to receive NAC, as suggested by the lower comorbidity scores in that cohort. Lastly, it is also important to recognize that an ALND may result in significant complications, such as lymphedema, pain, and decreased range of motion, consideration of which should be balanced with the benefits of doing an ALND.

In summary, we demonstrated that in women 70y with cN+ breast cancer, pN stage likely impacts adjuvant treatment decisions. However, in women who underwent surgery first, our data suggest that removing >12 LNs may not improve survival, and a procedure that removes at least 12 LNs may allow for adequate axillary staging to best tailor adjuvant treatment decisions. For elderly women who received NAC, there was no association between LN retrieval and OS, perhaps due to the fact that adjuvant treatment decisions after NAC are driven more by knowledge of persistent nodal positivity (rather than an exact number). Therefore, discussions at the patient's first clinic visit between the surgeon and the oncology team should include not only the surgical options, but also how the information from surgery may be used to determine subsequent therapies. Our work highlights the importance of multidisciplinary care and a more personalized approach to node-positive breast cancer, particularly in this elderly population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

DISCLOSURES

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Figure 1. Patient selection diagram based on data from the National Cancer Database (NCDB) from 2010–2015, applying the defined inclusion and exclusion criteria.

PUF: participant user file. M: metastasis status. cT: clinical tumor size stage. cN: clinical nodal stage. WHO: World Health Organization. ER: estrogen receptor. PR: progesterone receptor. HER2: human epidermal growth factor receptor 2.

Figure 2. Functional association of LN retrieval with OS based on multivariable Cox proportional hazards modeling with restricted cubic splines for the upfront surgery cohort (N=7995).

The optimal value of LN retrieval associated with a significant change in OS is indicated by the black arrow and vertical dotted line (21 LN, 90% CI 18–23). The median number of LNs retrieved (11) was used as the reference level for all HR estimates. Analysis based on a cohort of elderly women aged 70–90y with cT1–2 and cN1–3, and at least 1 LN removed at time of surgery; National Cancer Database, 2010–2015. Model adjusted for pT, pN, age, race/ethnicity, grade, ER (estrogen receptor) status, PR (progesterone receptor) status, HER2 (human epidermal growth factor receptor 2) status, facility type, facility location, insurance, surgery type, chemotherapy, radiation, endocrine. LN: lymph nodes. CI: confidence interval. HR: hazard ratio.

Figure 3. Functional association of LN retrieval with OS based on multivariable Cox proportional hazards modeling with restricted cubic splines for the neoadjuvant chemotherapy cohort (N=932).

No specific value of LN retrieval associated with a significant change in OS. The median number of LNs retrieved (12) was used as the reference level for all HR estimates. Analysis based on a cohort of elderly women aged 70–90y with cT1–2 and cN1–3, and at least 1 LN removed at time of surgery; National Cancer Database, 2010–2015. Model adjusted for pT, pN, age, race/ethnicity, grade, ER (estrogen receptor) status, PR (progesterone receptor) status, HER2 (human epidermal growth factor receptor 2) status, facility type, facility location, insurance, surgery type, chemotherapy, radiation, endocrine. LN: lymph nodes. HR: hazard ratio.

Table 1.
Summary of select patient demographics and facility characteristics.

Analysis based on a cohort of elderly women aged 70–90y with cT1–2 and cN1–3, and at least 1 LN removed at time of surgery; National Cancer Database, 2010–2015. Data presented as N (%) or Median (IQR) unless otherwise specified. IQR: interquartile range. LN: lymph node. NE: non-estimable due to low number of events.

	All Patients N=9,026 (100%)	Neoadjuvant Chemotherapy N=941 (10.4%)	Upfront Surgery N=8,085 (89.6%)	P-Value
Age				
Median (IQR)	76 (72 – 81)	73 (71 – 77)	77 (73 – 82)	<0.001
Median Follow-up Time				
Months (95% CI)	44.5 (43.8–45.5)	38.4 (36.7–41.3)	45.3 (44.3–46.2)	
Median Survival				
Months (95% CI)	83.8 (79.1 - NE)	NE	83.8 (79.1 - NE)	
Charlson/Deyo Comorbidity Score				
0	6,480 (71.8%)	739 (78.5%)	5,741 (71%)	<0.001
1	1,965 (21.8%)	162 (17.2%)	1,803 (22.3%)	
2	448 (5%)	34 (3.6%)	414 (5.1%)	
Race/Ethnicity				
Hispanic	371 (4.1%)	52 (5.5%)	319 (3.9%)	<0.001
Non-Hispanic Black	981 (10.9%)	146 (15.5%)	835 (10.3%)	
Non-Hispanic Other	255 (2.8%)	33 (3.5%)	222 (2.7%)	
Non-Hispanic White	7,007 (77.6%)	686 (72.9%)	6,321 (78.2%)	
Insurance Status				
Government	7,903 (87.6%)	810 (86.1%)	7,093 (87.7%)	0.26
Not Insured	49 (0.5%)	6 (0.6%)	43 (0.5%)	
Private	984 (10.9%)	117 (12.4%)	867 (10.7%)	
Facility Type				
Academic	2,230 (24.7%)	283 (30.1%)	1,947 (24.1%)	<0.001
Community	1,130 (12.5%)	90 (9.6%)	1,040 (12.9%)	
Comprehensive	4,664 (51.7%)	439 (46.7%)	4,225 (52.3%)	
Integrated Network	1,002 (11.1%)	129 (13.7%)	873 (10.8%)	

Table 2.
Summary of select disease characteristics and treatments.

Analysis based on a cohort of elderly women aged 70–90y with cT1–2 and cN1–3, and at least 1 LN removed at time of surgery; National Cancer Database, 2010–2015. Data presented as N (%) or Median (IQR). IQR: interquartile range. LN: lymph node. HR: hormone receptor status. HER2: human epidermal growth factor receptor 2. TNBC: triple-negative breast cancer.

	All Patients N=9,026 (100%)	Neoadjuvant Chemotherapy N=941 (10.4%)	Upfront Surgery N=8,085 (89.6%)	P-Value
LN Examined				
Median (IQR)	11 (6 – 17)	12 (6 – 16)	11 (6 – 17)	0.79
Positive LNs				
Median (IQR)	2 (1 – 5)	2 (1 – 5)	2 (1 – 5)	0.04
Histology				
Ductal	7,987 (88.5%)	854 (90.8%)	7,133 (88.2%)	0.002
Lobular	972 (10.8%)	75 (8%)	897 (11.1%)	
Other	67 (0.7%)	12 (1.3%)	55 (0.7%)	
Grade				
1	1,022 (11.3%)	72 (7.7%)	950 (11.8%)	<0.001
2	3,841 (42.6%)	329 (35%)	3,512 (43.4%)	
3	4,163 (46.1%)	540 (57.4%)	3,623 (44.8%)	
Hormone Receptor Status				
HR+	7,046 (78.1%)	575 (61.1%)	6,471 (80%)	<0.001
HR–	1,980 (21.9%)	366 (38.9%)	1,614 (20%)	
Molecular Subtype				
HER2+	1,531 (17%)	263 (27.9%)	1,268 (15.7%)	<0.001
HR+/HER2–	6,066 (67.2%)	418 (44.4%)	5,648 (69.9%)	
TNBC	1,429 (15.8%)	260 (27.6%)	1,169 (14.5%)	
Tumor Size (mm)				
Median (IQR)	25 (17 – 35)	28 (20 – 40)	25 (17 – 35)	<0.001
Clinical T Stage				
cT1	3,490 (38.7%)	210 (22.3%)	3,280 (40.6%)	<0.001
cT2	5,536 (61.3%)	731 (77.7%)	4,805 (59.4%)	
Clinical N Stage				
cN1	7,552 (83.7%)	732 (77.8%)	6,820 (84.4%)	<0.001
cN2	1,115 (12.4%)	138 (14.7%)	977 (12.1%)	
cN3	359 (4%)	71 (7.5%)	288 (3.6%)	
Pathological T Stage				
pT1	3,426 (38%)	532 (56.5%)	2,894 (35.8%)	<0.001
pT2	5,083 (56.3%)	343 (36.5%)	4,740 (58.6%)	
pT3	401 (4.4%)	51 (5.4%)	350 (4.3%)	

	All Patients N=9,026 (100%)	Neoadjuvant Chemotherapy N=941 (10.4%)	Upfront Surgery N=8,085 (89.6%)	P-Value
pT4	116 (1.3%)	15 (1.6%)	101 (1.2%)	
Pathological N Stage				
pN1	5,195 (57.6%)	451 (47.9%)	4,744 (58.7%)	<0.001
pN2	2,130 (23.6%)	203 (21.6%)	1,927 (23.8%)	
pN3	1,031 (11.4%)	90 (9.6%)	941 (11.6%)	
pN0	670 (7.4%)	197 (20.9%)	473 (5.9%)	
Local-regional Treatment				
Lumpectomy alone	747 (8.3%)	55 (5.8%)	692 (8.6%)	<0.001
Lumpectomy+radiation	2,850 (31.6%)	323 (34.3%)	2,527 (31.3%)	
Mastectomy alone	3,084 (34.2%)	188 (20%)	2,896 (35.8%)	
Mastectomy+radiation	2,345 (26%)	375 (39.9%)	1,970 (24.4%)	
Endocrine Therapy				
Received, HR+	5,888 (65.2%)	490 (52.1%)	5,398 (66.8%)	<0.001
Received, HR–	47 (0.5%)	5 (0.5%)	42 (0.5%)	
Not received, HR+	1,158 (12.8%)	85 (9%)	1,073 (13.3%)	
Not received, HR–	1,933 (21.4%)	361 (38.4%)	1,572 (19.4%)	

Table 3.
Summary of LNs retrieved and treatments received by pathological nodal (pN) stage.

Analysis based on a cohort of elderly women aged 70–90y with cT1–2 and cN1–3, and at least 1 LN removed at time of surgery; National Cancer Database, 2010–2015. Data presented as N (%) or Median (IQR). IQR: interquartile range. XRT: radiation therapy.

	Upfront Surgery				Neoadjuvant Chemotherapy			
	pN0	pN1	pN2	pN3	pN0	pN1	pN2	pN3
Total N (%)	459 (5.7%)	4,745 (58.7%)	1,942 (24.0%)	939 (11.6%)	135 (14.3%)	488 (51.9%)	216 (22.9%)	102 (10.8%)
Median # nodes retrieved (IQR)	3 (2–7)	10 (4–15)	13 (10–18)	19 (15–24)	7 (3–14)	10 (5–15)	13 (9.5–17)	18 (14–22)
Minimum # nodes retrieved to capture 90% of pN stage	14	20	22	30	21	20	22	26
Adjuvant chemotherapy N (%)	96 (20.9%)	1,679 (35.4%)	979 (50.4%)	536 (57.1%)	-	-	-	-
Lumpectomy +adjuvant radiation N (%)	173 (75.2%)	1,762 (79.9%)	425 (75.2%)	167 (76.6%)	48 (78.7%)	189 (87.9%)	62 (83.8%)	24 (85.7%)
Mastectomy +adjuvant radiation N (%)	15 (6.5%)	664 (26.1%)	823 (59.8%)	468 (64.9%)	33 (44.6%)	167 (61.2%)	115 (81.0%)	60 (81.1%)

Table 4.
Unadjusted 1-year and 5-year overall survival rates stratified by LN retrieval groups.

Analysis based on a cohort of elderly women aged 70–90y with cT1–2 and cN1–3, and at least 1 LN removed at time of surgery; National Cancer Database, 2010–2015. LN: lymph node. CI: confidence interval.

LN Retrieval Groups	Upfront Surgery		Neoadjuvant Chemotherapy	
	1-year survival (95% CI)	5-year survival (95% CI)	1-year survival (95% CI)	5-year survival (95% CI)
< 6	0.96 (0.95–0.97)	0.68 (0.65–0.71)	0.99 (0.98–1)	0.72 (0.62–0.84)
6–11	0.95 (0.94–0.96)	0.64 (0.62–0.67)	0.98 (0.97–1)	0.71 (0.64–0.79)
12–17	0.95 (0.94–0.96)	0.64 (0.62–0.67)	0.97 (0.95–0.99)	0.58 (0.5–0.68)
18–23	0.95 (0.94–0.96)	0.66 (0.63–0.7)	0.98 (0.95–1)	0.75 (0.67–0.85)
> 23	0.94 (0.93–0.96)	0.64 (0.6–0.69)	0.93 (0.87–0.99)	0.63 (0.51–0.78)
Total	0.95 (0.95–0.95)	0.65 (0.64–0.67)	0.98 (0.97–0.99)	0.68 (0.63–0.72)

Table 5.
Cox proportional hazard model of overall survival

(upfront surgery: N=7,626, event=1,968; neoadjuvant chemotherapy: N=909, event=201). Model adjusted for age, pT, pN, grade, ER (estrogen receptor) status, PR (progesterone receptor) status, HER2 (human epidermal growth factor receptor 2) status, facility type, facility location, insurance, surgery receipt, chemotherapy receipt, endocrine therapy receipt, and radiation receipt. LN: lymph node. HR: hazard ratio. CI: confidence interval

	Upfront Surgery			Neoadjuvant Chemotherapy		
LN Retrieval Groups	HR (95% CI)	P-value	Overall p-value	HR (95% CI)	P-value	Overall p-value
18–23	-REF-		<0.001	-REF-		0.58
<6	1.44 (1.21 – 1.70)	<0.001		0.91 (0.48 – 1.72)	0.76	
6–11	1.30 (1.11 – 1.51)	<0.001		1.12 (0.65 – 1.95)	0.68	
12–17	1.10 (0.95 – 1.27)	0.19		1.25 (0.74 – 2.09)	0.41	
> 23	1.08 (0.88 – 1.33)	0.46		1.30 (0.69 – 2.45)	0.42	