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ORIGINAL ARTICLE – BREAST ONCOLOGY

Association of LN Evaluation with Survival in Women Aged 70 Years or Older With Clinically Node-Negative Hormone Receptor Positive Breast Cancer

Anees B. Chagpar, MD, MSc, MPH, MA, MBA[1], Christos Hatzis, PhD[2], Lajos Pusztai, MD, DPhil[2], Michael P. DiGiovanna, MD, PhD[2], Meena Moran, MD[3], Sarah Mougalian, MD[2], Tara Sanft, MD[2], Suzanne Evans, MD[3], Erin Hofstatter, MD[2], Lynn D. Wilson, MD[3], and Donald R. Lannin, MD[1]

[1]Department of Surgery, Yale University School of Medicine and Yale Cancer Center, New Haven, CT; [2]Department of Medicine, Yale University School of Medicine and Yale Cancer Center, New Haven, CT; [3]Department of Therapeutic Oncology, Yale University School of Medicine and Yale Cancer Center, New Haven, CT

ABSTRACT

Background. Some suggest that lymph node (LN) evaluation not be performed routinely in women aged ≥70 years with clinically (c) LN-negative (−), hormone receptor (HR)-positive (+) breast cancer. We sought to determine the association of omission of LN evaluation on survival.

Methods. Patients who met the above criteria and were diagnosed from 2004 to 2012 were identified in the NCDB and SEER databases. Overall survival (OS) and breast cancer-specific survival (BCSS) were determined.

Results. Using the NCDB, we identified 157,584 cLN− HR+ patients aged ≥70 years in whom survival and LN evaluation data were available. A total of 126,638 patients (80.2%) had regional LN surgery. With a median follow-up of 41.6 months, there was a significant difference in OS between those who had LN evaluation and those who did not (median OS: 100.5 vs. 70.9 months, respectively, $p < 0.001$). After adjusting for patient age, race, insurance, income, comorbidities, tumor characteristics and treatment, patients who had undergone LN evaluation still had a lower hazard rate for death than those who had not (hazard ratio = 0.633; 95% confidence interval [CI] 0.613–0.654, $p < 0.001$). We then did a parallel analysis using SEER data that showed LN evaluation was associated with a lower hazard rate for both BCSS (hazard ratio = 0.452; 95% CI 0.427–0.479, $p < 0.001$) and non-BCSS (hazard ratio = 0.465; 95% CI 0.447–0.482, $p < 0.001$).

Conclusions. Roughly 20% of patients older than aged 70 years with cLN−, HR+ breast cancer did not have LN evaluation. Those who did had better OS controlling for sociodemographic, pathologic, and treatment variables; however, this may be due to patient selection.

In 2016, as part of the "Choosing Wisely" Campaign, the Society of Surgical Oncology recommended that surgeons "don't routinely use sentinel node biopsy in clinically node-negative women ≥70 years of age with HR+ invasive breast cancer."[1] Although it is generally accepted that lymph node (LN) evaluation is not associated with an improvement in survival, it is well-known that LN status is a key prognostic marker and may influence adjuvant therapy decisions.[2] Elderly patients, and particularly those with clinically LN-negative (−), hormone receptor (HR)-positive (+) breast cancer, are more likely to have indolent disease. While some may argue that LN evaluation in such patients is unlikely to change adjuvant management, we have previously demonstrated that LN evaluation, and LN status, is significantly correlated with the use of adjuvant systemic and radiation therapy *(presented at Southwestern Surgical Congress, Maui, Hawaii, April 2–5, 2017; publication in review at American Journal of Surgery)*. The association of LN evaluation with survival remains to be elucidated. We sought to determine in this study of the National Cancer Data Base (NCDB) and the Surveillance, Epidemiology and End Results (SEER)

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A. B. Chagpar, MD, MSc, MPH, MA, MBA
e-mail: Anees.chagpar@yale.edu

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database whether omission of LN evaluation is associated with overall survival.

METHODS

Patients who were aged ≥70 years when they were diagnosed with cLN− HR+ breast cancer from the years 2004 to 2012 were identified in the National Cancer Database (NCDB). The NCDB is a national resource which is jointly sponsored by the American College of Surgeons and the American Cancer Society. Sourced by hospital registry data collected from more than 1500 Commission on Cancer accredited facilities, the NCDB captures data on ~70% of cancer patients in the United States. We limited our analysis to patients whose tumor size was recorded and was less than 20 cm and to those who had follow-up of at least 0.5 months.

Overall survival differences between patients who had regional LN evaluation compared with those who did not were assessed using the technique of Kaplan and Meier, with log-rank tests. Bivariate analyses were performed to determine clinicopathologic covariates, which varied significantly between the two groups. Cox proportional regression analysis was performed to determine differences in overall survival between the group having LN evaluation and those who did not, controlling for the covariates found to be significant on bivariate analysis. In addition, given that the rate of LN evaluation changed over time as did overall survival given the length of follow-up available at different time points, we assessed the impact of LN evaluation on overall survival in a stratified analysis of patients with greater or less than 36 months of follow-up. Statistical analyses from NCDB were performed using IBM SPSS Statistics, version 22.

To evaluate the effect of lymph node evaluation on breast cancer-specific survival, we also performed a similar analysis using data from the Surveillance, Epidemiology, and End Results (SEER) Program.[3] Statistical analyses from SEER were performed using both SPSS and R Statistics. Given that this analysis used publically available deidentified data, this work was deemed exempt from the Yale University Human Investigations Committee.

RESULTS

There were 157,942 cLN− HR+ patients aged ≥70 years who were identified in the NCDB from 2004 to 2012 and who met our criteria. Whether lymph node evaluation was performed or not was unknown in 358 patients; the remaining 157,584 patients formed the cohort of interest. Median patient age was 77 (range 70–90) years, and the median tumor size was 14 (range 1–195) mm. A total of 126,638 patients (80.2%) had regional LN surgery. Of the 125,826 in whom LN status was known, 18,967 (15.0%) were found to be LN+; the median number of positive LNs was 1 (range; 1–57). Socioeconomic, pathologic, and demographic variables that correlated with LN evaluation are shown in Table 1. Overall, 69.2% of patients received endocrine therapy; however, the proportion of patients receiving endocrine therapy varied based on LN evaluation (Table 1).

With a median follow-up of 41.6 months, there was a significant difference in OS between those who had LN evaluation and those who did not (median survival 100.5 vs. 70.9 months, respectively; $p < 0.001$). A multivariate Coxs proportional hazards model for overall survival, controlling for patient age, tumor size, race, gender, ethnicity, community size, region, insurance status, patient comorbidities (Charlson–Deyo Score), income, tumor grade, type of surgery, receipt of radiation therapy, chemotherapy, and endocrine therapy, is shown in Table 2. While receipt of radiation therapy and endocrine therapy were both independently associated with a lower hazard for death, LN evaluation also was independently associated with a lower hazard for death (hazard ratio = 0.633; 95% confidence interval [CI] 0613–0.654, $p < 0.001$; Fig. 1). In a separate analysis, in which we excluded patients who did not have surgery for their primary breast cancer, we found that the association of LN evaluation with a lower hazard of death independent of all of the factors noted above (including receipt of radiation therapy and hormonal therapy) was maintained (hazard ratio = 0.639; 95% CI 0.618–0.660, $p < 0.001$).

Over time, the proportion of patients who did not have LN evaluation decreased. In 2004, 29.2% of cLN− HR+ patients aged ≥70 years had no LN evaluation, whereas in 2012, 18.7% had no LN evaluation ($p < 0.001$). Because patients diagnosed in later years had a shorter possible follow-up time, we hypothesized that there may be a time-dependence to the effect of LN evaluation on overall survival. To evaluate this hypothesis, we separately analyzed patients who had follow-up or death within 36 months and those who had at least 36 months of follow-up. In both circumstances, LN evaluation was associated with longer overall survival (mean survival 31.6 vs. 24.2 months, $p < 0.001$, and 108.1 vs. 90.7 months, $p < 0.001$, respectively). We further evaluated patients diagnosed in 2004 and those diagnosed in 2012 and found in each of those 2 years that LN evaluation was associated with longer survival (mean survival 100.6 vs. 73.7 months, $p < 0.001$ and 34.7 vs. 31.0 months, $p < 0.001$).

Analysis Using SEER Database

Because the NCDB database only includes overall survival, we conducted a parallel analysis using the SEER database to assess the relationship of lymph node

TABLE 1 Factors correlated with LN evaluation (NCDB data)

	No LN evaluation	LN evaluation	*p* value
Mean patient age (yr; 95% CI)	82.2 (82.1–82.2)	77.0 (77.0–77.0)	<0.001
Mean tumor size (mm; 95% CI)	18.0 (17.8–18.2)	16.6 (16.6–16.7)	<0.001
Race			
White	27,766 (89.7%)	114,744 (90.6%)	<0.001
Black	2328 (7.5%)	8053 (6.4%)	
Other	852 (2.8%)	3841 (3.0%)	
Male gender	364 (1.2%)	1789 (1.4%)	0.001
Hispanic ethnicity	801 (2.8%)	3715 (3.1%)	0.002
Community description/size			
Metro area: >1 million (M)	17,227 (57.8%)	64,347 (52.3%)	<0.001
Metro area: 250,000–1 M	6576 (22.1%)	27,469 (22.3%)	
Metro area: <250,000	2545 (8.5%)	13,020 (10.6%)	
Urban area: 20,000+	1587 (5.3%)	7103 (5.8%)	
Urban area: 2500–19,999	1534 (5.1%)	9053 (7.4%)	
Rural area: <2500	330 (1.1%)	2127 (1.7%)	
Type of facility			
Community Cancer Program	4215 (19.9%)	16,938 (80.1%)	<0.001
Comprehensive Community Cancer Program	16,034 (18.6%)	70.249 (81.4%)	
Academic/Research Program	8535 (22.0%)	30,336 (78.0%)	
Integrated Network Cancer Program	2067 (18.7%)	9001 (81.3%)	
Region			
New England	3693 (11.9%)	7283 (5.8%)	<0.001
Middle Atlantic	5502 (17.8%)	19,358 (15.3%)	
South Atlantic	5936 (19.2%)	26,111 (20.6%)	
East North Central	6214 (20.1%)	24,185 (19.1%)	
East South Central	1450 (4.7%)	7352 (5.8%)	
West North Central	1969 (6.4%)	10,622 (8.4%)	
West South Central	1555 (5.0%)	8936 (7.1%)	
Mountain	1108 (3.6%)	6129 (4.8%)	
Pacific	3519 (11.4%)	16,662 (13.2%)	
Insurance			
Uninsured	120 (0.4%)	379 (0.3%)	<0.001
Private	2891 (9.5%)	13,873 (11.1%)	
Medicaid	344 (1.1%)	1226 (1.0%)	
Medicare	27,100 (88.7%)	109,418 (87.3%)	
Other govt.	81 (0.3%)	413 (0.3%)	
Charlson–Deyo score			
0	23,613 (76.3%)	99,068 (78.2%)	<0.001
1	5370 (17.4%)	22,212 (17.5%)	
2	1963 (6.3%)	5358 (4.2%)	
Median income			
<$38,000	4438 (14.5%)	18,458 (14.7%)	<0.001
$38,000–$47,999	6508 (21.3%)	29,151 (23.2%)	
$48,000–$62,999	8161 (26.8%)	35,055 (27.9%)	
$63,000+	11,397 (37.4%)	42,851 (34.1%)	
Tumor grade			

TABLE 1 continued

	No LN evaluation	LN evaluation	*p* value
1	10,348 (36.5%)	41,725 (34.7%)	<0.001
2	14,147 (49.9%)	61,849 (51.4%)	
3	3854 (13.6%)	16,800 (14.0%)	
Surgery			
None	6575 (21.3%)	100 (0.1%)	<0.001
Lumpectomy	19,346 (62.7%)	81,419 (64.3%)	
Mastectomy	4920 (16.0%)	45,088 (35.6%)	
Radiation therapy	6431 (21.3%)	65,579 (52.4%)	<0.001
Chemotherapy	789 (2.7%)	10,930 (9.0%)	<0.001
Endocrine therapy	16,096 (54.6%)	88,715 (72.8%)	<0.001

evaluation to breast cancer specific survival. SEER captures patient data in a subset of geographical areas in the United States and hence overlaps with the NCDB database; however, SEER includes more detailed information regarding cause of death.

There were 116,059 women aged 70 and older with invasive, HR+ breast cancer diagnosed from 2004 to 2012. The population demographic was very similar to the NCDB patients shown in Table 1. The mean age was 78 (77 for those with LN evaluation and 82 without). There were 87% white, 7% blacks, and 6% other race, and additionally 6% had Hispanic ethnicity. Similar to the NCDB patients, 79.8% underwent lymph node evaluation and the remainder did not. Also similar to the NCDB, 39.9% underwent radiation therapy (45.5% of those with LN evaluation and 17.5% of those without). Unfortunately, SEER does not provide information about use of chemotherapy or endocrine therapy.

In contrast to the NCDB database, the SEER database only uses clinical stage when pathological stage is not available. As a result, we selected patients with clinically negative nodes for the patients who did not undergo lymph node evaluation, but for the patients who did undergo lymph node biopsy, we cannot determine whether they were clinically node-positive or -negative. Of those who underwent LN evaluation, 26.4% had positive nodes, which is somewhat higher than the NCDB patients.

In the entire group, 33% of the deaths were due to breast cancer and 67% due to other causes. As shown in Fig. 2a, the overall survival was similar to that seen in the NCDB analysis and was much better for patients who underwent lymph node evaluation. However as shown in Fig. 2b and c, both the breast cancer and non-breast cancer survival were better in the lymph node-evaluated patients. This suggests that the effect is due to patient selection using factors that cannot be adjusted for in the multivariate Cox analysis and not due to a direct therapeutic effect of LN evaluation on the breast cancer.

Table 3 shows a Cox regression model using LN evaluation, patient age, tumor size, race, ethnicity, tumor grade, and receipt of radiation therapy. Even when adjusted for these other variables, LN evaluation was associated with a similar reduction in the hazard ratio for both breast cancer and non-breast cancer deaths, suggesting again that this was due to selection of good prognosis patients to undergo LN evaluation. Interestingly, the results are similar to those for radiation therapy, suggesting that the benefit associated with radiation also is due to patient selection rather than a direct benefit from radiation.

DISCUSSION

It has long been suggested that LN evaluation and removal of clinically negative LNs does not influence survival.[2] However, it has also been well-accepted that LN status is a key prognostic marker, and one which can affect adjuvant therapy decisions. Hence, the SSO "Choosing Wisely" guideline caused some controversy in that it advocated eliminating the routine use of SLNB in elderly patients with cLN− HR+ breast cancer. We hypothesized that patients who did not have LN evaluation would be less likely to receive adjuvant therapy and therefore may have a worse survival. Patients who did not have LN evaluation were older, had more comorbidities, and were less likely to receive surgery for their primary tumor or other adjuvant therapy. Despite controlling for tumor size, grade, patient age, comorbidities, and treatment factors, we found that patients who did not have LN evaluation still had a worse survival compared with those who had LN evaluation. The parallel analysis with SEER data suggests, however, that this may be related to selection bias and other factors that were not adequately captured in the NCDB. In other words, surgeons may have avoided LN evaluation based on their clinical judgement of which patients had limited longevity, independent of the factors captured in the database that were controlled for in the analysis.

TABLE 2 Multivariate Cox proportional hazard model for overall survival (NCDB data)

	HR (95% CI)	*p* value
LN evaluation	0.633 (0.613–0.654)	<0.001
Mean patient age	1.075 (1.073–1.078)	<0.001
Mean tumor size	1.014 (1.013–1.015)	<0.001
Race		
White	Referent	0.011
Black	0.985 (0.936–1.037)	
Other	0.860 (0.778–0.950)	
Female gender	0.745 (0.680–0.8150	<0.001
Hispanic ethnicity	0.777 (0.712–0.849)	<0.001
Community description/size:		<0.001
Metro area: >1 million (M)	Referent	
Metro area: 250,000–1 M	1.091 (1.057–1.127)	
Metro area: <250,000	1.149 (1.101–1.199)	
Urban area: 20,000+	1.064 (1.007–1.125)	
Urban area: 2500–19,999	1.057 (1.000–1.116)	
Rural area: <2500	1.020 (0.918–1.133)	
Region		
New England	Referent	<0.001
Middle Atlantic	1.010 (0.954–1.069)	
South Atlantic	1.029 (0.975–1.087)	
East North Central	1.096 (1.038–1.157)	
East South Central	1.071 (0.998–1.150)	
West North Central	1.139 (1.068–1.215)	
West South Central	1.012 (0.943–1.085)	
Mountain	0.998 (0.926–1.076)	
Pacific	0.876 (0.826–0.929)	
Insurance		
Uninsured	Referent	0.452
Private	1.112 (.869–1.424)	
Medicaid	1.244 (0.945–1.637)	
Medicare	1.119 (0.876–1.428)	
Other govt.	1.077 (0.765–1.515)	
Charlson–Deyo score		
0	Referent	<0.001
1	1.510 (1.465–1.556)	
2	2.408 (2.303–2.518)	
Median income		
<$38,000	Referent	<0.001
$38,000–$47,999	0.979 (0.941–1.020)	
$48,000–$62,999	0.929 (0.892–0.968)	
$63,000+	0.900 (0.863–0.939)	
Tumor grade		
1	Referent	<0.001
2	1.108 (1.077–1.139)	
3	1.366 (1.315–1.418)	
Surgery		

TABLE 2 continued

	HR (95% CI)	*p* value
None	Referent	<0.001
Lumpectomy	0.525 (0.500–0.552)	
Mastectomy	0.509 (0.483–0.537)	
Radiation therapy	0.675 (0.653–0.698)	<0.001
Chemotherapy	1.006 (0.952–1.063)	0.836
Endocrine therapy	0.738 (0.718–0.757)	<0.001

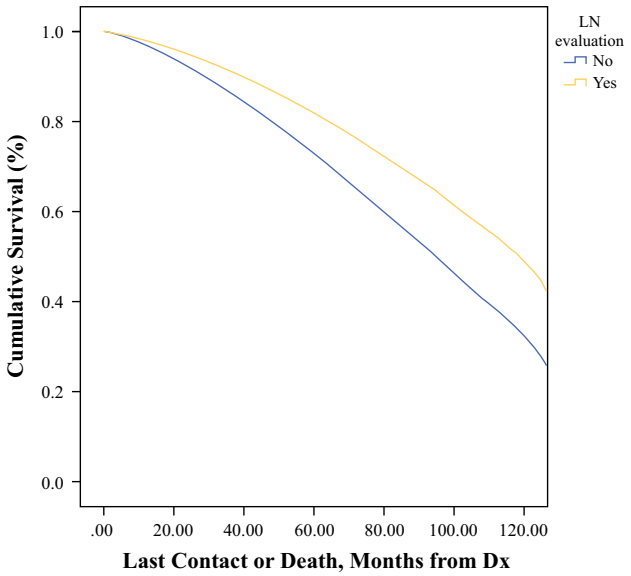

FIG. 1 Cox proportional hazards model for LN evaluation (NCDB data). Multivariable Cox proportional hazard model for overall survival based on LN evaluation using NCDB

A limitation of this study is that neither the NCDB nor SEER provided data regarding locoregional recurrence or disease-free survival. Hence, we cannot comment on this. While our study found that patients who had LN evaluation had an improved overall survival compared with those who did not, independent of sociodemographic, clinicopathologic, and treatment variables, these data are contrary to the NSABP B-04 trial, which found no survival impact of LN removal in cLN negative patients.[2] There almost certainly are unaccounted variables in our analysis that affected survival outcomes. Neither the NCDB nor SEER, for example, contained data regarding compliance with treatment or detailed specifics regarding therapies delivered. It is possible that patients who had LN evaluation were more likely to be compliant with and/or to seek out more aggressive therapies than those who did not and may enjoy better survival as a result. While our findings indicate a positive association between LN evaluation and survival, we cannot infer causation.

Data have been mixed regarding the survival impact of avoiding LN evaluation in the elderly. For example, in a retrospective Italian study, Limite et al. found no difference in either overall or disease-free survival in their cohort of patients older than age 65 years based on whether LN evaluation was performed.[4] Similarly, Martelli et al. found, in their study of 671 patients older than age 70 years (172 of whom had an axillary LN dissection and 499 of whom who did not) that there was no difference in breast cancer mortality nor distant metastases between the two groups.[5] In a study of the SEER registry, Aziz et al. found that those who had an ALND had a better 5-year unadjusted cause-specific survival than those who did not (92.1 vs. 90.6%, hazard ratio = 0.85, $p = 0.002$). However, after adjusting for differences in the probability of receiving an ALND in a propensity analysis, the adjusted hazard rate decreased to 0.89 and significance diminished ($p = 0.066$).[6] A study from the University of Texas M.D. Anderson Cancer Center also found that patients older than age 80 years who did not have LN evaluation had worse overall ($p < 0.001$) and disease-free ($p = 0.04$) survival.[7] In their study of 212 patients older than age 80 years, lymph node evaluation was omitted in 39%, often due to the perception of significant comorbidities or poor overall health. However, they noted that 80% of their patients were ASA class 1 or 2. This raises the issue of whether patients who did not have LN evaluation truly had a worse prognosis and therefore avoided the additional procedure, or whether not having LN evaluation resulted in a worse prognosis due to undertreatment.

Some have noted that undertreatment, including the omission of LN evaluation in the elderly, results in worse outcomes, whereas others have found this not to be the case.[8–10] We note that the sample sizes of these earlier studies vary broadly, and this influences the power of the analysis, particularly the ability to perform adequate multivariate adjustments. In a more recent study of data from the SEER registry evaluating the impact of adherence to following established standards of care in terms of LN evaluation and receipt of radiation therapy in patients older than age 55 years with stage 1 breast cancer, Sun et al.

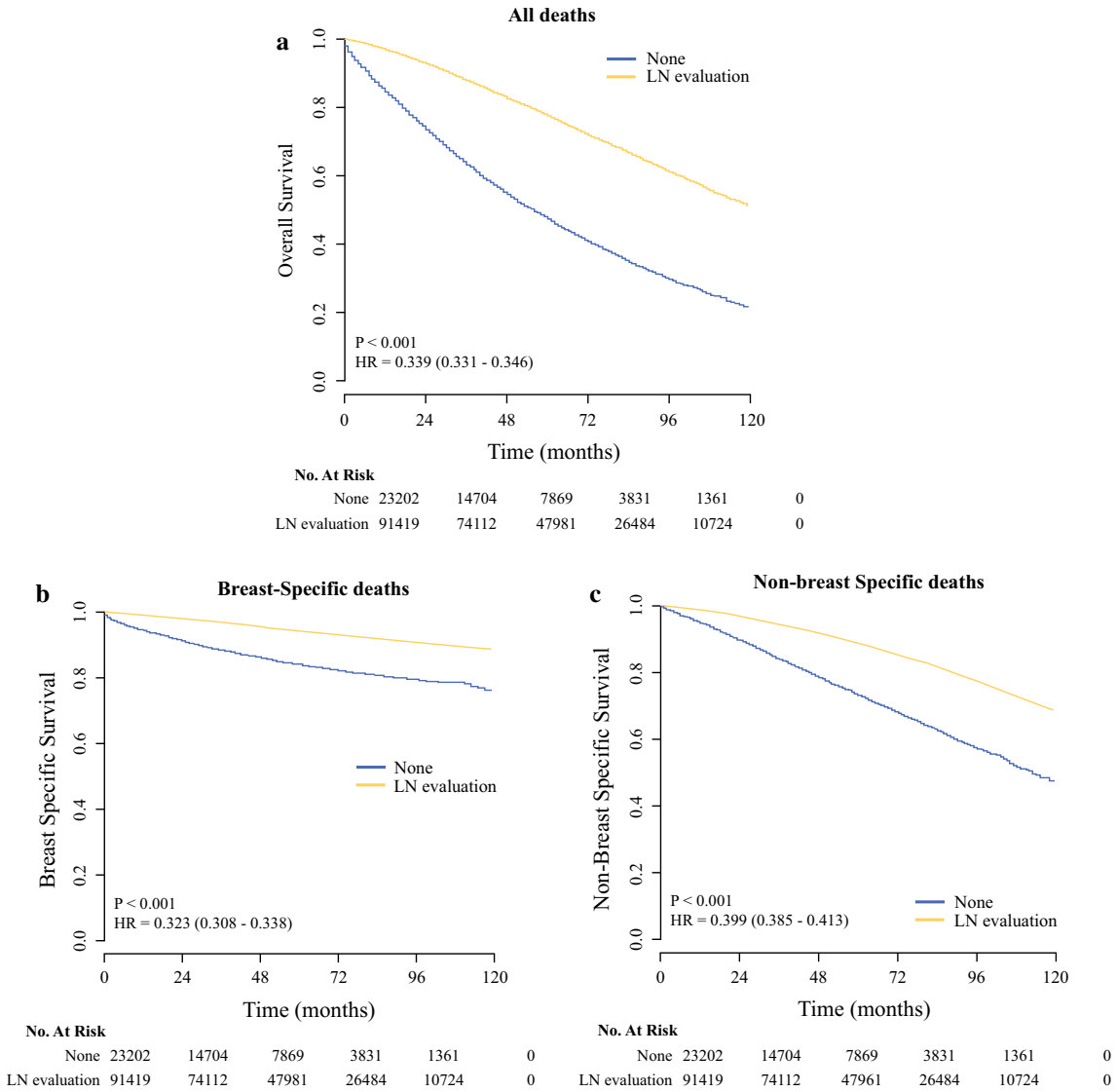

FIG. 2 Kaplan–Meier curves for overall (**a**), breast-specific (**b**), and non-breast-specific survival (**c**) Survival based on LN evaluation. SEER data 2004–2012

found that adherence to the guidelines was associated with improved overall 10-year survival rate even after propensity score matching, and those who underwent LN evaluation had 1.3% lower breast cancer-specific mortality than those who did not ($p < 0.001$).[11]

Some studies have found that LN status does not affect survival in patients older than age 70 years.[12,13] Others, however, have found positive LN status to be independently associated with disease progression in elderly patients.[14] LN evaluation is not without its risks, including numbness, decreased range of motion of the shoulder, and the potential for lymphedema.[15] In addition, many surgeons require general anesthesia even for a sentinel LN biopsy and may otherwise like to avoid this in an elderly patient. Given that only 15% of these patients would be found to be LN-positive if they underwent LN evaluation, the benefit of this information in altering their treatment course must be weighed against these risks. While some have argued that, particularly for HR+ patients, endocrine therapy would be the mainstay and therefore LN evaluation would be of little added value, several studies have found that this information *does* impact care by increasing the use of endocrine therapy in patients, particularly in those with smaller tumors.[16–18] These findings largely echo the associations found in our study.

Given life tables to predict longevity, geriatric assessment tools to predict comorbidities, and clinical nomograms that can help to predict the likelihood of LN metastases in elderly patients, surgeons have a number of tools to use to tailor the use of LN evaluation in a selective

TABLE 3 Multivariate Cox proportional hazard model (SEER data)

	Overall survival		Breast cancer-specific survival		Non-breast cancer-specific survival	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
LN evaluation	0.418 (0.408–0.429)	<0.001	0.452 (0.427–0.479)	<0.001	0.465 (0.447–0.482)	<0.001
Patient age (per year increase in age)	1.006 (1.006–1.006)	<0.001	1.005 (1.005–1.006)	<0.001	1.006 (1.006–1.007)	<0.001
Tumor size (per mm increase in size)	1.005 (1.005–1.006)	<0.001	1.007 (1.006–1.007)	<0.001	1.005 (1.005–1.005)	<0.001
Race:		<0.001		<0.001		<0.001
White	Referent		Referent		Referent	
Black	1.157 (1.108–1.207)		1.501 (1.382–1.631)		1.134 (1.064–1.207)	
Other	0.715 (0.673–0.759)		0.831 (0.735–0.941)		0.754 (0.694–0.820)	
Hispanic ethnicity	0.819 (0.777–0.864)	<0.001	1.061 (0.956–1.178)	0.264	0.861 (0.799–0.927)	<0.001
Tumor grade						
1	Referent	<0.001	Referent	<0.001	Referent	<0.001
2	1.290 (1.254–1.327)		2.198 (2.033–2.376)		1.153 (1.109–1.198)	
3	1.808 (1.750–1.868)		4.874 (4.501–5.277)		1.319 (1.258–1.383)	
Radiation therapy	0.565 (0.551–0.580)	<0.001	0.678 (0.642–0.717)	<0.001	0.606 (0.584–0.628)	<0.001

fashion to individual patients.[19,20] Indeed, our results suggest that surgeons are already quite good at selecting healthy patients who would have the most chance of benefiting from the sentinel node biopsy. The SSO Choosing Wisely guideline likely could be followed without substantially adversely affecting survival outcomes in elderly cLN− HR+ patients who have excellent predicted survival (e.g., those with low histologic grade, high endocrine therapy sensitivity by Oncotype Dx recurrence score, etc.) and those with limited life expectancy due to advanced age or from significant comorbidities. On the other hand, the selective use of LN evaluation in selected higher risk, healthy elderly patients may provide staging information and potential therapeutic impact that could contribute to the better survival seen in our analysis. Therefore, management decisions with regards to LN evaluation in this population should be taken in a multidisciplinary context.

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