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Clinical Investigation

Prognostic Significance of the Number of Positive Lymph Nodes in Women With T1-2N1 Breast Cancer Treated With Mastectomy: Should Patients With 1, 2, and 3 Positive Lymph Nodes Be Grouped Together?

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Summary

Our study was designed to analyze and compare the survival of T1-2N1 post-mastectomy patients according to whether they have 1, 2, or 3 positive lymph nodes. Using the SEER database, we found that patients with 1, 2, and 3 positive nodes have very distinct outcomes, with increasing number of positive nodes associated with worse overall survival and cause-specific survival. Our result challenges the conventional grouping of patients with 1-3 positive nodes.

Purpose: To determine whether patients with 1, 2, or 3 positive lymph nodes (LNs) have similar survival outcomes.

Methods and Materials: We analyzed the Surveillance, Epidemiology, and End Results registry of breast cancer patients diagnosed between 1990 and 2003. We identified 10,415 women with T1-2N1M0 breast cancer who were treated with mastectomy with no adjuvant radiation, with at least 10 LNs examined and 6 months of follow-up. The Kaplan-Meier method and log−rank test were used for survival analysis. Multivariate analysis was performed using the Cox proportional hazard model.

Results: Median follow-up was 92 months. Ten-year overall survival (OS) and cause-specific survival (CSS) were progressively worse with increasing number of positive LNs. Survival rates were 70%, 64%, and 60% (OS), and 82%, 76%, and 72% (CSS) for 1, 2, and 3 positive LNs, respectively. Pairwise log−rank test P values were $<.001$ (1 vs 2 positive LNs), $<.001$ (1 vs 3 positive LNs), and .002 (2 vs 3 positive LNs). Multivariate analysis showed that number of positive LNs was a significant predictor of OS and CSS. Hazard ratios increased with the number of positive LNs. In addition, age, primary tumor size, grade, estrogen receptor and progesterone receptor status, race, and year of diagnosis were significant prognostic factors.

Conclusions: Our study suggests that patients with 1, 2, and 3 positive LNs have distinct survival outcomes, with increasing number of positive LNs associated with worse OS and CSS. The conventional grouping of 1-3 positive LNs needs to be reconsidered.

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Introduction

In node-positive breast cancer, the conventional grouping of 1-3 versus 4 involved axillary nodes has been used in making treatment decisions (1). In 2001, the American Society of Clinical Oncology recommended postmastectomy radiation therapy (PMRT) in patients with 4 or more positive lymph nodes (2). However, for those with tumor <5 cm and 1-3 positive lymph nodes (T1-2N1), the guideline stated that "There is insufficient evidence to make recommendations or suggestions for the routine use of PMRT."

In recent years, the distinction of 1-3 versus 4 positive nodes and their respective benefit from PMRT has been challenged. A subset of analysis of the Danish 82b and 82c trials pooled 1152 node-positive patients with at least 8 lymph nodes removed. The same magnitude of overall survival (OS) benefit was observed for patients with 1-3 and those with ≥4 involved lymph nodes (3). This finding supports the notion that PMRT may be equally beneficial in patients with 1-3 and 4 positive lymph nodes. In addition, the Early Breast Cancer Trialist' Collaborative Group (4) reported a meta-analysis of 8505 women with lymph node-positive disease treated with mastectomy and axillary surgery. They reported a 17% reduction in local recurrence at 5 years, translating to a 4.4% reduction in overall mortality at 15 years, supporting a benefit of PMRT in any node-positive patients. Unfortunately, Intergroup S9923, the phase 3 trial randomizing women with 1-3 positive nodes to PMRT versus no RT was closed early in 2003 owing to insufficient accrual.

Along a similar line, the National Cancer Institute of Canada Clinical Trial Group (NCIC-CTG) MA20 study randomized post-lumpectomy patients with 1-3 positive nodes to regional nodal irradiation (RNI) versus no RNI. Preliminary results at 5 years showed that the addition of RNI reduced the risk of locoregional and distant recurrence (5). Regional nodal irradiation also improved disease-free survival, with a trend toward improved OS. Results of MA20 can be extrapolated to postmastectomy patients, providing support for PMRT in T1-2N1 postmastectomy patients. However, MA20 also raises the question of whether all patients with 1-3 positive lymph nodes should receive PMRT or whether there is an identifiable cohort that is at higher risk.

Because of the conventional grouping of 1-3 versus 4 positive lymph nodes in retrospective and prospective studies, outcomes of patients with 1-3 positive nodes have been analyzed and reported as a unified group. As such, there is a paucity of data examining whether, within this group, patients have similar survival outcomes. Patients with 1 positive node may not necessarily be equal to those with 2 or 3 positive nodes. In this study, we sought to analyze and compare the OS and cause-specific survival (CSS) in T1-2N1 postmastectomy patients according to whether they have 1, 2, or 3 positive lymph nodes, using a cohort of women from the Surveillance, Epidemiology, and End Results (SEER) database.

Methods and Materials

Study population

The SEER cancer registry maintained by the National Cancer Institute was used to identify the patient population for this study. We identified women with pathologically confirmed invasive breast cancer diagnosed between 1990 and 2003. We chose this time period because (*1*) patients were more likely to have received doxorubicin-based chemotherapy, (*2*) patients were less likely to have received neoadjuvant chemotherapy, and (*3*) the routine use of axillary lymph node dissection alone or in conjunction with a positive sentinel lymph node was prevalent.

We then narrowed the study population to women who underwent mastectomy with pathologic tumor size ≤5 cm and 1-3 positive lymph nodes. To avoid the potential confounding effects of radiation, we excluded patients who received adjuvant radiation therapy. We also excluded patients with fewer than 10 nodes dissected to ensure adequate nodal clearance. From this cohort, we further excluded those with <6 months of follow-up, bilateral tumors, stage IV disease at presentation, and history of prior malignancies. In addition, patients with incomplete information regarding grade (2786), estrogen receptor (ER) status (2670), and progesterone receptor (PR) status (376) were excluded. A total of 10,415 women formed the study population.

Study endpoints

Primary endpoint was OS, defined as the interval between the date of diagnosis and the date of death from any cause. The secondary end point was CSS, defined as the interval between the date of diagnosis and the date of death from breast cancer. Individuals with unknown cause of death were censored, but not excluded, in the breast cancer CSS analysis.

Follow-up time was calculated from the month and year of initial diagnosis to the date of last contact or death. Vital status and data of last contact were available for all patients. The follow-up time was available through December 2008 at the time of analysis.

According to SEER (www.seer.gov), "…cancer registries use algorithms to process causes of death from death certificate in order to identify a single, disease-specific, underlying cause of death. In some cases, attribution of a single cause of death may be difficult and misattribution may occur. For example a death may be attributed to the site of metastasis instead of the primary site…. To capture deaths related to the specific cancer but not coded as such, the SEER cause-specific death classification variables are defined by taking into account causes of deaths in conjunction with tumor sequence (ie, only one tumor or the first of subsequent tumors), site of the original cancer diagnosis, co-morbidities (eg, AIDS and/or site-related diseases)."

The reliability of using death certificates in determining CSS has been examined. German et al (6) reported a concordance rate >90% for breast cancer when comparing cause of death from death certificates recorded by the state and cancer site recorded by registry. In patients with distant-stage disease, Lund et al (7) reported 85% agreement between coded cause of death and initial diagnosis. A recent study by Howlader et al (8) reported similar estimates of relative survival and CSS for breast cancer calculated from SEER, supporting the use CSS in estimating cancer mortality, especially when suitable life tables are not available to calculate relative survival.

Statistical analysis

Pearson's χ^2 test was used to assess the associations between 1, 2, and 3 positive lymph nodes groups and covariates.

Survival estimates were calculated using the Kaplan-Meier method and reported with their 95% confidence intervals for 5-, 10-, and 15-year time points. We compared OS and CSS between

nodal subgroups using the log−rank test. To determine whether the number of positive lymph nodes is an independent predictor of OS and/or CSS, we performed multivariate analysis using the Cox proportional hazard model. Age, tumor size, number of positive lymph nodes, grade, ER and PR status, year of diagnosis, and race were included as variables. Year of diagnosis has been shown to be a prognostic factor in a number of studies, with more recent years of diagnosis correlating with lower risk of death and breast cancer-specific death (9-11). We included year of diagnosis in the multivariate analysis to reduce any confounding effect of this variable on the number of positive lymph nodes.

Data were reported as hazard ratios with their 95% confidence intervals. Statistical significance was defined as a P value $<.05$. For multiple pair-wise comparisons, the Bonferroni correction was used to assess for clinical significance, with P value defined as $P < .05/n$, where n is the number of comparisons. Statistical analysis was performed using IBM Statistics SPSS 20 (Armonk, NY) and STATA (StataCorp, College Station, TX).

Results

Of the 10,415 patients included in the study, the median age was 57 years (range, 23-97 years). The median tumor size was 21 mm (range, 1-50 mm). The median number of nodes examined was 15 (range, 10-57). Table 1 summarizes the patient characteristics.

Table 1 Clinical characteristics of the entire study population and according to the number of positive lymph nodes

Variable	Total	Positive nodes			P*
		1	2	3	
N	10,145	5606	3051	1758	
Age at diagnosis (y)					.28
≤40	1129	589 (11)	327 (11)	213 (12)	
41-50	2470	1298 (23)	739 (24)	433 (25)	
51-59	2223	1199 (21)	656 (21)	368 (21)	
≥60	4593	2520 (45)	1329 (44)	744 (42)	
Median	57				
Range	23-97				
Year of diagnosis					.014
1990-1994	2709	1419 (25)	798 (26)	492 (28)	
1995-1999	3137	1648 (29)	942 (31)	547 (31)	
2000-2003	4569	2539 (45)	1311 (43)	719 (41)	
Tumor size					<.0001
T1	5054	2947 (53)	1401 (46)	706 (40)	
T2	5361	2659 (47)	1650 (54)	1052 (60)	
Median	21				
Range	0.1-5				
Grade					<.0001
Well differentiated	1041	635 (11)	281 (9)	125 (7)	
Moderately differentiated	4637	2503 (45)	1368 (45)	766 (44)	
Poor or undifferentiated	4737	2468 (44)	1402 (46)	867 (49)	
ER status					.64
Positive	7934	4291 (77)	2313 (76)	1330 (76)	
Negative	2481	1315 (23)	738 (24)	428 (24)	
PR status					.95
Positive	6927	3731 (67)	2023 (66)	1173 (67)	
Negative	3488	1875 (33)	1028 (34)	585 (33)	
Nodes examined					.0038
≤15	5341	2950 (53)	1543 (51)	848 (48)	
>15	5074	2656 (47)	1508 (49)	910 (52)	
Median	15				
Range	10-57				
Nodal ratio (%)					<.0001
<20	9723	5606 (100)	3051 (100)	1066 (61)	
≥20	692	0 (0)	0 (0)	692 (39)	
Race					.0053
White	8595	4695 (84)	2481 (81)	1419 (81)	
Black	911	442 (8)	292 (10)	177 (10)	
Other or unknown	909	469 (8)	278 (9)	162 (9)	

Abbreviations: ER = estrogen receptor; nodal ratio = number of positive lymph nodes divided by the total number of lymph nodes dissected; PR = progesterone receptor.

Values are number (percentage).

* Pearson's χ^2 test.

In all, 5606 (54%), 3051 (29%), and 1758 (17%) patients had 1, 2, and 3 positive lymph nodes, respectively. Regarding treatment, all patients underwent mastectomy, and no patients received PMRT. Because of the limitation of the SEER registry, systemic therapy information was not available for the study cohort.

Median follow-up was 92 months. Kaplan-Meier estimates of OS and CSS, stratified by the number of positive lymph nodes, showed progressively worse survival with increasing number of positive lymph nodes (Fig. 1). Pairwise log−rank test *P* values were <.001 (1 vs 2 positive LNs), <.001 (1 vs 3 positive LNs), and .002 (2 vs 3 positive LNs) for both OS and CSS. Table 2 lists 5-, 10-, and 15-year OS and CSS survival rates with their 95% confidence intervals, stratified by the number of positive lymph nodes.

To determine whether the number of positive lymph nodes is an independent predictor of OS and CSS, we performed multivariate analyses using the Cox proportional hazard model (Tables 3 and 4). The result showed that the hazard of death from breast cancer and from any cause increased with the number of positive lymph nodes. For OS, the hazard ratio was 1.150, comparing 2 versus 1 positive LNs. The hazard ratio increased to 1.324, comparing 3 versus 1 positive LNs. For CSS, the hazard ratio increased from 1.324, comparing 2 versus 1 positive LNs, to 1.538 comparing 3 versus 1 positive LNs (all *P* values <.001).

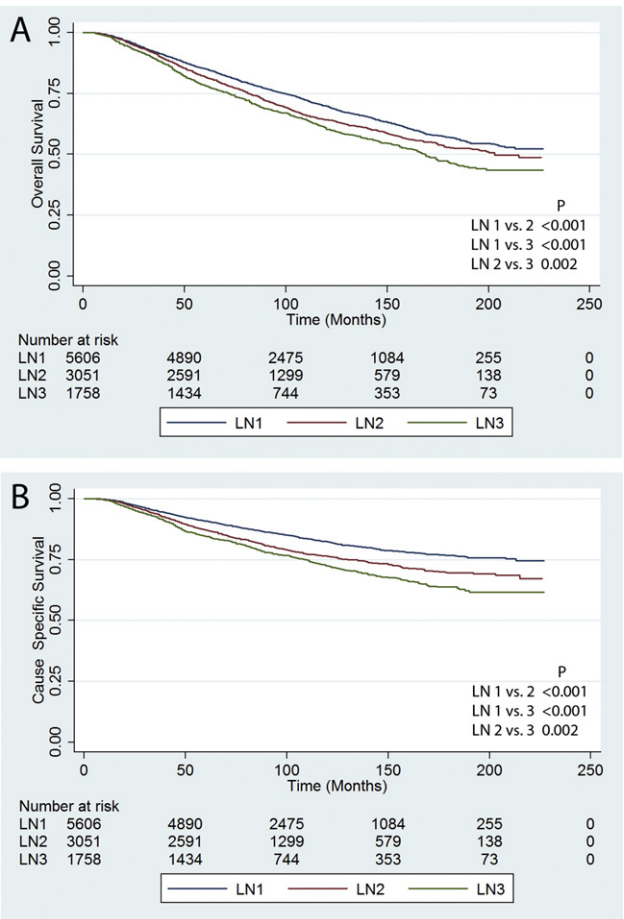

Fig. 1. Overall survival (A) and cause-specific survival (B) for all patients stratified by the number of positive lymph nodes. Pairwise log−rank *P* values are shown above. Clinical significance defined as $P < .05/3$, or .0167.

Table 2 Kaplan-Meier overall survival and cause-specific survival by the number of positive lymph nodes

	Survival rates, % (95% CI)		
Parameter	1 positive LN	2 positive LNs	3 positive LNs
OS			
5 y	85 (84-86)	82 (80-83)	78 (76-80)
10 y	70 (68-71)	64 (62-66)	60 (58-63)
15 y	57 (55-59)	53 (50-56)	47 (43-50)
CSS			
5 y	91 (90-92)	87 (86-88)	85 (83-86)
10 y	82 (81-84)	76 (75-78)	72 (70-75)
15 y	77 (75-78)	70 (67-72)	63 (60-67)

Abbreviations: CI = confidence interval; CSS = cause-specific survival; LN = lymph node; OS = overall survival.

In addition, age, primary tumor size, grade, ER and PR status, race, and year of diagnosis were significant predictors of OS and CSS (Tables 3 and 4).

Discussion

Our study is among the first to separately analyze and compare survival outcomes of patients according to whether they have 1, 2, or 3 positive lymph nodes. It demonstrated clear differences in survival among this group of patients, with increasing number of

Table 3 Multivariate Cox proportional hazard analysis of overall survival

Variable	HR	95% CI	*P*
Age at diagnosis (y)			
≤40	Reference		
41-50	0.778	0.674-0.898	.001
51-59	0.929	0.805-1.073	.317
≥60	2.359	2.089-2.664	<.001
Tumor size			
T1	Reference		
T2	1.568	1.463-1.681	<.001
Grade			
Well differentiated	Reference		
Moderately differentiated	1.309	1.137-1.506	<.001
Poor or undifferentiated	1.598	1.386-1.842	<.001
ER status			
Positive	Reference		
Negative	1.158	1.050-1.277	.003
PR status			
Positive	Reference		
Negative	1.204	1.102-1.315	<.001
Positive lymph nodes			
1	Reference		
2	1.15	1.064-1.242	<.001
3	1.324	1.211-1.446	<.001
Race			
White	Reference		
Black	1.326	1.189-1.478	<.001
Other	0.786	0.686-0.899	<.001
Year of diagnosis (per y)	0.962	0.954-0.971	<.001

Abbreviations: CI = confidence interval; HR = hazard ratio.

Table 4 Multivariate Cox proportional hazard analysis of cause-specific survival

Variable	HR	95% CI	*P*
Age at diagnosis (y)			
≤40	Reference		
41-50	0.807	0.694-0.938	.005
51-59	0.846	0.724-0.988	.035
≥60	1.158	1.009-1.329	.036
Tumor size			
T1	Reference		
T2	1.733	1.579-1.902	<.001
Grade			
Well differentiated	Reference		
Moderately differentiated	1.712	1.356-2.162	<.001
Poor or undifferentiated	2.54	2.013-3.204	<.001
ER status			
Positive	Reference		
Negative	1.296	1.144-1.467	<.001
PR status			
Positive	Reference		
Negative	1.321	1.175-1.486	<.001
Positive lymph nodes			
1	Reference		
2	1.324	1.197-1.465	<.001
3	1.538	1.372-1.724	<.001
Race			
White	Reference		
Black	1.328	1.160-1.521	<.001
Other	0.865	0.733-1.020	.086
Year of diagnosis (per y)	0.95	0.939-0.961	<.001

Abbreviations: CI = confidence interval; HR = hazard ratio.

positive lymph nodes associated with worse OS and CSS. The similar trend observed for both OS and CSS suggests that mortality from breast cancer remains a significant cause of death in this population.

Tai et al (12) published a similar study using the population-based Saskatchewan provincial registry. They included 755 patients who underwent lumpectomy or mastectomy. Approximately 40% received adjuvant radiation therapy. Nineteen percent received supraclavicular and axillary nodal irradiation. Tai et al reported similar OS and CSS in those with 1 and 2 positive nodes and a worse survival outcome in those with 3 positive nodes. In multivariate analysis, the higher number of positive nodes (1-2 vs 3) predicted worse CSS. However, the inclusion of radiation patients complicates the interpretation of their results because radiation has been shown to improve survival. For this reason, we specifically excluded radiation patients in our study.

Our results are consistent with that reported by Vinh-Hung et al (11). They conducted a SEER analysis of 4787 patients with T1-2 node-positive breast cancer who underwent mastectomy without adjuvant radiation therapy. The authors found a continuum of worse outcome associated with increasing number of positive lymph nodes. They were not able to identify a prognostic cutoff in the number positive lymph nodes. Our findings and that by Vinh-Hung et al (11) challenge the conventional risk grouping of 1-3 versus 4 positive nodes and the assumption that 1-3 positive nodes cancers "behave" similarly. It suggests a continuum of increasing number of lymph nodes associated with worse outcome.

Our study has several limitations. First, it lacks information on systemic therapy. Chemotherapy and endocrine therapy have been shown to impact survival. However, one could postulate that women with 3 positive nodes were more likely to receive chemotherapy than those with 1 positive lymph node. Despite that, the 3 positive nodes cohort still had worse survival, suggesting the lack of systemic therapy information is not likely to change the conclusion of the study. Second, under-coding of radiation in the SEER registry has been reported (13), especially in those who underwent mastectomy and chemotherapy. Even though our intent was to exclude those who received PMRT, it is possible that some were accidentally included owing to under-ascertainment of radiation receipt by SEER. A similar argument can be made that women with 3 positive nodes were more likely to receive PMRT than those with 1 positive node; yet the 3 positive nodes cohort still had worse survival, suggesting radiation under-coding is not likely to affect the result. Third, important clinical and pathologic variables that impact locoregional control and survival are not recorded in SEER, such as margin status, angiolymphatic invasion, extracapsular extension, HER-2/neu status, and medical comorbidities. Therefore, we were unable to account for their impact in our analysis. Fourth, as discussed in detail in Methods and Materials, SEER uses death certificates to determine CSS. This approach has disadvantages, because misattribution of death may occur. However, several studies have demonstrated reasonable accuracy in breast cancer, supporting the validity of using cause-specific survival in our investigation (6-8). Last, owing to the inherent limitation of the SEER database, we are not able to provide information on locoregional recurrence and patterns of failure. As a result, there is a missing link between the number of lymph nodes and locoregional recurrence. Hence, we are not able to draw conclusions on whether the heterogeneity within the 1-3 positive nodes cohort has any implications on the benefits of PMRT.

Are involved lymph nodes simply a prognostic factor, or are they also markers of locoregional disease that can respond to surgery and radiation? Can PMRT change the survival patterns of women with 1, 2, or 3 positive lymph nodes? These questions have been long debated and are certainly beyond the scope of our study. However, our study does suggest that T1-2N1 patients are a more heterogeneous group than previously thought. Patients with 1 positive node do not equal those with 2 or 3 positive nodes. Many radiation oncologists found the 5-year disease-free survival benefit in the MA20 trial (5) somewhat unexpected. A very simple explanation may be that the trial may have included more patients with 2 or 3 positive lymph nodes, shifting the patient population toward a higher risk group. An analysis of the percentage makeup of the nodal subsets may shed light on what patients are most likely to derive benefit from regional nodal irradiation.

The heterogeneity of T1-2N1 patients may also reflect a wide spectrum of competing risks of locoregional versus systemic disease, perhaps more so than in those with 4 or more positive lymph nodes and in T1-2 node-negative patients. One could postulate that in some T1-2N1 patients, locoregional disease is the source of dissemination and radiation to the chest wall and regional nodes can directly impact survival. In others, the intrinsic malignant potential of the tumor may ultimately dictate disease outcome regardless of the success of locoregional treatment.

It is possible that the number of involved lymph nodes and other clinical factors are simply surrogates of molecular signatures that ultimately distinguish cancers from one another. Molecular profiling of breast cancers was initially developed to assess the

risk of systemic disease (14). The 21-gene expression assay (Oncotype-DX; Genomic Health, Redwood City, CA) and the 70-gene expression profile (Mammaprint; Agendia, Amsterdam, The Netherlands) have been incorporated into clinical practice to help guide the individualized decision on systemic therapy. Until recently, data on molecular predictors of locoregional recurrence have been lacking. In 2010 Voduc et al showed that molecular subtypes, such as luminal-A, luminal-B, HER-2-enriched, or basal, are predictive of locoregional recurrence (15, 16). The 21-gene Oncotype-Dx recurrence score has also been associated with the risk of locoregional disease (17). However, these predictive factors require further validation before they can be used clinically. Other predictors that may be more specific to locoregional recurrence are yet to be identified. These findings underscore the importance of developing individualized prediction algorithms incorporating clinical, pathologic, and molecular characteristics in making treatment decisions. Radiation oncology, as a field, has traditionally relied solely on clinicopathologic factors in making treatment plans. In the future, not only the number of lymph nodes, tumor size, or grade are important, but also the intrinsic genetic signatures that may dictate the biology of each tumor.

Conclusion

Our study suggests that T1-2 patients with 1, 2, and 3 positive lymph nodes have distinct survival outcomes, with increasing number of positive lymph nodes associated with worse OS and CSS. The heterogeneity observed in this cohort may explain the inconsistencies in the previously conducted studies on the role of PMRT in T1-2N1 patients. It is possible the percentage makeup of patients with 1, 2, and 3 positive lymph nodes may influence the study outcome. Our result challenges the conventional grouping of 1-3 positive lymph nodes. However, because of the inherent limitation of the SEER database, our study does not provide information on the association between the number of positive lymph nodes and locoregional recurrence. Thus, whether the distinct survival outcomes observed in patients with 1, 2, and 3 involved lymph nodes may be affected by PMRT remains to be determined.

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