# The Prognostic Significance of the Percentage of Positive/Dissected Axillary Lymph Nodes in Breast Cancer Recurrence and Survival in Patients with One to Three Positive Axillary Lymph Nodes

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**BACKGROUND.** Adjuvant therapy for women with T1–T2 breast carcinoma and 1–3 positive lymph nodes is controversial due to discrepancies in reported baseline locoregional recurrence (LRR) risks. This inconsistency has been attributed to variations in lymph node staging techniques, which have yielded different numbers of dissected lymph nodes. The current study evaluated the prognostic impact of the percentage of positive/dissected lymph nodes on recurrence and survival in women with one to three positive lymph nodes.

**METHODS.** The study cohort was comprised of 542 women with pathologic T1–T2 breast carcinoma who had 1–3 positive lymph nodes and who had undergone mastectomy and received adjuvant systemic therapy without radiotherapy. Ten-year Kaplan–Meier (KM) LRR, distant recurrence (DR), and overall survival (OS) rates stratified by the number of positive lymph nodes, the number of dissected lymph nodes, and the percentage of positive lymph nodes were examined using different cut-off levels. Multivariate analysis was performed to evaluate the prognostic significance of the percentage of positive lymph nodes in disease recurrence and survival.

**RESULTS.** The median follow-up was 7.5 years. LRR, DR, and OS rates correlated significantly with the number of positive lymph nodes and the percentage of positive lymph nodes, but not with the number of dissected lymph nodes. The cut-off level at which the most significant difference in LRR was observed was 25% positive lymph nodes (the 10-year KM LRR rates were 13.9% and 36.7% in women with $\leq$ 25% and $>$ 25% positive lymph nodes, respectively; $P < 0.0001$). Higher DR rates and lower OS rates were observed among patients who had $>$ 25% positive lymph nodes compared with patients who had $\leq$ 25% positive lymph nodes (DR: 53.0% vs. 30.3%, respectively; $P < 0.0001$; OS: 43.4% vs. 62.6%, respectively; $P < 0.0001$). In the multivariate analysis, the percentage of positive lymph nodes and the histologic grade were significant, independent factors associated with LRR, DR, and OS.

**CONCLUSIONS.** The presence of $>$ 25% positive lymph nodes was an adverse prognostic factor in patients with 1–3 positive nodes and may be used to identify patients at high risks of postmastectomy locoregional and distant recurrence who may benefit with adjuvant radiotherapy and more aggressive systemic therapy regimens. ***Cancer* 2005;103:2006–14.** © *2005 American Cancer Society.*

**KEYWORDS: mastectomy, positive lymph nodes, locoregional recurrence, survival, breast carcinoma.**

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Although there is consensus that adjuvant radiotherapy after mastectomy is indicated for patients with advanced primary tumors that measure $>$ 5 cm or $\geq$ 4 positive axillary lymph nodes, the role of postmastectomy radiotherapy (PMRT) in patients who have tumors


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that measure ≤ 5 cm and 1–3 positive axillary lymph nodes is less clear.[1–3] This controversy is related to discrepancies in the reported locoregional recurrence (LRR) risks in the absence of radiotherapy among these patients. In two randomized trials of PMRT that were conducted by the Danish Breast Cancer Cooperative Group, LRR rates in patients with 1–3 positive lymph nodes who received systemic therapy but did not receive radiotherapy were approximately 30% at 10 years.[4,5] These risks were considerably greater compared with the rates observed in the British Columbia Cancer Agency (BCCA) randomized trial (16% at 10 years and 33% at 15 years)[6] and in retrospective studies of patients who were enrolled in systemic therapy trials (12–20% at 10 years).[7–10] This inconsistency has been attributed to variations in the extent of axillary lymph node staging, resulting in different numbers of dissected axillary lymph nodes.

Recently, several institutional series reported that the percentage of positive lymph nodes may be a useful prognostic factor for survival in women with lymph node-positive breast carcinoma.[11–13] However, relatively few data are available to define the effect of the percentage of positive lymph nodes on risks of LRR. Because postmastectomy radiotherapy has the potential to optimize locoregional control and improve survival,[4–6,14] we were interested in evaluating whether the percentage of positive lymph nodes may be applied in patients with one to three positive lymph nodes to distinguish those at high risk who may benefit with adjuvant therapy from those at low risk who may be spared treatment-related toxicities. In this report, we provide an analysis of the prognostic significance of the percentage of positive/dissected axillary lymph nodes in a cohort of women with breast carcinoma who had pathologic T1 (pT1) or pT2 tumors and 1–3 positive lymph nodes who underwent mastectomy and received systemic therapy without adjuvant radiotherapy.

## MATERIALS AND METHODS

The Breast Cancer Outcomes Unit data base prospectively records tumor, treatment, and outcomes data on all patients with breast carcinoma who are referred to the BCCA. The data base was used to identify 542 women who were diagnosed between January 1, 1989 and December 31, 1997 who were referred to the BCCA with pT1–pT2 breast carcinoma and 1–3 positive lymph nodes and who underwent mastectomy, which achieved clear margins, and axillary dissection of the Level I and II axillary lymph nodes. All patients received adjuvant systemic therapy. The analysis also excluded patients with established indications for PMRT, including pT3–pT4 tumors and/or ≥ 4 positive lymph nodes, patients who presented with distant metastasis, patients with unknown pathologic information on tumor and lymph node stage, histologic grade, lymphovascular invasion (LVI) status, and estrogen receptor (ER) status. Because the objective was to evaluate the prognostic significance of the percentage of positive lymph nodes in the absence of PMRT, patients who received radiotherapy were excluded.

Data were extracted on each patient's date of pathologic diagnosis, dates and sites of disease recurrence, and date of death as of December 1, 2003. Patients were followed at the BCCA and in the community. For patients who were discharged from the BCCA and followed by their primary care physicians, recurrence information was obtained from the community physician on an annual basis. Death information was obtained from the Department of Vital Statistics on a monthly basis. Patients were censored 6 months prior to the date of data retrieval, thus ensuring that the majority of data on disease recurrence and death up to that time had been received.

Primary outcomes examined were LRR, distant recurrence (DR), and overall survival (OS). LRR was defined as the first site of tumor recurrence involving the ipsilateral chest wall (local) and/or the axillary, supraclavicular or infraclavicular, and internal mammary lymph nodes (regional). Patients with LRR that occurred simultaneously with DR were scored as having an LRR event. Patients who had LRR events that occurred after DR were censored at the time of DR.

Patient age at diagnosis was examined initially in 5-year intervals and subsequently was dichotomized at 45 years, the cut-off age at which the most statistically significant difference in LRR was observed on univariate analysis. The tumor factors analyzed were histology (ductal or lobular carcinoma); tumor classification (T1 or T2); histologic grade (Grade 1, 2, or 3); LVI status (present or absent); and ER status (positive or negative). Lymph node factors analyzed included the number of positive axillary lymph nodes (1, 2, or 3), the number of axillary lymph nodes removed (≤ 5 lymph nodes, 6–10 lymph nodes, 11–15 lymph nodes, ≥ 16 lymph nodes; ≤ 10 lymph nodes, or > 10 lymph nodes), and the percentage of positive lymph nodes. The percentage of positive lymph nodes was examined in 5-point intervals, with the cut-off percentage chosen at the level at which the most statistically significant differences in LRR were observed. Adjuvant systemic therapy was analyzed as hormone therapy alone, chemotherapy alone, or both.

### Statistical Analysis

The 10-year Kaplan–Meier (KM) LRR, DR, and OS rates and the associated standard errors (SE) were computed for each patient and tumor characteristic. Statistical significance of outcomes differences was determined using the log-rank test. Multivariate analyses of prognostic variables for each outcome were performed using Cox proportional hazards modeling with and without the percentage of positive lymph nodes as a covariate. All statistical tests were 2-tailed, with the level of significance established at $P < 0.05$. All analyses were conducted using SPSS software (version 11.0.1; SPSS Inc., Chicago, IL).

## RESULTS

The median follow-up was 7.5 years (range, 0.21–14.7 years). The median patient age at the time of diagnosis was 60 years (range, 26–94 years).

### Tumor and Treatment Characteristics

Table 1 summarizes data on tumor and treatment characteristics of the study cohort. All patients underwent modified radical mastectomy with clear surgical margins. Axillary lymph node staging was performed in all patients. The median number of lymph nodes removed was 10 (range, 1–39 lymph nodes removed). The median percentage of positive lymph nodes was 18.7% (range, 2.6–100.0%). Adjuvant systemic therapy was used in all patients (chemotherapy alone, 23.1%; hormone therapy alone, 59.8%; both chemotherapy and hormone therapy, 17.2%). Of 218 patients who received chemotherapy, 154 patients received doxorubicin and cyclophosphamide; 62 patients received cyclophosphamide, methotrexate, and fluorouracil; and 2 patients received fluorouracil, doxorubicin, and cyclophosphamide.

**TABLE 1**
**Characteristics of the Study Cohort**

| Characteristic | No. of patients (%) |
|---|---|
| Age | |
| < 45 yrs | 92 (17.0) |
| ≥ 45 yrs | 450 (83.0) |
| Histology | |
| Ductal | 507 (93.5) |
| Lobular | 35 (6.5) |
| Tumor classification | |
| T1 | 243 (44.8) |
| T2 | 299 (55.2) |
| Grade | |
| 1 | 42 (7.7) |
| 2 | 269 (49.6) |
| 3 | 231 (42.6) |
| Lymphovascular invasion | |
| Absent | 270 (49.8) |
| Present | 272 (50.2) |
| Estrogen receptor status | |
| Positive | 426 (78.6) |
| Negative | 116 (21.4) |
| No. of positive lymph nodes | |
| 1 | 326 (60.1) |
| 2 | 147 (27.2) |
| 3 | 69 (12.7) |
| No of dissected lymph nodes | |
| ≤ 5 | 66 (12.2) |
| 6–10 | 205 (37.8) |
| 11–15 | 173 (31.9) |
| ≥ 16 | 98 (18.1) |
| Systemic therapy | |
| Chemotherapy alone | 125 (23.1) |
| Hormone therapy alone | 324 (59.8) |
| Both | 93 (17.2) |

### KM Recurrence and Survival Outcomes

Overall, 46 patients (8.5%) experienced local chest wall recurrence, and 40 patients (7.4%) experienced regional recurrence. The combined LRR rate was 14.6% ($n = 79$ patients). DR occurred in 174 patients (32.1%). The corresponding 10-year KM estimates (± standard error) were 16.7 ± 1.8% for LRR and 34.0 ± 2.2% for DR. The 10-year KM OS rate was 59.4 ± 2.3%.

### Univariate Analysis

Table 2 presents comparisons of 10-year KM LRR, DR, and OS stratified by the number of positive lymph nodes, the number of dissected lymph nodes, and the percentage of positive lymph nodes using different cut-off levels. LRR, DR, and OS were correlated significantly with the number of positive lymph nodes and the percentage of positive lymph nodes, but not with the number of dissected lymph nodes. The cut-off level at which the most significant difference in LRR was observed was ≤ 25% and > 25% positive lymph nodes (Fig. 1). The 10-year LRR rates were 13.9% with ≤ 25% positive lymph nodes, compared to 36.7% with > 25% positive lymph nodes ($P < 0.0001$) (Fig. 2). Patients with > 25% positive lymph nodes also experienced significantly higher rates of DR (Fig. 3) and lower OS (Fig. 4).

Table 3 presents univariate comparisons of LRR, DR, and OS according to other clinical characteristics, including patient age, tumor factors, and type of systemic therapy. T2 tumor classification, Grade 3 histology, and the presence of LVI were associated with increased LRR and DR and with reduced OS. Age < 45 years and ER-negative status were additional factors associated with LRR and DR, but not with OS. In the comparison of systemic therapies, hormone therapy alone was associated with lower OS compared with

**TABLE 2**
**Ten-Year Kaplan–Meier Locoregional Recurrence, Distant Recurrence, and Overall Survival According to the Number of Positive Lymph Nodes, the Number of Dissected Lymph Nodes, and the Percentage of Positive Lymph Nodes**

| Variable | No. of patients | Ten-year Kaplan-Meier estimates ± SE (%) | | |
|---|---|---|---|---|
| | | LRR | DR | OS |
| All patients | 542 | 16.7 ± 1.8 | 34.0 ± 2.2 | 59.4 ± 2.3 |
| No of positive lymph nodes | | | | |
| 1 | 326 | 11.8 ± 1.9 | 27.1 ± 2.8 | 65.1 ± 3.0 |
| 2 | 147 | 26.8 ± 4.6 | 44.3 ± 4.4 | 51.8 ± 4.4 |
| 3 | 69 | 24.0 ± 6.3 | 52.0 ± 7.4 | 50.3 ± 6.6 |
| *P* value | | 0.002 | 0.0001 | 0.002 |
| No. of dissected lymph nodes | | | | |
| ≤ 5 | 66 | 16.5 ± 4.8 | 36.8 ± 6.7 | 54.4 ± 6.4 |
| 6–10 | 205 | 19.2 ± 3.4 | 33.0 ± 3.5 | 62.3 ± 3.6 |
| 11–15 | 173 | 17.5 ± 3.7 | 32.9 ± 3.8 | 57.6 ± 4.3 |
| ≥ 16 | 98 | 15.2 ± 5.1 | 39.0 ± 6.1 | 59.8 ± 5.7 |
| *P* value | | 0.54 | 0.98 | 0.85 |
| ≤ 10 | 271 | 18.6 ± 2.9 | 33.8 ± 3.1 | 60.3 ± 3.1 |
| > 10 | 271 | 15.2 ± 2.7 | 34.2 ± 3.2 | 58.4 ± 3.4 |
| *P* value | | 0.16 | 0.99 | 0.51 |
| Percentage of positive lymph nodes | | | | |
| ≤ 10% | 203 | 11.6 ± 2.8 | 29.8 ± 3.7 | 64.6 ± 3.9 |
| 11–15% | 112 | 13.4 ± 3.9 | 27.7 ± 4.9 | 61.5 ± 5.1 |
| 16–20% | 88 | 14.2 ± 4.4 | 34.0 ± 6.2 | 60.5 ± 5.7 |
| 21–25% | 48 | 13.4 ± 5.1 | 35.6 ± 7.2 | 61.0 ± 7.7 |
| 26–30% | 23 | 28.8 ± 10.1 | 35.0 ± 7.7 | 46.1 ± 10.8 |
| > 30% | 68 | 38.7 ± 3.4 | 55.8 ± 7.2 | 42.3 ± 6.2 |
| *P* value | | 0.0002 | 0.004 | 0.002 |
| ≤ 10% | 203 | 11.6 ± 2.8 | 29.9 ± 3.7 | 64.6 ± 3.9 |
| > 10% | 339 | 22.1 ± 2.6 | 37.3 ± 2.9 | 56.2 ± 2.9 |
| *P* value | | 0.02 | 0.15 | 0.03 |
| ≤ 20% | 403 | 14.0 ± 2.0 | 30.3 ± 2.6 | 62.9 ± 3.9 |
| > 20% | 139 | 27.7 ± 4.8 | 46.5 ± 4.8 | 49.4 ± 4.5 |
| *P* value | | 0.001 | 0.002 | 0.002 |
| ≤25% | 451 | 13.9 ± 1.9 | 30.3 ± 2.4 | 62.6 ± 2.6 |
| > 25% | 91 | 36.7 ± 6.8 | 53.0 ± 6.0 | 43.4 ± 5.4 |
| *P* value | | < 0.0001 | < 0.0001 | < 0.0001 |

SE: standard error; LRR: locoregional recurrence; DR: distant recurrence; OS: overall survival.

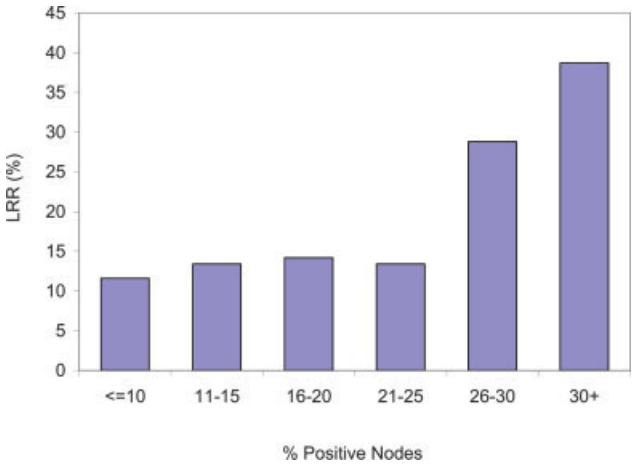


**FIGURE 1.** Bar graph of locoregional recurrence (LRR) versus the percentage of positive lymph nodes.

chemotherapy alone or in combination with hormone therapy.

### Multivariate Analysis

On multivariate analysis (Table 4), with the percentage of positive lymph nodes included in the model, the number of positive lymph nodes and the number of dissected lymph nodes were not significant. The presence of > 25% positive lymph nodes was associated with significantly higher LRR (hazard ratio [HR], 2.32), higher DR (HR, 1.97), and lower OS (HR, 1.79; $P < 0.05$ for all). Aside from the percentage of positive lymph nodes, histologic grade was the other factor associated with all three outcomes of LRR, DR and OS. Age < 45 years was associated significantly with higher LRR, whereas T classification and LVI were additional factors that were associated significantly with DR.

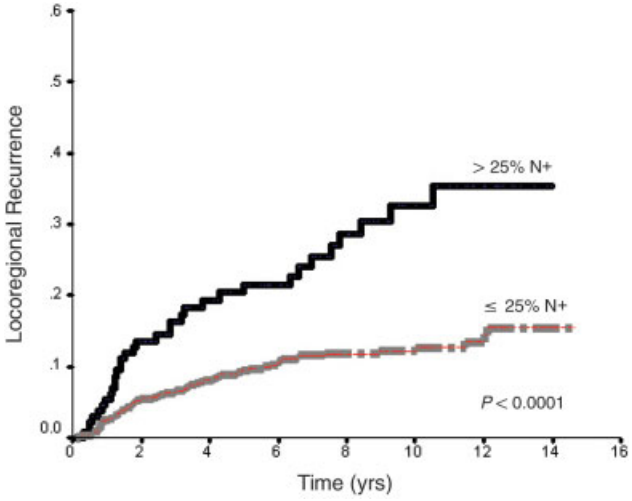


**FIGURE 2.** Kaplan–Meier locoregional recurrence according to the percentage of positive lymph nodes (≤ 25% vs. > 25%).

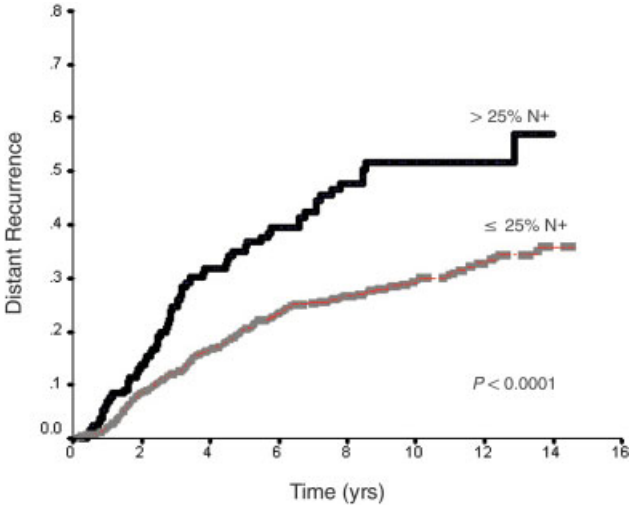


**FIGURE 3.** Kaplan–Meier distant recurrence according to the percentage of positive lymph nodes (≤ 25% vs. > 25%).

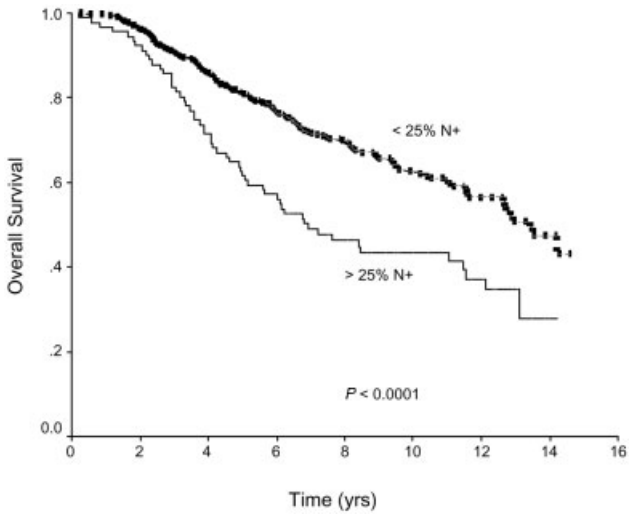


**FIGURE 4.** Kaplan–Meier overall survival according to the percentage of positive lymph nodes (≤ 25% vs. > 25%).

## DISCUSSION

Studies investigating the prognostic impact of the percentage of positive lymph nodes largely have reported OS and disease-free survival, which pertain to any type of recurrence.[11–13] Few studies have focused on LRR outcomes.[9] The use of the percentage of positive lymph nodes in the context of appraising LRR risk and guiding adjuvant locoregional therapy decisions, thus, is unclear. The findings of the current analysis suggest that the percentage of positive axillary lymph nodes has significant prognostic value in predicting recurrence and survival in patients with T1–T2 breast carcinoma who have 1–3 positive lymph nodes, a population in whom the use of adjuvant radiotherapy is controversial.

The LRR risk of 16.7% at 10 years that was demonstrated in women with T1–T2 tumors and 1–3 positive lymph nodes in the current study was consistent with other series of patients who both underwent mastectomy and received systemic therapy.[7–10] In the current analysis, the presence of > 25% positive lymph nodes identified a patient subset with a risk of LRR > 30%, warranting consideration of postmastectomy radiotherapy. LRR and DR increased with increasing number of positive lymph nodes but appeared to be independent of the number of dissected lymph nodes. The number of positive lymph nodes (but not the number of dissected lymph nodes) was a significant predictor of LRR, DR, and OS when the percentage of positive lymph nodes was not included in the multivariate analysis. However, when it was included as a covariate in the model, it was found that the percentage of positive lymph nodes was highly significant, and the absolute number of positive lymph nodes lost its significance. These findings support the suggestion that the percentage of positive lymph nodes is useful in estimating recurrence risks and should be considered in conjunction with the absolute number of positive lymph nodes in adjuvant therapy decisions.

### LRR

Few studies have examined the prognostic role of the percentage of positive lymph nodes in postmastectomy LRR in patients who are treated with systemic therapy. Katz et al. analyzed 1031 patients in 5 trials of

**TABLE 3**
**Ten-Year Kaplan–Meier Locoregional Recurrence, Distant Recurrence, and Overall Survival Rates According to Patient, Tumor, and Treatment Characteristics**

| Characteristic | No. of patients | Ten-year Kaplan-Meier estimates ± SE (%) | | |
|---|---|---|---|---|
| | | LRR | DR | OS |
| Age (yrs) | | | | |
| < 45 yrs | 92 | 34.0 ± 6.0 | 43.8 ± 5.5 | 64.7 ± 5.2 |
| ≥ 45 yrs | 450 | 13.6 ± 1.8 | 32.5 ± 2.5 | 58.2 ± 2.6 |
| *P* value | | 0.0002 | 0.04 | 0.17 |
| Histology | | | | |
| Ductal | 507 | 17.2 ± 1.9 | 35.1 ± 2.4 | 58.5 ± 2.4 |
| Lobular | 35 | 19.7 ± 9.9 | 26.6 ± 9.9 | 71.7 ± 8.3 |
| *P* value | | 0.51 | 0.22 | 0.20 |
| Tumor classification | | | | |
| T1 | 243 | 14.1 ± 2.6 | 26.5 ± 3.1 | 62.2 ± 3.5 |
| T2 | 299 | 20.3 ± 2.9 | 41.1 ± 3.2 | 57.2 ± 3.1 |
| *P* value | | 0.10 | 0.0003 | 0.03 |
| Grade | | | | |
| 1 | 42 | 7.7 ± 4.3 | 11.5 ± 5.6 | 73.2 ± 7.5 |
| 2 | 269 | 13.6 ± 2.7 | 30.4 ± 3.3 | 62.2 ± 3.4 |
| 3 | 231 | 24.0 ± 3.2 | 43.3 ± 3.5 | 53.5 ± 3.4 |
| *P* value | | 0.002 | < 0.0001 | 0.01 |
| LVI | | | | |
| Absent | 270 | 14.5 ± 2.8 | 25.8 ± 3.1 | 64.2 ± 3.4 |
| Present | 272 | 20.8 ± 2.8 | 42.8 ± 3.2 | 54.3 ± 3.2 |
| *P* value | | 0.03 | < 0.0001 | 0.005 |
| ER status | | | | |
| Positive | 426 | 14.5 ± 2.0 | 32.2 ± 2.5 | 60.1 ± 2.6 |
| Negative | 116 | 25.0 ± 4.3 | 42.7 ± 5.1 | 57.3 ± 4.8 |
| *P* value | | 0.002 | 0.01 | 0.14 |
| Systemic therapy | | | | |
| Chemotherapy alone | 125 | 26.8 ± 4.9 | 36.6 ± 4.8 | 71.6 ± 4.4 |
| HT alone | 324 | 13.9 ± 2.2 | 32.8 ± 2.9 | 52.7 ± 3.1 |
| Both | 93 | 15.3 ± 4.0 | 36.7 ± 5.4 | 67.3 ± 5.3 |
| *P* value | | 0.06 | 0.81 | 0.0001 |

SE: standard error; LRR: locoregional recurrence; DR: distant recurrence; OS: overall survival; LVI: lymphovascular invasion; ER: estrogen receptor; HT: hormone therapy.

doxorubicin-based chemotherapy at The University of Texas M. D. Anderson Cancer Center, 404 of whom had T1–T2 tumors with 1–3 positive lymph nodes.[7] In their multivariate analysis, which was restricted to these patients, extralymph node extension ≥ 2 mm, < 10 lymph nodes removed, and tumor size > 4 cm were associated significantly with LRR. In another report that used recursive partitioning analysis on the entire sample, including patients with tumors that measured > 5 cm and ≥ 4 positive lymph nodes, patients with ≥ 20% positive lymph nodes were identified as a high-risk subset with LRR risks of approximately 40% at 8 years.[8] Differences in patient samples and statistical analysis methods likely account for the different cut-off level of 20% in that study compared with the 25% cut-off level in the current analysis.

Recht et al. reported outcomes in 2016 patients, including 983 patients with T1–T2 tumors and 1–3 positive lymph nodes, who were enrolled in 4 trials of systemic therapy without radiotherapy that were conducted by the Eastern Cooperative Oncology Group.[9] The 10-year risk of LRR with or without simultaneous DR was 12% in patients with T1–T2 breast carcinoma and 1–3 positive lymph nodes. A multivariate analysis was performed on their entire sample, including patients with T3 disease and ≥ 4 positive lymph nodes. Increasing tumor size and the number of positive lymph nodes, decreasing number of lymph nodes examined, and ER-negative status were independent predictors for LRR.[9]

Wallgren et al. reported on 2250 women with 1–3 positive lymph nodes who were enrolled in 7 International Breast Cancer Study Group trials of systemic therapy. All patients in that study underwent axillary dissection with the requirement of a minimum of eight lymph nodes removed for study entry. Factors that were associated with increased LRR in that study were high histologic grade and vascular invasion among premenopausal patients and high histologic grade and tumor size > 2 cm among postmenopausal patients.[10]

Our retrospective study is limited by biases in patient and treatment selection. However, because the current knowledge on postmastectomy recurrence largely has been derived from patients enrolled in prospective clinical trials who inherently may have different characteristics compared with patients in the general population, the current study is of potential value in providing information on clinical outcomes in a large, potentially more representative sample of patients who were managed in community practice.

Variations in lymph node staging techniques have the potential to impact locoregional disease control. In particular, the extent of axillary dissection has been implicated as a contributing factor for the disparities in LRR rates reported in the literature among patients with one to three positive lymph nodes.[2,3] There is general agreement that the Level I and II lymph nodes located lateral to and deep to the pectoralis minor muscle should be removed for accurate staging and to reduce axillary recurrence.[15–21] A study of 13,851 patients registered by the Danish Breast Cancer Cooperative Group suggests that the number of lymph nodes removed with Level I and II dissection should be at least 10 to exclude misclassification of patients with positive lymph nodes as lymph node-negative.[16] In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 study, the estimate of quantitative lymph node status (1–3 vs. ≥ 4 positive lymph nodes) was more reliable when at least 10 lymph

**TABLE 4**
**Multivariate analysis of Locoregional Recurrence, Distant Recurrence, and Overall Survival**

| | Without % positive lymph nodes as covariate | | | With % positive lymph nodes as covariate | | |
|---|---|---|---|---|---|---|
| **Characteristic** | **LRR** | **DR** | **OS** | **LRR** | **DR** | **OS** |
| Age (< 45 yrs vs. ≥ 45 yrs) | | | | | | |
| *P* value | 0.003 | 0.08 | 0.05 | 0.002 | 0.06 | 0.06 |
| HR | 2.14 | | 0.68 | 2.16 | 1.42 | 0.69 |
| 95%CI | 1.30–3.54 | | 0.47–0.99 | 1.31–3.54 | 0.99–2.03 | 0.48–1.01 |
| Histology | | | | | | |
| *P* value | 0.90 | 0.55 | 0.45 | 0.89 | 0.62 | 0.52 |
| Tumor classification (T2 vs. T1) | | | | | | |
| *P* value | 0.23 | 0.009 | 0.18 | 0.24 | 0.008 | 0.19 |
| HR | | 1.55 | | | 1.55 | |
| 95%CI | | 12–2.14 | | | 1.12–2.14 | |
| Grade (Grade 3 vs. Grade 1 or 2) | | | | | | |
| *P* value | 0.008 | 0.005 | 0.04 | 0.008 | 0.005 | 0.04 |
| HR | 1.92 | 1.58 | 1.34 | 1.90 | 1.57 | 1.34 |
| 95%CI | 1.19–3.10 | 1.14–2.19 | 1.01–1.76 | 1.18–3.06 | 1.14–2.15 | 1.02–1.77 |
| LVI (present vs. absent) | | | | | | |
| *P* value | 0.25 | 0.006 | 0.11 | 0.19 | 0.004 | 0.11 |
| HR | | 1.58 | | | 1.61 | |
| 95%CI | | 1.14–2.19 | | | 1.16–2.23 | |
| ER status (negative vs. positive) | | | | | | |
| *P* value | 0.07 | 0.12 | 0.18 | 0.06 | 0.11 | 0.19 |
| No. of positive lymph nodes | | | | | | |
| *P* value | 0.01 | 0.003 | 0.003 | 0.27 | 0.13 | 0.14 |
| 2 vs. 1 | | | | | | |
| HR | 2.05 | 1.73 | 1.61 | | | |
| 95%CI | 1.24–3.39 | 1.24–2.42 | 1.25–2.17 | | | |
| 3 vs. 1 | | | | | | |
| HR | 1.90 | 1.63 | 1.56 | | | |
| 95%CI | 1.00–3.61 | 1.06–2.49 | 1.06–2.28 | | | |
| No. of dissected lymph nodes (≤ 10 vs. > 10) | | | | | | |
| *P* value | 0.01 | 0.16 | 0.39 | 0.35 | 0.76 | 0.49 |
| HR | 1.98 | | | | | |
| 95%CI | 1.23–3.19 | | | | | |
| Percent of positive lymph nodes (> 25% vs. ≤ 25%) | | | | | | |
| *P* value | — | — | — | 0.01 | 0.005 | 0.007 |
| HR | | | | 2.32 | 1.97 | 1.79 |
| 95%CI | | | | 1.19–4.53 | 1.23–3.17 | 1.17–2.73 |

LRR: locoregional recurrence; DR: distant recurrence; OS: overall survival; HR: hazard ratio; 95%CI: 95% confidence interval; LVI: lymphovascular invasion; ER: estrogen receptor.

nodes were removed.[15,22] Accordingly, the higher LRR rates in the Danish randomized trials, compared with other series, have been attributed to limited axillary surgery removing a median of 7 lymph nodes,[4,5] potentially compromising staging accuracy and regional disease control. It is worth noting that, while the median number of lymph nodes removed in the current population-based study was 10, the 10-year LRR rate of 16.7% in the absence of PMRT was comparable to the rates reported in series in which > 15 lymph nodes were removed.[7–10]

## DR and Survival

The role of the percentage of positive lymph nodes in predicting distant metastasis and survival was highlighted recently in several institutional series.[11–13] Although those studies differed in patient selection, follow-up, and types of surgery and adjuvant therapies, they showed consistently that the percentage of positive lymph nodes is a significant independent prognostic indicator of survival in women with lymph node-positive breast carcinoma. Voordeckers et al. reported an analysis of OS and cause-specific survival as a function of the percentage of positive lymph nodes in 741 patients with node-positive disease treated with breast-conserving therapy or mastectomy, 97% of whom received radiotherapy.[11] In that study, several cut-off levels were used. In their Cox proportional hazards model, the percentage of positive lymph nodes was the most significant factor for survival.

Similar to our findings, the absolute number of positive lymph nodes lost significance when the percentage of positive lymph nodes was taken into account.[11]

In an analysis of 453 patients with Stage I and II breast carcinoma who underwent either breast-conserving therapy or mastectomy, van der Wal et al. reported that, among patients with positive lymph node status, age, the number of dissected lymph nodes, and the percentage of positive lymph nodes were significant prognostic factors for survival.[12] These findings corroborate those of a smaller series from Megale Costa et al. of 168 patients who had a short mean follow-up of only 26 months.[13] Similar to the current series, the presence of 20–30% positive lymph nodes in those studies was associated with higher risks of disease recurrence and overall mortality. Patients with > 25% positive lymph nodes may be appropriate candidates for trials that evaluate novel systemic therapy strategies with newer agents and varying dose intensities to optimize systemic disease control.

The use of lymph node characteristics to guide breast carcinoma management in the modern setting must be considered in the context of rapidly evolving techniques in surgical sampling and pathologic processing. Sentinel lymph node biopsy (SNB) is emerging as an accurate staging modality that is associated with fewer morbidities compared with axillary dissection.[23] Immunohistochemical detection of tumor cells in lymph nodes has led to the increased diagnosis of lymph node micrometastasis and recent changes in the American Joint Committee on Cancer classification system.[24,25] The clinical implications associated with SNB alone compared with axillary dissection are being addressed by two important clinical trials. The NSABP B-32 trial randomizes patients with clinically lymph node-negative disease to undergo SNB followed by axillary dissection versus SNB followed by axillary dissection only if the sentinel lymph nodes are positive.[26] The American College of Surgeon Oncology Group trial randomizes patients with positive sentinel lymph nodes to undergo axillary dissection versus no further surgery. Until the prognostic, therapeutic, and survival implications of these evolving surgical and pathologic practices are established by long-term data, the current results suggest that axillary dissection in the presence of positive sentinel lymph nodes should constitute the standard of care, because it provides valuable prognostic information to guide adjuvant therapy for patients who have lymph node-positive breast carcinoma.

In conclusion, the percentage of positive lymph nodes should be considered in adjuvant therapy decisions for women with one to three positive lymph nodes who undergo mastectomy. The presence of > 25% positive lymph nodes identified patients at higher risk of LRR and DR who may benefit from adjuvant radiotherapy and more aggressive systemic treatment regimens.

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