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ORIGINAL ARTICLE

Percent positive axillary lymph node metastasis predicts survival in patients with non-metastatic breast cancer

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Abstract

Purpose. We retrospectively evaluated the impact of percent positive axillary nodal involvement on the therapeutic outcomes in patients with non-metastatic breast cancer receiving postmastectomy radiotherapy and chemotherapy. **Materials and methods.** Between January 1994 and December 2002, the medical records of 939 eligible non metastatic breast carcinoma patients were analyzed. Chest wall radiotherapy was indicated in case of positive surgical margin, tumor size equal or more than 4 cm, skin-fascia invasion. Lymphatic irradiation was applied for more than three metastatic axillary lymph nodes, incomplete axillary dissection (<10 lymph nodes), extracapsular extension or perinodal fat tissue invasion. A total dose of 50 Gy was given to chest wall and lymph node regions with 2 Gy daily fractions. Statistical analyses were performed by Kaplan-Meier method, Log-rank test and Cox's regression analysis. **Results.** The median follow-up for all patients alive was 62 months. The 5-year overall survival (OS) and disease-free survival (DFS) for entire cohort were 81%, and 65%, respectively. Univariate analysis for OS revealed significance for tumour size (≤ 5 cm vs. > 5 cm, $p < 0.001$), metastatic nodal involvement (0 vs. 1–3 vs. > 4 LN, $p < 0.001$), percent positive nodal involvement ([metastatic nodes/total nodes removed] $\times 100$; 0 vs. $\leq 25\%$ vs. 26–50% vs. $> 50\%$, $p < 0.001$), surgical margin status (negative vs. positive, $p = 0.05$), and hormonal treatment (present vs. absent, $p = 0.03$). DFS had similarly significance for age (≤ 40 years vs. > 40 years, $p = 0.006$), tumour size (0.02), metastatic nodal involvement ($p < 0.001$), percent positive nodal involvement ($p < 0.001$), and perinodal invasion (present vs. absent, $p = 0.01$). Multivariate analysis revealed significance for tumour size, percent positive nodal involvement, hormonal treatment, and surgical margin status for OS. Age and percent positive nodal involvement were found to be significant for DFS. **Conclusion.** Percent positive nodal involvement was found to be a significant prognostic factor for survival in all end-points.

In patients with invasive breast carcinoma who had been subjected to mastectomy, the majority of the recommendations concerning axillary radiotherapy are based on the number of positive nodes. However this number is to some extent dependent on the number of nodes removed during the axillary dissection [1]. The number of nodes removed during axillary dissection has been demonstrated to have a significant impact not only on regional nodal failure but also on local failure [2–6]. According to Eastern Cooperative Oncology Group (ECOG) data, axillary dissection with 6 lymph nodes removed can give adequate information when there were no metastases [4]. After inadequate axillary dissection (less than 6 nodes removed) both regional control and overall survival rates was shown to be significantly

reduced [2]. Axillary failure on the other hand was very rare even in the absence of radiotherapy, if the median number of nodes removed was > 12 without any metastatic foci [4,7]. However the most significant prognostic factor predicting the locoregional recurrence (LRR) is generally believed to be the number of metastatic lymph nodes (LNs). Retrospective analysis of 4 ECOG studies revealed locoregional recurrence rates as 13% when there was 1–3 LN metastases and 29% when more than 3 LN metastases in 2 016 patients who were treated with systemic chemotherapy but no radiotherapy after surgery [4]. The corresponding locoregional recurrence rates in 5 NSABP trials were 13% when there was 1–3 LN metastases, 24% when more than 3 LN metastases [8]. It was reported to be 32% when

there were 10 or more LN metastases. Today post-operative adjuvant radiotherapy is generally recommended when there are less than 10 lymph nodes removed or when there are more than 3 metastatic LNs [9–11].

It is suggested that the percent positive axillary nodal involvement represents a more precise predictor of axillary failure and survival than the absolute number of positive nodes [12]. Several studies tested this hypothesis in heterogeneous group of patients with invasive breast carcinoma treated by either breast conserving surgery or mastectomy some receiving radiotherapy and the percentage of involved nodes was found to be useful to select patients for axillary irradiation [12–15]. However, none of them tested this proposition in a group of patients who had high risk features and received post mastectomy radiotherapy and chemotherapy.

In this context, we retrospectively evaluated the impact of percent positive axillary nodal involvement on the therapeutic outcomes in patients with non-metastatic breast cancer receiving post mastectomy radiotherapy and chemotherapy in our institution. Our specific focus was to determine whether the percent positive nodal involvement has an impact on loco-regional control, overall (OS) or disease free survivals (DFS) and to evaluate whether there was a cut of rate in order to discriminate high risk patients from low risk ones.

Methods and materials

In this retrospective study, the medical records of 1 086 non metastatic breast carcinoma patients treated between January 1994 and December 2002 were analyzed. Among them 939 patients at least 6 LNs removed formed this analysis. Chest wall radiotherapy was indicated in case of positive surgical margin, tumour size of >4 cm, skin-fascia invasion. Lymphatic irradiation was added to chest wall radiotherapy when there was more than 3 metastatic axillary lymph nodes, incomplete axillary dissection (<10 LNs), extra capsular extension or perinodal fat tissue invasion. A total dose of 46–50 Gy, given in 23–25 fractions over a period of 5 weeks, was delivered to the whole chest wall. When treated, the supraclavicular fossa received a dose of 50 Gy prescribed at 3 cm through an anterior supraclavicular–axillary field. A posterior axillary field was routinely added. In patients with inner quadrant tumours of >4 cm and/or more than 50% axillary nodal involvement internal mammary lymph nodes were also irradiated. The form of chemotherapy was 6–8 cycles of cyclophosphamide, adriamycin, 5-fluorouracil (CAF) in 487 patients and cyclophosphamide, methotrexate, 5-fluorouracil

(CMF) in 251 patients. The other schedules were as CA (Cyclophosphamide, Adriamycin) in 50 patients or CE (Cyclophosphamide, Epirubicin) and Docetaxel in 64 patients or 6–8 courses of CNF (Cyclophosphamide, Vinorelbine, 5-Fluorouracil) in 13 patients. Chemotherapy was given as a neoadjuvant setting in 122 patients, and as an adjuvant setting in 743 patients.

The type of surgery was as modified radical mastectomy in 811 patients, simple mastectomy with axillary dissection in 54 patients, or radical mastectomy in 74 patients. When possible, re-excision was performed if the surgical margins were not free of disease. Despite all efforts, surgical margin was positive in 13 patients. In case of margin positivity and no re-excision were performed, radiotherapy dose was 60 Gy instead of 50 Gy.

Statistical analysis

Primary end points were overall and disease free survival rates. Follow-up time was calculated as the time interval between the date of diagnosis and the date of the first event or the date of last contact with the patient. Statistical analyses were performed by Kaplan-Meier method, Log-rank test and Cox's regression analysis. Statistical differences between groups were calculated using the log-rank test for the potential prognostic factors. The relation of the percent positive nodal involvement to the endpoints was also evaluated using Cox proportional hazards models. Due to co linearity, separate models were run with percent positive nodal involvement and total number of involved nodes. Since the two models are close and implicitly nested, the change in -2 log-likelihood was used along with the change in degrees of freedom, in order to compare models and assess superiority of percent positive nodal involvement. All data analyses were performed using SPSS 11.5 statistical software (SPSS Inc, Chicago, IL).

Results

A total of 939 eligible patients did receive regional irradiation and were available for this analysis. The median age for all patients was 47 years (ranged 19–84 years). Of 939 patients, 509 patients were premenopausal and 430 were postmenopausal. Patients' characteristics are shown in Table I.

The median number of excised axillary nodes was 18 (ranged, 6 to 74 nodes). Of 939 patients, 257 patients had no lymph node metastases, 263 patients had 1–3 positive nodes, and 419 had >3 positive nodes. The median percent positive axillary involvement was 18%. For the group of patients with 1–3 positive nodes, the median percentage was 10%.

Table I. Clinical and pathological features of patients.

Variables	Number of patients (%)
Age	
<40	226 (25%)
>40	713 (75%)
T stage	
TX	8 (1%)
T1	40 (4%)
T2	510 (55%)
T3	320 (34%)
T4	61 (6%)
Primary Tumor Size	
≤5 cm	513 (54.5%)
>5 cm	420 (45%)
Unknown	6 (0.5%)
Number of positive nodes	
N0	257 (26%)
N1-3	263 (28%)
N >4	419 (46%)
Percent Positive Axillary Nodal Involvement	
0%	260 (27%)
<25%	306 (33%)
25-50%	158 (17%)
>50%	215 (23%)
Histology	
Infiltratif ductal	851 (90%)
Lobular	47 (6%)
Other	41 (4%)
Grade	
1	441 (47%)
2-3	483 (51%)
Unknown	15 (2%)
Extracapsular extension	
No or not specified	853 (91%)
Yes	86 (9%)
Surgical Margin Status	
Positive	13 (2%)
Negative	926 (98%)
Hormone therapy	
Yes	345 (37%)
No	554 (63%)
Chemotherapy	
Yes	865 (92%)
No	74 (8%)

It was much higher, 50%, for the group with >3 positive nodes.

The median follow-up for all patients alive was 62 months (Range, 6-137 months). The 5-year OS and DFS for the entire cohort were 81%, and 65%, respectively.

Univariate analysis for OS revealed significance for tumour size (≤5 cm vs. >5cm, $p < 0.001$), metastatic nodal involvement (0 vs. 1-3 vs. ≥4 LN, $p < 0.001$), percent positive nodal involvement ([metastatic nodes/total nodes removed] × 100; 0 vs. ≤25% vs. 26-50% vs. >50, $p < 0.001$) (Figure 1), surgical margin status (negative vs. positive, $p = 0.05$),

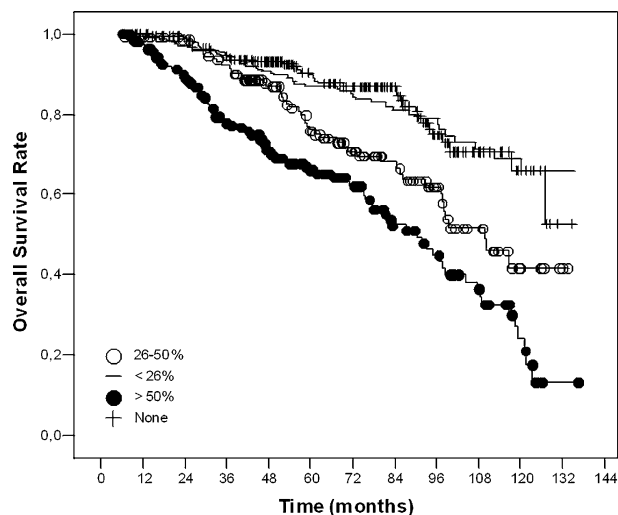


Figure 1. Kaplan-Meier curves for overall survival according to percent positive axillary nodal involvement.

and hormonal treatment (present vs. absent, $p = 0.03$) (Table II).

DFS had similarly significance for age (≤40 years vs. >40 years, $p = 0.006$), tumour size (0.02), metastatic nodal involvement ($p < 0.001$), percent positive nodal involvement ($p < 0.001$) (Figure 2),

Table II. Univariate analyses for overall survival.

Variables	Overall Survival%	p-value
Age		
≤40	78.2	0.38
>40	81.2	
Primary Tumor Size		
≤5 cm	84.9	<0.001
>5 cm	75.2	
Number of positive nodes		
N 0	89.9	<0.001
N1-3	85.0	
N >4	72.5	
Percent Positive Axillary Nodal Involvement		
0%	89.8	<0.001
<25%	87.0	
25-50%	76.1	
>50%	66.1	
Extracapsular extension		
No or not specified	80.1	0.44
Yes	82.7	
Surgical Margin Status		
Positive	Not reached	0.054
Negative	80.6	
Hormone therapy		
Yes	85.2	0.030
No	77.7	
Chemotherapy		
Yes	80.6	0.62
No	79	

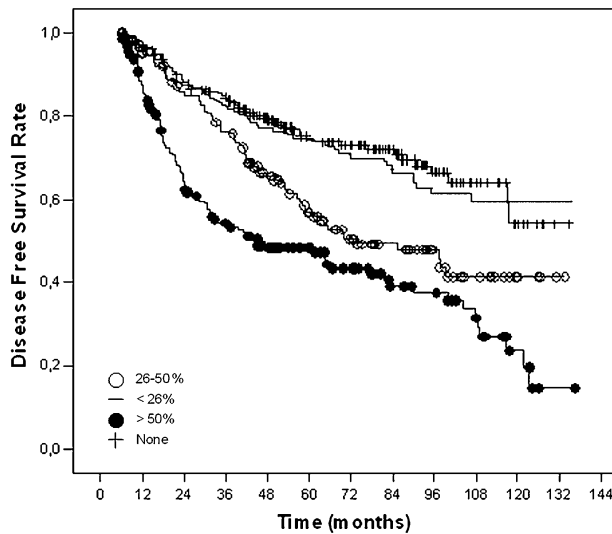


Figure 2. Kaplan-Meier curves for disease free survival according to percent positive axillary nodal involvement.

and perinodal invasion (present vs. absent, $p = 0.01$) (Table III).

Multivariate analysis revealed significance for percent positive nodal involvement, tumour size, hormonal treatment, and surgical margin status for OS (Table IV). Percent positive nodal involvement

Table III. Univariate analyses for disease free survival.

Variables	Overall Survival%	p-value
Age		
≤40	58	0.006
>40	66.8	
Primary Tumor Size		
≤5 cm	68.5	0.022
>5 cm	60.1	
Number of positive nodes		
N 0	74.8	<0.001
N1-3	74.9	
N>4	53.2	
Percent Positive Axillary Nodal Involvement		
0%	74.4	<0.001
<25%	74.9	
25-50%	56.9	
>50%	48.4	
Extracapsular extension		
No or not specified	64.4	0.93
Yes	66.4	
Surgical Margin Status		
Positive	50.0	0.22
Negative	64.7	
Hormone therapy		
Yes	68.3	0.086
No	62.2	
Chemotherapy		
Yes	64.2	0.67
No	69.0	

Table IV. Multivariate analysis for overall survival.

Variable	Risk Ratio (RR)	95.0% CI for RR		p-value
		Lower	Upper	
Tumor Size (0-5 vs > 5cm)	1.52	1.16	1.99	0.002
Percent positive LN involvement (Reference: no involvement)				<0.001
vs. ≤25%	0.93	0.60	1.45	0.763
vs. 26-50%	1.92	1.25	2.95	0.003
vs. 50+%	3.35	2.28	4.92	<0.001
Surgical Margin Involvement	3.69	1.17	11.68	0.026
Hormonal Treatment	1.34	1.00	1.78	0.048

and age on the other hand were found to be significant for DFS (Table V).

Patterns of failure for patients with 50% or more axillary nodal involvement were shown in Table VI. The most frequent patterns of failure were distant metastasis for those patients (81 relapse of 106 failures, 76%).

Discussion

The role of the percent positive lymph nodes in predicting distant metastasis and survival was recently demonstrated in several institutional series [13-18]. Although those studies differed in patient selection, follow-up, and type 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. In some of these series, patients did not receive

Table V. Multivariate analysis for disease free survival.

Variable	Risk Ratio (RR)	95.0% CI for RR		p-value
		Lower	Upper	
Percent positive LN inv. (Reference: no involvement)				<0.001
vs. ≤25%	1.07	0.77	1.49	0.701
vs. 26-50%	1.85	1.31	2.61	<0.001
vs. 50+%	3.11	2.29	4.23	<0.001
Age group (≤40 vs >40)	0.67	0.53	0.85	0.001

Table VI. Patterns of failure for patients with 50% or more axillary lymph node metastasis.

Failure Site	Number of Patients (%)
Local + Distant	14 (5%)
Regional	11 (4%)
Distant	215 (77%)
Local	36 (13%)
Loco-regional	3 (1%)
Total	279

radiotherapy at all, or received radiation therapy after breast conserving surgery [13,14,16,18]. One of the distinctive features of our study from those series is that all our patients received radiotherapy according to our institutional criteria. Secondly, we excluded patients treated with breast conserving surgery and only analyzed the results of patients with mastectomy and adequately treated axilla. Consequently the current series was based on a relatively large group of patients, who were homogeneously treated in a single institution. For these reasons, we believe that this data might provide a different point of view on the prognostic role of the percent positive axillary nodal involvement in the presence of post mastectomy radiotherapy.

Voordeckers et al. analyzed the OS and cause-specific survival rates as a function of the percent positive lymph nodes in 741 patients with node-positive disease treated with breast-conserving therapy or mastectomy, 97% of whom received radiotherapy [14]. In their multivariate analysis, the percentage of positive lymph nodes was the most significant factor for survival. Similar to our findings, the total number of positive lymph nodes lost significance when the percentage of positive lymph nodes was taken into account. Truong et al. reported the prognostic significance of the percentage positive axillary lymph nodes in 542 T1-2 breast cancers with 1–3 positive lymph nodes [13]. They suggested that patients with more than 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. 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. found 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 [16]. These findings agree with those of a smaller series from Megale Costa et al. of 168 patients who had a short mean follow-up of only 26 months [15]. In a combined analysis of M.D. Anderson Cancer Centre and British Colombia series, Woodward et al. revealed the risk of LRR as

9–15% for <10% nodal ratio and 18–25% for 10–20% nodal ratio in patients who had undergone to mastectomy without adjuvant radiotherapy [18]. In our study patients with $\leq 25\%$ LN involvement showed favourable prognosis compared to the others showing higher LN involvement. Five year DFS rates in patients with $\leq 25\%$ seem to behave similar to N0 patients when adequately treated. However it should be kept in mind that all the patients in this series were irradiated after mastectomy and received systemic therapy as chemotherapy and or hormonotherapy.

Adjuvant radiotherapy after mastectomy is usually recommended in patients with more than 3 LN metastases [9,11,19,20]. However the update analysis of Danish studies demonstrated that postoperative radiotherapy produced significant improvement both in DFS and OS not only in patients with 1–3 LN metastases but also patients with ≥ 4 LN metastases [21]. Twenty-year results of British Colombia trial showed similar results demonstrating significant survival advantages when radiotherapy was added to patients both 1–3 and ≥ 4 LN metastases [22]. In addition the recent meta-analysis by Early Breast Cancer Trialists Collaborative Trialists' Group revealed that adjuvant radiotherapy after mastectomy decreased 5 year local risk from 16 to 4% in patients with 1–3 LN metastases [23]. In a cohort of 5 996 patients, Tai et al. showed 25% involved lymph node ratio (LNR) as a cut-off point [17]. In that retrospective analysis, the authors demonstrated that regional radiotherapy significantly reduced the chance of any first recurrence in patients with 25–75% LNR but did not make a difference in patients with $\leq 25\%$ LNR. The cut-off point in our series is 25% similar to Tai et al.'s and patients with $\leq 25\%$ LNR showed more favourable outcome without any statistical difference than patients with N0 disease. So we think that it would be beneficial to change the guidelines in terms of radiotherapy indications and when considering as a significant prognostic factor, LNR can also be used for radiotherapy indication.

Differences in axillary lymph node staging techniques, particularly the extent of axillary dissection have the potential to impact loco-regional disease control [9,19]. In general, it has been suggested that the Level I and II lymph nodes should be removed for precise staging [24–26]. 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 consistent when at least ten lymph nodes were removed [27]. The Danish Breast Cancer Cooperative Group suggests that the number of lymph nodes removed with Level I and II dissection should be at least ten to exclude

down-staging of patients with positive lymph nodes as lymph node-negative [24]. In view of that, the Danish randomized trials have been criticized due to limited axillary surgery removing a median of seven lymph nodes, compromising staging precision and regional disease control [28,29]. It is noteworthy that, the median number of dissected lymph nodes in our series was 18, much higher than many reported series, suggesting the accuracy of axillary staging in this large cohort.

Fortin et al. argued the use of percent positive axillary lymph node involvement in the management of patients with 1–3 positive nodes since the percentage will always be lower particularly in this group after a complete dissection [30]. A percentage of higher values can be expected to occur only for patients with an incomplete dissection. Nevertheless, this is a very rare condition that occurred in only 4% of patients in our series (34 patients with >25%). In this context, it can be expected that the percent positive axillary involvement will not be useful in N1–3 group if they benefit from regional radiotherapy. However, the percentage of involved nodes in patients with more than 3 positive nodes can change their management. In our series survival is worse when $\geq 50\%$ of nodes is involved and this was relatively frequent, with 22% of more than 3 positive nodes patients having a percentage of $\geq 50\%$ involved nodes. Therefore, management can be expected to change based on the percentage of involved nodes, as opposed to solely the number of positive nodes determining recommendations. Since these patients with more than 3 positive lymph nodes are already potential candidate for regional radiotherapy, more aggressive systemic regimens should be searched.

In conclusion, we did demonstrate percent positive axillary nodal involvement predicts survival in non-metastatic post mastectomy breast cancer patients receiving regional radiotherapy. This prognostic factor can be used as a decision tool in the management of patients after post mastectomy radiotherapy, in addition to the other well known prognostic factors for recurrence. It seems that more efficient therapeutic approaches are certainly needed for patients with more than 50% axillary nodal metastases.

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