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The number of positive nodes and the ratio of positive to excised nodes are significant predictors of survival in women with micrometastatic node-positive breast cancer

Pauline T Truong[a,], Vincent Vinh-Hung[b], Gabor Cserni[c], Wendy A Woodward[d], Patricia Tai[e], Georges Vlastos[f], the authors are members of the International Nodal Ratio Working Group*

[a]*Department of Radiation Oncology, British Columbia Cancer Agency, Vancouver Island Centre, University of British Columbia, Victoria, BC, Canada*
[b]*Department of Radiation Oncology, Oncology Center, Academic Hospital, AZ-VUB, Vrije Universiteit, Brussel, Jette, Belgium*
[c]*Department of Surgical Pathology, Bács-Kiskun County Hospital, Kecskemét, Hungary*
[d]*Department of Radiation Oncology, University of Texas, MD Anderson Cancer Center, Houston, Texas, USA*
[e]*Department of Radiation Oncology, Allan Blair Cancer Centre, University of Saskatchewan, Regina, SK, Canada*
[f]*Division of Gynecology, Gynecology Oncology and Senology Unit, Geneva University Hospitals, Geneva, Switzerland*

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ABSTRACT

Background: To evaluate the prognostic impact of the number of positive nodes and the lymph node ratio (LNR) of positive to excised nodes on survival in women diagnosed with nodal micrometastatic breast cancer before the era of widespread sentinel lymph node biopsy.

Methods: Subjects were 62,551 women identified by the Surveillance Epidemiology and End Results database, diagnosed with pT1–2pN0-1 breast cancer between 1988 and 1997. Kaplan–Meier breast cancer-specific survival (BCSS) and overall survival (OS) were compared between three cohorts: node-negative (pN0, $n = 57{,}980$) nodal micrometastasis all $\leqslant 2$ mm (pNmic, $N = 1818$), and macroscopic nodal metastasis >2 mm but <2 cm (pNmac, $n = 2753$). Nodal subgroups were examined by the number of positive nodes (1–3 *versus* $\geqslant 4$) and the LNR ($\leqslant 0.25$ *versus* >0.25).

Results: Median follow-up was 7.3 yr. Ten-year BCSS and OS in pNmic breast cancer were significantly lower compared to pN0 disease (BCSS 82.3% *versus* 91.9%, $p < 0.001$ and OS 68.1% *versus* 75.7%, $p < 0.001$). BCSS and OS with pNmic disease progressively declined with increasing number of positive nodes and increasing LNR. OS with pNmic was similar to pNmac disease when matched by the number of positive nodes and by the LNR. Both pN-based and LNR-based classifications were significantly prognostic of BCSS and OS on Cox regression multivariate analysis.

Conclusion: Nodal micrometastasis is associated with poorer survival compared to pN0 disease. Mortality hazards with nodal micrometastasis increased with increasing number of positive nodes and increasing LNR. The number of positive nodes and the LNR should be considered in risk estimates for patients with nodal micrometastatic breast cancer.

* *Corresponding author:* Tel.: +1 250 519 5575; fax: +1 250 519 2018.
E-mail address: ptruong@bccancer.bc.ca (P.T Truong).
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1. Introduction

Advances in surgical staging and pathologic processing have contributed to increased diagnoses of micrometastatic nodal involvement in women with invasive breast cancer.[1] In the former American Joint Committee on Cancer (AJCC) 5th edition staging system, the presence of micrometastatic nodes $\leqslant$2 mm was classified as pN1a.[2] Older series have reported that survival associated with this nodal subgroup was similar to pathologic node-negative (pN0) disease.[3–5] This belief has since been challenged by studies reporting that nodal micrometastasis confers a worse prognosis warranting more aggressive treatment.[6–8] The 2002 AJCC 6th edition staging system has been revised to define micrometastatic nodal involvement (pN1mi) as deposits >0.2 mm but $\leqslant$2 mm.[9] At the same time, the AJCC staging system also revised pathologic nodal (pN) classification to reflect the prognostic significance of the absolute number of positive nodes in patients with breast cancer. In the context of patients with micrometastatic node-positive disease; however, relationships between the number of positive nodes and survival outcomes remain unclear.

With variations in surgical and pathological nodal staging practice, questions are increasingly raised regarding whether information on the number of excised nodes can refine the ability to distinguish different prognostic subgroups and individualise treatment recommendations. Recent studies have emerged examining the role of the lymph node ratio (LNR) of positive to excised nodes in predicting clinical outcomes. While these studies varied in patient samples, end-points and follow-up times, they showed consistency in the observation that the LNR is a significant prognostic factor for breast cancer recurrence and survival, in some cases superseding the absolute number of positive nodes.[10–14]

The current study aims to address the hypothesis that the number of positive nodes and the LNR of positive to excised nodes have long-term prognostic impact in women with micrometastatic node-positive breast cancer. The objectives of this analysis were (1) to compare survival outcomes in women with nodal micrometastasis to women with node-negative and macrometastatic node-positive disease as a function of the number of positive nodes and the ratio of positive to excised nodes and (2) to examine the prognostic significance of pN-based and LNR-based classifications in patients with nodal micrometastatic disease.

2. Methods

2.1. Study subjects

The Surveillance, Epidemiology and End Results (SEER) Programme of the National Cancer Institute is a collection of central cancer registries in the United States that collect and submit cancer incidence, prevalence, survival, stage at diagnosis data and other statistics to the National Cancer Institute. The SEER registry was used to identify 62,551 patients with the former AJCC 5th edition stage pT1-2, pN0, pN1a and pN1b, M0 breast cancer, diagnosed from 1988 to 1997. Since the primary objective was to examine the long-term prognostic impact of the number of positive nodes and the LNR, we selected subjects who were surgically treated before the advent of widespread sentinel node biopsy (SNB) to reduce the possible confounding effect of SNB yielding fewer numbers of excised nodes compared to axillary dissection. The choice of the study period to the year 1997 was based on reports documenting increased prevalence of SNB use from 1998 to 2000 in SEER registries[15] and at academic centres.[16]

2.2. Statistical analysis

Three nodal stage cohorts were analysed: pathologic node-negative (pN0; n = 57,980), nodal micrometastases all $\leqslant$2 mm (pNmic; n = 1818) and nodal macrometastases >2 mm but <20 mm (pNmac; n = 2753). Comparisons of the distributions of age at diagnosis, year of diagnosis, tumour (T) classification, the number of positive nodes, the number of excised nodes and the LNR of positive to excised nodes in the three cohorts were performed using Fisher's exact tests.

Primary outcomes were breast cancer-specific survival (BCSS), defined as the interval between the date of diagnosis and the date of death from breast cancer and overall survival (OS), defined as the interval between the date of diagnosis and the date of death from any cause. Survival estimates were calculated using Kaplan–Meier (KM) methods and compared between nodal subgroups using log rank chi square tests. BCSS and OS were compared across the nodal subgroups by the following parameters: number of positive nodes (1 *versus* 2 *versus* 3; 1–3 *versus* $\geqslant$4), number of excised nodes ($\leqslant$15 *versus* >15) and LNR ($\leqslant$0.25 *versus* >0.25). The selection of the cut-off for the number of excised nodes was based on the median of the current dataset and is consistent with large international trials reporting on axillary staging removing a median of 15 nodes.[17] The selection of LNR cut-off was based on a published analysis demonstrating the significance of LNR > 0.25 in predicting adverse survival in women with node-positive breast cancer treated with mastectomy.[14]

Multivariate analysis using Cox regression modelling was performed to evaluate the prognostic significance of the number of positive nodes and the LNR and to generate mortality hazard ratios and corresponding 95% confidence intervals (CI) using pN-based and LNR-based classifications. All tests were two-sided. Statistical significance was established at $p < 0.05$. All analyses were conducted using Statistical Package for the Social Sciences (Version 11.0.1, SPSS Inc, Chicago, Illinois).

3. Results

The median follow-up time was 7.3 yr (range 0.1–13.9 yr). The median patient age at diagnosis was 61 yr (range 25–95 yr).

3.1. Clinicopathologic Characteristics

Table 1 summarises the data on the characteristics of the study cohort. Axillary nodal staging was performed in all patients. The median number of excised nodes was 15 (range 1–50), and was similar across nodal subgroups. The proportions of pNmic and pNmac patients with 1–3 positive

Table 1 – Clinical characteristics in the entire Cohort and according to nodal subgroups

	Entire Cohort (*N* = 62,551) %	pN0 (*N* = 57,980) %	pNmic (*N* = 1818)%	pNmac (*N* = 2753)%	*P*
Age at diagnosis (yr)					
<50	26	23	34	34	<0.001
⩾50	74	77	66	66	
Year of diagnosis					
1988–1992	49	48	39	48	<0.001
1993–1997	51	52	61	52	
Type of surgery					
Mastectomy	60	57	63	68	<0.001
Breast conserving surgery	40	43	37	32	
Tumour size in cm Median (range)					
	1.5 (0.3–5.0)	1.5 (0.3–5.0)	1.8 (0.3–5.0)	2.0 (0.3–5.0)	
T stage classification					
T1	70	76	63	53	<0.001
T2	30	24	37	47	
Grade					
I	12	13	10	6	<0.001
II	31	31	34	31	
III	27	26	33	35	
Unknown	30	30	23	28	
Oestrogen receptors					
Positive	85	85	84	83	0.06
Negative	15	15	16	17	
Progesterone receptors					
Positive	79	79	80	79	0.43
Negative	21	21	20	21	
# Positive nodes					
0	74	100	0	0	
1–3	18	0	92	75	<0.001
⩾4	8	0	8	25	
# Excised nodes					
⩽15	56	58	54	52	<0.001
>15	44	42	46	48	
Lymph node ratio					
0.01–0.25		0	91	74	<0.001
>0.25		0	9	26	

nodes were 92% and 75%, respectively ($p < 0.001$). LNR > 0.25 was found in 9% of pNmic and 26% in pNmac patients ($p < 0.001$). T2 tumours were present in 24%, 37% and 47% of subjects with pN0, pNmic and pNmac disease, respectively ($p < 0.001$).

3.2. *Kaplan–Meier survival outcomes*

Ten-year KM BCSS and OS rates in patients with nodal micrometastatic disease were intermediate between node-negative and macroscopic node-positive disease (Figs. 1 and 2).

Comparisons of 10-yr BCSS and OS stratified by the number of positive nodes, number of excised nodes and LNR are summarised in Table 2. Women with pNmic disease experienced progressively lower BCSS and OS with increased number of positive nodes and with increased LNR. When matched by the number of positive nodes and by the LNR, BCSS was similar between pNmic and pNmac cohorts with ⩾4 positive nodes ($p = 0.52$) (Fig. 3a) and with LNR > 0.25 ($p = 0.95$) (Fig. 3b).

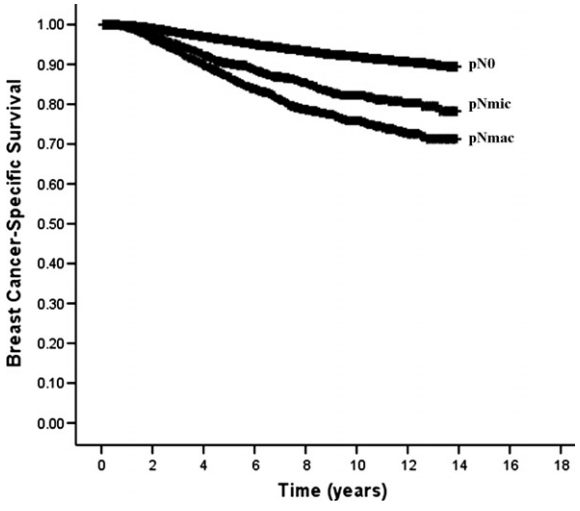

Fig. 1 – Breast cancer-specific survival according to nodal stage.

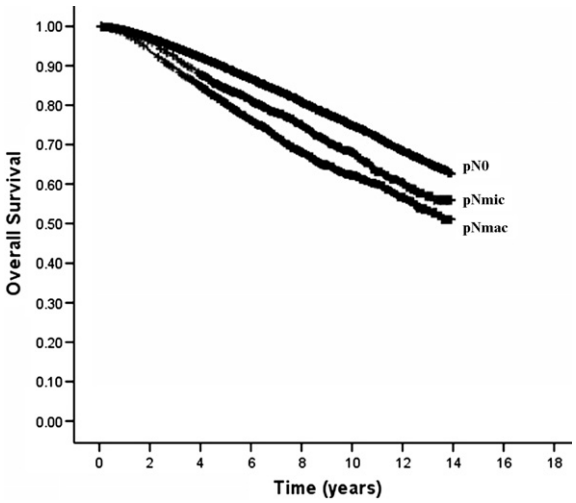

Fig. 2 – Overall survival according to nodal stage.

OS in pNmic patients was also similar to pNmac patients when matched by the number of positive nodes (Fig. 4a) and by the LNR (Fig. 4b).

3.3. *Multivariate analysis*

On Cox regression analysis (Table 3), pN-based and LNR-based classifications were significantly prognostic of BCSS and OS. The survival hazard ratios associated with ⩾4 positive nodes or LNR > 0.25 were similar in cohorts with micrometastatic and macrometastatic nodal disease and were approximately four times greater relative to node-negative disease.

4. Discussion

The survival and therapeutic implication of nodal micrometastases in patients with invasive breast cancer have remained unclear. The current population-based analysis demonstrated that, despite being perceived as small volume nodal disease, nodal micrometastastic disease was associated with significantly poorer survival compared to node-negative disease. Similar to patients with macroscopic nodal involvement, survival in women with nodal micrometastatic disease progressively declined with escalating number of positive nodes and ratio of positive to excised nodes. The number of positive nodes and the LNR were strong prognostic indicators for survival in women with nodal micrometastatic disease on multivariate analysis. These findings support the suggestion that both the absolute number of positive nodes and the LNR be jointly considered in appraising mortality risks and in treatment decisions for patients with nodal micrometastatic breast cancer.

The AJCC staging system was recently revised, grouping patients by the absolute number of positive nodes.[9] This classification improved stratification in overall survival,[18] but the confounding effect that the number of excised nodes may have on the yield of positive nodes and its impact on breast cancer-specific survival prognostic accuracy and management decisions remain unresolved. The LNR may be a more comprehensive approach to estimate prognosis since it takes into account the number of excised nodes and may accordingly adjust for differences in nodal staging.[10] In a statistical modelling study of 4387 patients with T1-2, node-positive breast cancer treated with mastectomy, Vinh-Hung and colleagues applied Cox regression models to examine hazard ratios for breast cancer-specific and overall mortality associated with escalating numbers of positive nodes. The plot of hazard

Table 2 – Comparisons of 10-year Kaplan–Meier breast cancer-specific survival (BCSS) and overall survival (OS) by the number of positive nodes, number of excised nodes and lymph node ratio

	% 10-year BCSS (standard error)				% 10-year OS (standard error)			
	pN0	pNmic	pNmac	*P*	pN0	pNmic	pNmac	*P*
All patients	91.9 (0.1)	82.3 (1.2)	75.8 (1.0)	<0.001	75.7 (0.2)	68.1 (1.4)	62.4 (0.4)	<0.001
# Positive nodes								
0	91.9 (0.1)	–	–		75.7 (0.2)	–	–	
1	–	84.7 (1.3)	83.4 (1.4)	0.24	–	70.3 (1.7)	68.9 (1.7)	0.70
2	–	81.8 (2.9)	79.6 (2.0)	0.30	–	71.2 (3.7)	66.2 (2.3)	0.02
3	–	74.0 (5.2)	72.8 (3.2)	0.76	–	58.8 (5.5)	61.2 (3.4)	0.19
P	–	0.008	0.004			0.004	0.05	
1 – 3	–	83.5 (1.2)	80.5 (1.1)	0.02	–	69.7 (1.5)	66.8 (1.3)	0.10
⩾ 4	–	68.8 (4.8)	62.1 (2.3)	0.52	–	50.9 (5.2)	49.3 (2.2)	0.75
P	–	0.0000	0.0000		–	<0.001	<0.001	
# Excised nodes								
⩽15	91.8 (0.2)	82.7 (1.6)	75.9 (1.4)	0.001	73.1 (0.3)	68.0 (2.0)	60.9 (1.6)	0.005
>15	92.1 (0.2)	81.9 (1.7)	75.6 (1.5)	0.002	77.4 (0.3)	68.4 (2.1)	63.6 (1.6)	0.01
P	0.54	0.67	0.70		<0.001	0.55	0.38	
Lymph node ratio								
0.01–0.25	–	84.1 (1.2)	80.6 (1.1)	0.01	–	70.2 (1.5)	67.1 (1.3)	0.11
>0.25	–	62.6 (5.2)	61.9 (2.3)	0.95	–	46.6 (5.3)	48.5 (2.3)	0.82
P	–	<0.001	<0.001		–	<0.001	<0.001	

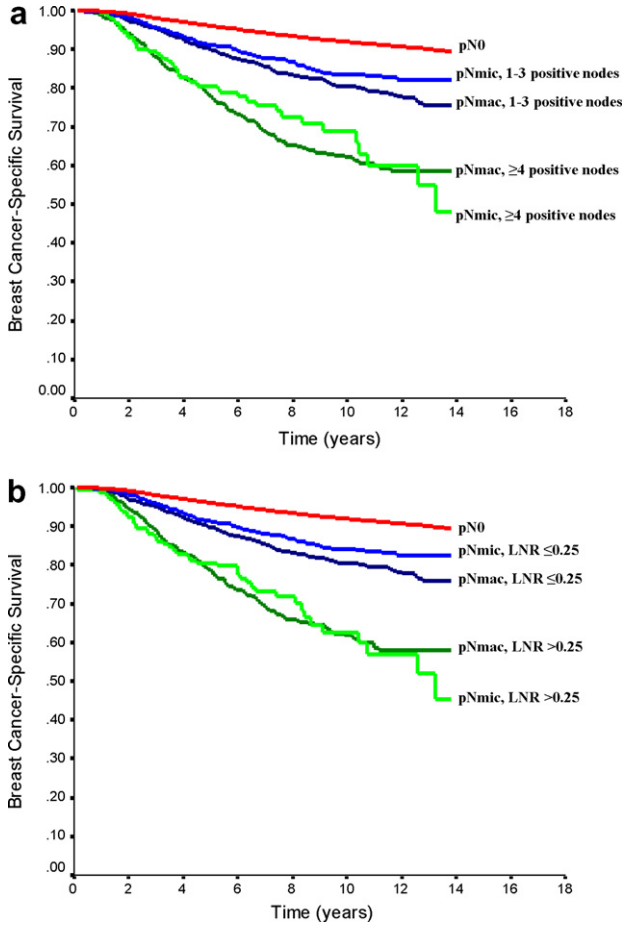

Fig. 3 – Breast cancer-specific survival stratified by (a) number of positive nodes and (b) lymph node ratio.

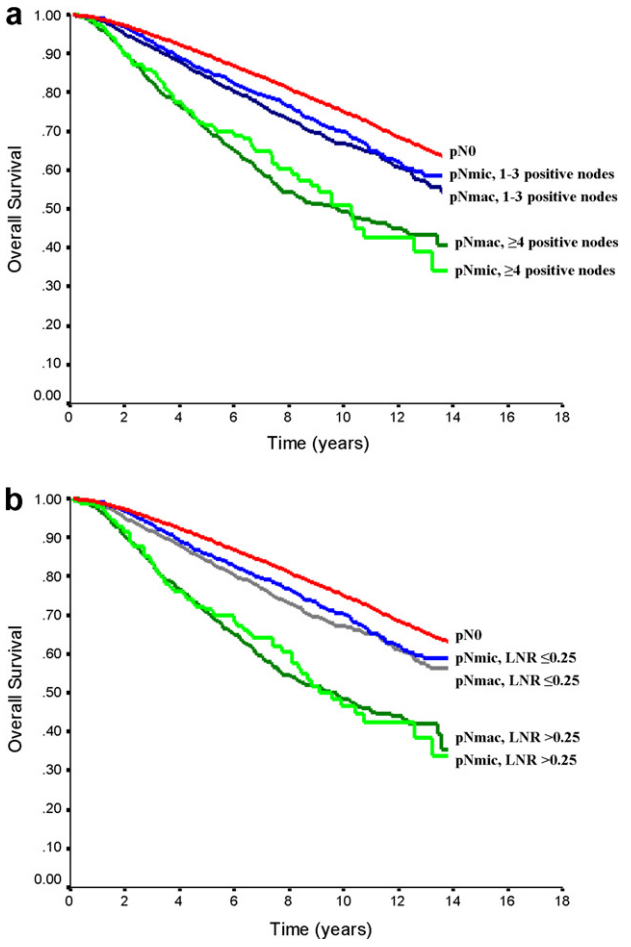

Fig. 4 – Overall survival stratified by (a) number of positive nodes and (b) lymph node ratio.

ratios as a function of number of positive nodes showed a continuously increased risk with each additional positive node without any identifiable cut points.[19] In another SEER data analysis of 83,686 women with T1-2 breast cancer staged by axillary dissection, these investigators examined multiple Cox models for breast cancer-specific mortality based on different expressions of nodal involvement. Comparisons of these models suggested that the LNR provided at least the same prognostic value as the traditional staging using absolute number of positive nodes but offered the advantage of standardisation to the number of excised nodes.[11]

The finding in the current analysis that the LNR was a strong prognostic factor for survival in patients with node-positive breast cancer is consistent with other population-based analyses.[10–14] In a series from the Netherlands of 453 patients with Stages I–II breast cancer treated with mastectomy or breast conserving therapy, van der Wal and colleagues reported that the LNR was a significant predictor of survival that superseded the number of positive nodes.[12] In another series from Belgium with 741 patients with node-positive breast cancer, examining LNRs using different cut-offs ($\leqslant$0.10, 0.11–0.50, > 0.50), Voordeckers and colleagues found the LNR to be the most significant predictor for overall survival.[13] The present analysis corroborates these studies and supports the use of the LNR to estimate survival prognosis for patients with breast cancer, including those with nodal micrometastatic disease.

With advances in pathologic processing techniques including the use of immunohistochemistry (IHC) and reverse transcription-polymerase chain reactions (RT-PCR), the AJCC 6th edition currently classifies isolated tumour cells $\leqslant$0.2 mm as pN0(i+) and RT-PCR positive samples as pN0(mol+).[9] Distinct from the current study which focused on the number of positive nodes, including $\geqslant$4 positive nodes and the LNR in patients treated before the era of widespread SNB staging, investigators from Santa Monica, California, examined SEER data in patients diagnosed between 1992 and 2003 with invasive breast cancer and 0–3 axillary nodes. Overall survival in patients with pN1mi/pN0(i+) disease was intermediate between patients with pN0 (HR 1.35) and patients with 1–3 macroscopic positive nodes (HR 0.82).[20] Investigators from Milan reported on 1959 patients with AJCC 6th edition stage pT1-3, pN0 (n = 1400), pN1mi/pN0(i+) (n = 282) and macroscopic disease with one single positive node (n = 327), treated between 1997 and 2000.[21] Despite higher rates of anthracycline-based chemotherapy use, patients with pN1mi/pN0(i+) disease experienced lower disease-free survival compared to pN0 disease (HR 1.58, 95% CI 1.01–2.47, p = 0.047). The poorer disease-free survival was independent of whether the pN1mi/pN0(i+) involvement was detected by

Table 3 – Multivariate analysis of breast cancer-specific survival (BCSS) and overall survival (OS)

	BCSS *P* Hazard Ratio (95% CI)		OS *P* Hazard Ratio (95% CI)	
	Without LNR as covariate	With LNR as covariate	Without LNR as covariate	With LNR as covariate
Age (< 50 *versus* ⩾50 y)	0.003 1.10 (1.03–1.19)	0.003 1.11 (1.04–1.18)	<0.001 0.42 (0.40–0.45)	<0.001 0.43 (0.40–0.45)
Year of diagnosis (1988–92 *versus* 1993–97)	<0.001 1.23 (1.16–1.32)	<0.001 1.23 (1.16–1.32)	<0.001 1.08 (1.04–1.12)	<0.001 1.08 (1.04–1.12)
T stage (T2 *versus* T1)	<0.001 2.60 (2.45–2.76)	<0.001 2.60 (2.44–2.78)	<0.001 1.62 (1.57–1.68)	<0.001 1.62 (1.57–1.68)
# Excised nodes (<15 *versus* ⩾15)	0.05 1.06 (1.00–1.13)	0.24 1.04 (0.98–1.10)	<0.001 1.20 (1.16–1.24)	<0.001 1.18 (1.14–1.23)
# Positive nodes	<0.001	–	<0.001	–
($pNmic_{1-3}$ *versus* pN0)	1.88 (1.63–2.16)		1.31 (1.19–1.45)	
($pNmic_{\geqslant 4}$ *versus* pN0)	4.00 (2.94–5.45)		2.42 (1.89–3.09)	
($pNmac_{1-3}$ *versus* pN0)	2.08 (1.85–2.34)		1.36 (1.25–1.48)	
($pNmac_{\geqslant 4}$ *versus* pN0)	4.06 (3.53–4.67)		2.26 (2.02–2.53)	
Lymph node ratio	–	<0.001	–	<0.001
$pNmic_{\leqslant 0.25}$ *versus* pN0		1.82 (1.58–2.10)		1.30 (1.18–1.44)
$pNmic_{>0.25}$ *versus* pN0		4.52 (3.39–6.03)		2.49 (1.96–3.15)
$pNmac_{\leqslant 0.25}$ *versus* pN0		2.09 (1.86–2.34)		1.37 (1.26–1.49)
$pNmac_{>0.25}$ *versus* pN0		4.00 (3.48–4.60)		2.17 (1.94–2.43)

SNB or by completion axillary dissection.[21] The hazard ratio reported in that series is comparable to the current report demonstrating an HR of 1.88, 95% CI 1.63–2.16 for BCSS with nodal micrometastasis with one to three positive nodes relative to pN0 disease, and suggests that despite increased systemic therapy use in modern practice,[22] nodal micrometastasis remains an adverse factor for poorer outcomes. In addition, the high mortality risks in patients with ⩾4 positive nodes involved by micrometastasis or LNR > 0.25 demonstrated in our analysis raises the concern that the current pN1mi categorisation may suggest a false perception of favourable risk in these subsets. The mortality hazards observed in these patients support the contention that they may be more suited in a higher risk nodal staging classification.

In contemporary practice, SNB performed by experienced surgeons and yielding negative nodes may spare patients the morbidity of axillary dissection.[23,24] The question of whether SNB yielding micrometastatic deposits necessitates completion axillary dissection is a current topic of debate.[15,25–29] Maggard and colleagues reported that 25% of patients with micrometastasis detected on SNB had residual axillary involvement found on completion axillary dissection.[15] Viale and colleagues reported another series of 634 patients, 109 of whom had micrometastasis found on SNB. The rate of having axillary nodal involvement on axillary dissection increased from 15% with micrometastasis ⩽1 mm to 36% in patients with foci >1 mm.[25] Studies are emerging to suggest that the ratio of positive to excised sentinel nodes can be a useful predictor of non-sentinel involvement in patients with SN-positive disease.[29–31] Nomograms have been developed to predict the likelihood of having additional positive nodes on axillary dissection after detection of SN-positive disease,[32–36] but validation testing has yielded varying results.[36–38] A recent report has also suggested that predictive reliability is limited in cases of micrometastatic positive sentinel nodes.[38] Since the prognostic role of micrometastases detected with SNB and what constitutes optimal locoregional management after SNB detection of micrometastatic involvement remain unclear, prospective trials and outcomes analyses will continue to be needed to address these questions in contemporary practice.

Variations in the methods of pathologic processing can affect the rates of detecting micrometastatic nodal involvement.[39–41] During the era of our study from 1987 to 1997, it is likely that majority of cases of micrometastatic disease were diagnosed using hematoxylin–eosin (H&E) staining, rather than IHC or RT-PCR, and it is also likely that the proportion of nodal lesions belonging in the current isolated tumour cell category was minimal.[1] Most centres have continued to use H&E staining as a minimum standard in nodal assessment. However, contemporary studies examining step sectioning and IHC protocols support the use of serial sectioning and IHC assessment to reduce the risk of false-negative results with H&E histologic examination alone.[39] In a meta-analysis of 25 studies reporting on non-SN involvement associated with micrometastatic or IHC-positive SN involvement, Cserni and colleagues reported that the risk on non-SN metastasis was approximately 10–15%,

but this incidence was lower if the SN positivity was detected by IHC alone.[28] These findings highlight the importance of considering the pathological method used to diagnose nodal involvement in estimating risks with omitting axillary dissection after small volume sentinel node involvement and the importance of the ongoing efforts to promote consistency among pathologists in assessing and reporting small volume nodal involvement.[40,41]

During the era of our study, the SEER database lacked data on the number of patients who had SNB prior to axillary dissection. Since 1998, the SEER registry has started to capture data regarding the type of surgery used to establish pathologic nodal staging. This will serve as a valuable resource for future studies examining the prognostic and therapeutic implications of nodal micrometastasis diagnosed by SNB with or without axillary dissection. Until such data with long-term follow-up are available, the current report documenting reduced survival in women with nodal micrometastastic breast cancer with increasing number of positive nodes and lymph node ratios supports the consideration of completion axillary dissection in the presence of H&E positive micrometastatic nodes since comprehensive information regarding the number of positive to excised nodes can be of value in identifying higher risk patients warranting more aggressive adjuvant therapy.

5. Conclusion

Nodal micrometastases $\leqslant$2 mm, despite being perceived to be small volume nodal involvement, are associated with significantly poorer survival compared to node-negative disease. Mortality hazards with nodal micrometastases increased with the number of positive nodes and the LNR. The number of positive nodes and the LNR should be considered in risk estimates and treatment decisions for patients with nodal micrometastatic breast cancer.

Conflict of interest statement

None declared.

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