

**Keywords:** breast neoplasms; lymph node ratio; pN1; prognostic factor; predictive factor; post-mastectomy radiation therapy

# Clinical relevance of lymph node ratio in breast cancer patients with one to three positive lymph nodes

S I Kim<sup>1,7</sup>, S-H Cho<sup>2,7</sup>, J S Lee<sup>1</sup>, H-G Moon<sup>3</sup>, W C Noh<sup>4</sup>, H J Youn<sup>5</sup>, B K Ko<sup>6</sup> and B-W Park<sup>\*,1</sup>

<sup>1</sup>Department of Surgery, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Republic of Korea;

<sup>2</sup>Department of Statistics and Actuarial Science, Soongsil University, 369 Sangdo-ro, Dongjak-gu, Seoul 156-743, Republic of Korea; <sup>3</sup>Department of Surgery, Seoul National University College of Medicine, 103 Daehak-ro, Jongno-gu, Seoul 110-799, Republic of Korea; <sup>4</sup>Department of Surgery, Korea Institute of Radiological and Medical Science, Gongneung-Dong, No-won-gu, Seoul 139-709, Republic of Korea; <sup>5</sup>Department of Surgery, Chonbuk National University Medical School, 20 Geonjiro, Deokjin-gu, Jeonju 561-712, Republic of Korea and <sup>6</sup>Department of Surgery, University of Ulsan College of Medicine, 877 Jeonha 1-dong, Dong-gu, Ulsan 682-714, Republic of Korea

**Background:** To test the hypotheses that breast cancer patients with one to three positive lymph nodes (pN1) consist of heterogeneous prognostic subsets and that the ratio of positive nodes to total nodes dissected (lymph node ratio, LNR) might discriminate patients with a higher risk as candidates for post-mastectomy radiation therapy (PMRT).

**Methods:** Using information from 7741 node-positive patients, we first identified cutoff values of the LNR using the nonparametric bootstrap method. Focusing on 3477 patients with pN1 disease, we then evaluated the clinical relevance of the LNR categorised by the estimated cutoff values (categorised LNR, cLNR).

**Results:** Among 3477 patients with pN1 disease, 3059 and 418 patients were assigned into the low and intermediate cLNR groups, respectively, based on a cutoff value of 0.18. The prognostic factors associated with poor overall survival (OS) included younger age, T2 stage, negative oestrogen/progesterone receptors, high histologic grade, and intermediate cLNR. Post-mastectomy radiation therapy significantly increased OS in patients assigned to the intermediate cLNR (hazard ratio, 0.39; 95% confidence interval, 0.17–0.89;  $P=0.0248$ ), whereas patients in the low cLNR group derived no additional survival benefit from PMRT.

**Conclusion:** This study suggests that PMRT should be recommended for patients with pN1 disease and an intermediate cLNR.

The staging system of breast cancer allows physicians to estimate the prognosis of patients and guides treatment planning. Since the sixth edition of the American Joint Committee on Cancer (AJCC) staging system, patients with one to three positive axillary lymph nodes have been defined as having positive lymph nodes (pN1) disease (Singletary *et al*, 2002; Edge, 2010). Although the AJCC staging system reflects the disease state by emphasising the prognostic importance of the absolute number of affected lymph nodes (Kim *et al*, 2006), the rationale behind four nodes as the

cutoff between pN1 and pN2 is unclear. Recently, the ratio of the number of pN1 to the number of total dissected lymph nodes (lymph node ratio, LNR) has been proposed as an alternative prognostic factor instead of the absolute number of positive nodes (Vinh-Hung *et al*, 2003a, b; Voordeckers *et al*, 2004; Truong *et al*, 2005a; Kuru, 2006; Woodward *et al*, 2006; Truong *et al*, 2008; Vinh-Hung *et al*, 2009; Chagpar *et al*, 2011; Tausch *et al*, 2012).

One of the most controversial issues regarding the treatment of breast cancer is defining the indications of post-mastectomy

\*Correspondence: Dr B-W Park; E-mail: bwpark@yuhs.ac

<sup>7</sup>These authors contributed equally to this work.

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radiation therapy (PMRT). A general consensus has been reached to advise PMRT for patients with four or more involved axillary nodes (Recht *et al*, 2001; Goldhirsch *et al*, 2009, 2011); however, the role of PMRT in patients with pN1 disease is still widely debated (Ragaz *et al*, 1997; Overgaard *et al*, 1999; Ragaz *et al*, 2005; Smith *et al*, 2005; Nielsen *et al*, 2006; Overgaard *et al*, 2007; Kim *et al*, 2011).

In this study, we hypothesised that patients with pN1 disease might consist of heterogeneous prognostic subsets of patients and that the LNR might be used to improve the prognostication. Furthermore, we tested LNR as a potential discriminator of patients with a higher risk who might benefit from subsequent PMRT.

## PATIENTS AND METHODS

**The Korean breast cancer registry.** All data used in this study were retrieved from the Korean Breast Cancer Registry (KBCR), which has prospectively maintained an online database to store information on each patient's Korean personal identification number, age, type of surgery, primary tumour size, number of positive/dissected nodes, oestrogen receptor (ER)/progesterone receptor (PR) status, histologic grade, and details of adjuvant therapy. Nation-wide collaborative efforts from 102 general hospitals, including 41 university hospitals, have contributed to the KBCR database since 1996 (Ahn *et al*, 2007). Exploiting the patient's identification number as a unique identifier, we amalgamated the KBCR database with two population-based sources of information: the Korean Central Cancer Registry, which provides patient's survival data, and the Korean National Statistical Office, which publishes complete death statistics.

**Cut-off values of the LNR.** To define the optimal cutoff values of LNR, we first investigated the prognostic value of LNR as a continuous variable. Using multivariate Cox proportional hazards regression models, we assessed the statistical significance of the LNR adjusted for clinico-pathologic characteristics including age, tumour size, ER/PR status, histologic grade, and PMRT. As a next step, we carefully identified the upper and lower cutoff values of the LNR to classify breast cancer patients into three distinct subgroups: low, intermediate, and high. These optimal cutoff values were intended to minimise information loss by categorising the continuous variable of the LNR (categorised LNR, cLNR). All possible combinations of lower and upper cutoff values ranging from 0.001 to 0.85 with an increment of 0.001 were considered. The robustness of the estimated cutoff values was examined using the nonparametric bootstrap method (Efron, 1979) with generation of 10 000 bootstrap samples to attain the empirical sampling distributions of the estimated cutoff values.

Identification of the optimal cutoff points of the LNR was based on a population of primary breast cancer patients who had at least one positive axillary lymph node and underwent definitive mastectomy between 1998 and 2009. All of the patients received anthracycline- and taxane-based adjuvant chemotherapy according to the NCCN (National Comprehensive Cancer Network) guideline (Carlson *et al*, 1996). For reliable estimation of nodal involvement, patients who had fewer than 10 dissected lymph nodes were excluded. We also excluded patients who received neoadjuvant chemotherapy or breast conservation therapy, and those with ductal carcinoma *in situ* or stage IV disease at the time of diagnosis. As a result, a total of 7741 patients were analysed to define the optimal cutoff values of LNR.

**Study population patients with pN1 disease.** In this study, we intended not only to evaluate the prognostic value of the LNR but also, more importantly, to identify patients with a higher risk with pN1 disease who would benefit from PMRT after definitive initial

surgery. Therefore, we restricted our study population to 3817 patients who had one to three pN1. To address the current controversy regarding PMRT, we further limited the study population to a patient cohort with T1/T2 lesions. A total of 3477 patients with pN1 disease and small tumours (T1/T2), who were treated with or without PMRT, were ultimately enrolled as our main study population. Post-mastectomy radiation therapy covered chest wall and regional lymph nodes in each patient. Irradiated volume was treated with 4 or 6-MV photons and/or electrons with median radiation dose of 50–50.4 Gy with 1.8–2 Gy per fraction. Regional lymph nodes include supraclavicular, high, and a part of low axillary lymph nodes. Internal mammary lymph nodes were included depending on physician's preference.

Focusing on these patients with pN1 disease, we first evaluated the prognostic value of the cLNR adjusted for clinico-pathologic characteristics and then investigated the clinical relevance of cLNR with respect to PMRT.

**Statistics.** The primary end point of this study was overall survival (OS) defined as the time from the date of surgery to death of any cause. According to the Akaike Information Criteria, the independent prognostic factors significantly associated with OS were selected in stepwise manner avoiding over-parameterisation. The treatment effect of PMRT in patients with pN1 disease was assessed for each of the cLNR groups using the likelihood ratio test. Based on the log-rank test, the Kaplan–Meier OS estimates of the cLNR groups were also compared with measure, the unadjusted treatment effects of PMRT. *P*-values < 0.05 were considered statistically significant. All statistical analyses were performed using R (<http://www.r-project.org>). This study was approved by the Korean Breast Cancer Registry Committee and the Institutional Review Boards of Severance Hospital.

## RESULTS

**Cutoff values of LNR.** According to the multivariate analysis, the continuous variable of the LNR was the independent prognostic factor most significantly associated with OS (hazard ratio (HR), 7.57; 95% confidence interval (CI), 5.83–9.82; *P* < 0.0001; Supplementary Table 1). On verification of the prognostic value of the LNR, the optimal lower and upper cutoff values of LNR were estimated to be 0.18 and 0.64, respectively. According to the empirical sampling distribution of the estimated cutoff values based on 10 000 bootstrap samples, the most frequent values were observed around 0.18 and 0.64, respectively (lower cutoff: mean = 0.18, s.e. = 0.02; upper cutoff: mean = 0.64, s.e. = 0.06; Figure 1).

**Prognostic value of the categorised LNR in patients with pN1 disease.** The characteristics of the study population with pN1 disease are summarised in Table 1. Among a total of 3477 patients, 1255 (36.1%) and 2222 (63.9%) patients had T1 and T2 lesions, respectively. The mean number of dissected lymph nodes was 18.76 (s.d., 7.27). The number of patients with one, two, and three pN1 was 1699 (48.9%), 1049 (30.2%), and 729 (21.0%), respectively. As our main study population excluded patients who had fewer than 10 dissected lymph nodes, the values of the LNR ranged from 0 to 0.3. Using the lower cutoff value of 0.18, 3059 (88.0%) and 418 (12.0%) patients were assigned into the low and intermediate cLNR groups, respectively.

The median follow-up time was 3.3 years. Based on the multivariate analysis, younger age (< 35 years), large tumour size (T2 lesion), negative ER/PR status, and high histologic grade (II and III) were significantly associated with poor OS (Table 2). The cLNR was also a significant independent prognostic factor. Compared with the low cLNR group, the adjusted HR of the intermediate cLNR group was 1.81 (95% CI, 1.34–2.45, *P* = 0.0001;

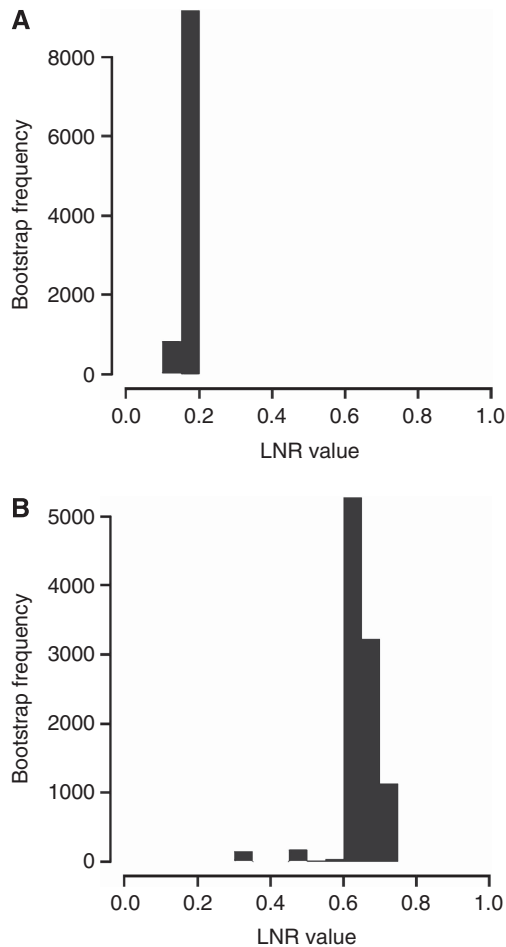


Figure 1. Empirical distributions of the estimated LNR cutoff values based on 10 000 bootstrap samples: (A) lower cutoff; (B) upper cutoff.

Table 2). There was a statistically significant separation between the Kaplan–Meier survival curves of the low and intermediate cLNR groups ( $P = 0.0018$ ) (Figure 2). The estimated survival rate at 10 years was higher in the low cLNR group (76.7%) than in the intermediate cLNR group (61.4%).

**Predictive value of categorised LNR for efficacy of PMRT in patients with pN1 disease.** The study population included 443 (12.7%) patients who received PMRT after mastectomy. As indicated by the interaction terms between PMRT and the cLNR groups, there was a significant benefit of PMRT for the intermediate cLNR group (likelihood ratio test,  $P = 0.0248$ ; Table 2). In contrast, there was no apparent benefit of PMRT for patients with a low cLNR (likelihood ratio test,  $P = 0.2415$ ). For patients with an intermediate cLNR, PMRT significantly reduced relative risk (HR, 0.39; 95% CI, 0.17–0.89) and absolute risk (25.48%; s.e., 15.36%; Supplementary Figure 1).

As expected, for the intermediate cLNR group PMRT greatly increased the estimated survival rate at 10 years from 56.13% to 81.61% (Table 3, Figure 3C), and Kaplan–Meier survival curves according to PMRT or no PMRT indicated a statistically significant difference ( $P = 0.0047$ ). In contrast, there was no significant increase in the estimated survival rates at 10 years for patients with PMRT in the low cLNR group (76.47% vs 79.10; Table 3, Figure 3B) and in the whole study population with pN1 disease (74.35% vs 79.48%; Table 3, Figure 3A). Consistent with these findings, PMRT did not have a significant effect on the Kaplan–Meier survival curves for the low pLNR group ( $P = 0.0706$ ) or for all patients with pN1 disease ( $P = 0.6033$ ).

## DISCUSSION

The presence of axillary lymph node metastasis is the single most important prognostic factor in patients with breast cancer (Carter *et al*, 1989; Fitzgibbons *et al*, 2000; Vinh-Hung *et al*, 2003a), and the prognostic importance of the total number of pN1 has long been recognised (Carter *et al*, 1989; Fisher *et al*, 1993; Recht *et al*, 1999; Fitzgibbons *et al*, 2000; Edge, 2010). The latest AJCC staging system defined patients with one to three positive axillary lymph nodes as pN1 disease (Singletary *et al*, 2002; Edge, 2010), while patients with more than four positive axillary lymph nodes are classified as pN2 or pN3. Although patients with pN2 or pN3 disease have a clearly worse prognosis than those with pN1 disease (Axelsson *et al*, 1992; Kim *et al*, 2006), the biologic rationale for four nodes as the threshold between pN1 and pN2 is unclear.

We hypothesised that patients with pN1 disease might comprise different prognostic subsets of patients, mainly for the following two reasons: first, in past analysis of the SEER (Surveillance, Epidemiology and End Results) database, (Vinh-Hung *et al* 2003a) reported that the relative mortality hazard continues to increase with each involved node without any obvious cutoff point. Second, the current staging system of breast cancer is based merely on the number of pN1 without considering the total number of lymph nodes dissected. In cases where only a few lymph nodes are examined, there is the potential possibility of downstaging the axilla (Vinh-Hung *et al*, 2009; Danko *et al*, 2010).

The LNR has been proposed as an alternative measure to improve the prognostication system in patients with node-positive disease (Vinh-Hung *et al*, 2003a,b; Voordeckers *et al*, 2004; Truong *et al*, 2005a; Kuru, 2006; Woodward *et al*, 2006; Truong *et al*, 2008; Vinh-Hung *et al*, 2009; Danko *et al*, 2010; Chaggar *et al*, 2011; Tausch *et al*, 2012). Compared with the number-based staging system, the ratio-based staging system exploits additional information on the total number of lymph nodes dissected. However, the use of additional information does not rule out the issue of misclassification. For example, if the total number of lymph nodes removed is very small, a high LNR may result from insufficient dissection of the axillary lymph node. In this case, the ratio-based staging system may result in upstaging of patients.

For reliable estimation of nodal involvement by the LNR, it would be desirable to define a minimum number of dissected lymph nodes. Previous observational studies have shown that sampling fewer than 10 axillary nodes more than doubles the risk of subsequent loco-regional failure (Recht *et al*, 1999; Katz *et al*, 2000, 2001; Woodward *et al*, 2003), and that the estimation of nodal involvement is more reliable when at least 10 nodes are excised (Fisher *et al*, 2002). The AJCC requires that a minimum of six axillary lymph nodes be removed and examined whereas other authorities recommend that at least 10 lymph nodes be examined (National Institutes of Health, 1991; The Steering Committee, 1998). To ensure that patients in this study received appropriate axillary dissection, we restricted the study population to patients who had a minimum of 10 dissected lymph nodes.

We initially aimed to evaluate the clinical value of the LNR among patients with pN1 disease. As a preliminary step, we confirmed the prognostic value of the LNR as a continuous variable for all node-positive patients using multivariate Cox regression analysis (Supplementary Table 1). Subsequently, we categorised the LNR by lower and upper cutoff values of 0.18 and 0.64, respectively, and all node-positive patients were assigned into low, intermediate, and high cLNR groups, respectively. As expected, there were significant separations among the Kaplan–Meier OS estimates for the three cLNR groups ( $P < 0.0001$ ; Supplementary Figure 2).

Next, we evaluated the clinical value of the cLNR, focusing on patients with pN1 disease. For patients with pN1 disease, the LNR

Table 1. Comparison of clinico-pathologic factors between patients with PMRT and without PMRT

	All patients (n = 3477)		PMRT (n = 443)		No PMRT (n = 3034)		P-value
	n	%	n	%	n	%	
<b>Age</b>							
≤35	300	8.6	53	12	53	12	0.0097
>35	3177	91.4	390	88	390	88	
<b>Sex</b>							
Male	20	0.58	2	0	2	0	0.9742
Female	3457	99.4	3016	100	3016	100	
<b>T stage</b>							
T1	1255	36.1	158	35.7	158	35.7	0.8823
T2	2222	63.9	285	64.3	285	64.3	
No. of dissected lymph nodes	Mean = 18.76, s.d. = 7.27		Mean = 18.19, s.d. = 6.76		Mean = 18.84, s.d. = 7.34		0.0597
<b>No. of positive node</b>							
1	1699	48.9	148	33.4	148	33.4	<0.0001
2	1049	30.2	148	33.4	148	33.4	
3	729	21.0	147	33.2	147	33.2	
<b>Histologic grade</b>							
I	386	11.1	47	10.6	47	10.6	0.7857
II, III	3091	88.9	396	89.4	396	89.4	
<b>Oestrogen receptor</b>							
Negative	1268	36.5	167	37.7	167	37.7	0.6012
Positive	2209	63.5	276	62.3	276	62.3	
<b>Progesterone receptor</b>							
Negative	1516	43.6	178	40.2	178	40.2	0.1329
Positive	1961	56.4	265	59.8	265	59.8	
<b>Endocrine therapy</b>							
None	1355	39	169	38.1	169	38.1	0.7434
Done	2122	61	274	61.9	274	61.9	
<b>cLNR</b>							
Low (≤0.18)	3059	88	349	78.8	349	78.8	<0.0001
Intermediate (0.18–0.3)	418	12	94	21.2	94	21.2	

Abbreviations: cLNR = categorised lymph node ratio; PMRT = post-mastectomy radiation therapy.

ranged from 0 to 0.3 because only patients with at least 10 dissected nodes were included in our study population. As a result, all of the patients with one positive node were assigned into the low cLNR group, while patients having two and three positive nodes were assigned into low and intermediate cLNR groups according to the total number of dissected nodes. By multivariate analysis, we demonstrated that the cLNR further classified patients with pN1 disease into two heterogeneous prognostic subsets, with patients in the intermediate cLNR group having a clearly worse prognosis than those in the low cLNR group in terms of OS.

After ascertaining that the cLNR was indeed significantly associated with OS, we further investigated the treatment effects of PMRT in patients with pN1 disease. A clear survival benefit of PMRT was observed in patients assigned to the intermediate cLNR group, in which PMRT was associated with a 61% reduction in overall mortality (Table 2). Truong *et al* (2005b) also suggested that the percentage of node positive (>25% of removed nodes) were statistically significant independent factors associated with

greater loco-regional recurrence, meriting consideration of PMRT in patients with pN1 and T1/T2 disease.

Currently, the general consensus is that PMRT is indicated for patients with four or more involved axillary nodes. However, there is no agreement on whether all patients with pN1 disease should be recommended for PMRT (Recht *et al*, 2001; Goldhirsch *et al*, 2009, 2011). The previous retrospective study using the SEER database reported no remarkable survival benefit of PMRT for patients with pN1 disease (Smith *et al*, 2005). However, according to the latest analysis of the Early Breast Cancer Trialists' Collaboration Group, PMRT reduced local recurrence risk and mortality in patients with node-positive disease regardless of the degree of nodal involvement (Clarke *et al*, 2005). More importantly, recent randomised prospective trials demonstrated improved survival after PMRT in all node-positive women (Ragaz *et al*, 1997; Overgaard *et al*, 1999; Ragaz *et al*, 2005; Nielsen *et al*, 2006), and the survival increment was at least equally beneficial in patients with pN1 disease (Overgaard *et al*, 2007). Despite the level 1 evidence of the above



randomised trials supporting the benefits of PMRT, it should be noted that these randomised trials have been criticised for their less extensive axillary surgery and relatively high risk of loco-regional

recurrence (Overgaard *et al*, 1997, 1999; Recht *et al*, 1999; Katz *et al*, 2000; Woodward *et al*, 2003; Ragaz *et al*, 2005; Nielsen *et al*, 2006). As such, we believe that interpretation of the benefit of PMRT should be limited to patients with fewer than 10 dissected lymph nodes. The ongoing randomised MRC/EORTC SUPREMO trial is designed to evaluate the results of chest wall irradiation in the management of the patients who underwent MRM with pN1 disease. It may provide us better information regarding the role of PMRT in this patient group (Kunkler *et al*, 2008).

According to results of this study, we suggest that the indications of PMRT in patients with pN1 disease are as follows: first, among patients with at least 10 dissected lymph nodes, PMRT should be recommended for patients with two and three positive nodes, who would be classified into an intermediate cLNR group. Second, an additional survival benefit of PMRT is less clear for patients with one positive lymph node and at least 10 dissected lymph nodes.

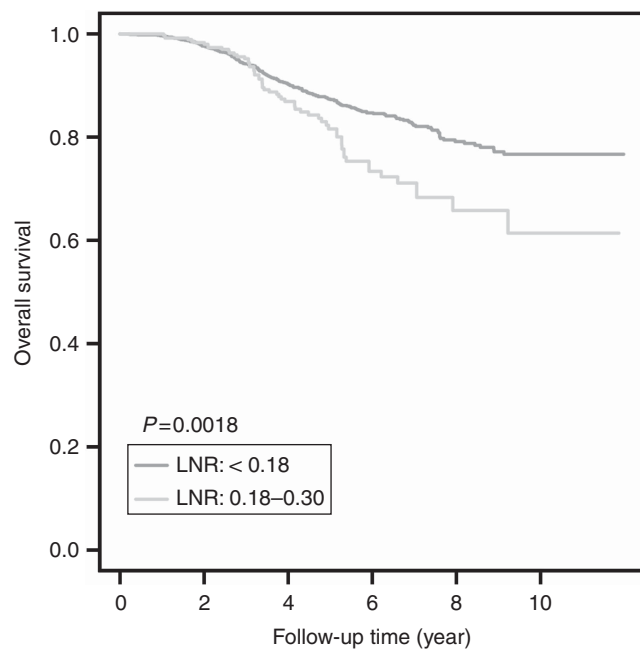
The inherent limitation of this retrospective study is that patients were assigned to PMRT without randomisation, and it is therefore possible that unrecognised biases might influence our results. Nevertheless, most of the clinico-pathologic characteristics such as T stage, histologic grade, ER/PR, and number of dissected node were well-balanced between the two groups of patients with or without PMRT (Table 1). However, we did find that patients with three positive nodes and younger age were more likely to receive PMRT and consequently the patients who were treated with PMRT might have been biased toward having a worse prognosis. This limitation of our study was in part balanced by several strengths. First, LNR research to date has been limited because there is no clear consensus about the cutoff points and many researchers have therefore used their own criteria (Voordeckers *et al*, 2004; Truong *et al*, 2005a; Kuru, 2006; Truong *et al*, 2008; Danko *et al*, 2010; Chagpar *et al*, 2011; Tausch *et al*, 2012). However, we objectively determined robust cutoff values using a nonparametric resampling method that does not require any predefined assumptions or distributional specifications. Second, this study not only evaluated the prognostic value of the cLNR, but also tested the clinical benefit of PMRT in patients with pN1 disease. To the best of our knowledge, there has been no previous report explicitly using cLNR as a predictive marker for PMRT, especially focusing on patients with pN1 disease. Third, the data analysed in this study were retrieved from the nation-wide KBCR. Therefore, we could minimise the selection bias often created by sampling from a single institution. Finally, all of the patients included in this study were treated with systemic adjuvant chemotherapy, thus avoiding biases related to systemic treatment that might affect evaluation of the benefit of PMRT.

In conclusion, our study showed that the cLNR enhanced risk stratification in patients with pN1 disease and that patients with intermediate cLNR had a worse prognosis than those with low cLNR. The cLNR also identified a subgroup of patients with pN1

**Table 2.** Multivariate analysis of overall survival of breast cancer patients with pN1 disease

Variable	Hazard ratio	95% CI	P-value
Age, ≥36	0.55	0.41–0.74	<0.0001
Tumour size, T2	1.31	1.02–1.67	0.0336
Oestrogen receptor, positive	0.68	0.53–0.89	0.0042
Progesterone receptor, positive	0.54	0.42–0.71	<0.0001
Histologic grade, II and III	1.65	1.03–2.63	0.0380
cLNR, intermediate	1.81	1.34–2.45	0.0001
cLNR, low: PMRT, yes	1.25	0.86–1.82	0.2415
cLNR, intermediate: PMRT, yes	0.39	0.17–0.89	0.0248

Abbreviations: CI = confidence interval; cLNR = categorised lymph node ratio; PMRT = post-mastectomy radiation therapy; pN1 = positive lymph nodes.



No. at risk (cum. no. of events)  
 Low 3059 (0) 2110 (57) 1252 (186) 633 (245) 238 (271) 117 (277)  
 Intermed 418 (0) 312 (6) 180 (35) 75 (54) 25 (59) 12 (60)

**Figure 2.** Kaplan–Meier OS estimates of breast cancer patients with pN1 disease according to the cLNR risk groups.

**Table 3.** Kaplan–Meier overall survival estimates at 10 years for patients with pN1 disease classified by the cLNR risk groups

Group	No. of patients	PMRT: no		PMRT: yes			
		10-Year OS (%)	95% CI	No. of Patients	10-Year OS (%)	95% CI	No. of Patients
All patients	3477	74.35	70.93–77.93	3034	79.48	73.11–86.40	443
Low cLNR	3059	76.47	73.01–80.10	2710	79.10	71.81–87.14	349
Intermediate cLNR	418	56.13	43.40–72.58	324	81.61	69.78–95.45	94

Abbreviations: CI = confidence interval; cLNR = categorised lymph node ratio; OS = overall survival; PMRT = post-mastectomy radiation therapy; pN1 = positive lymph nodes.

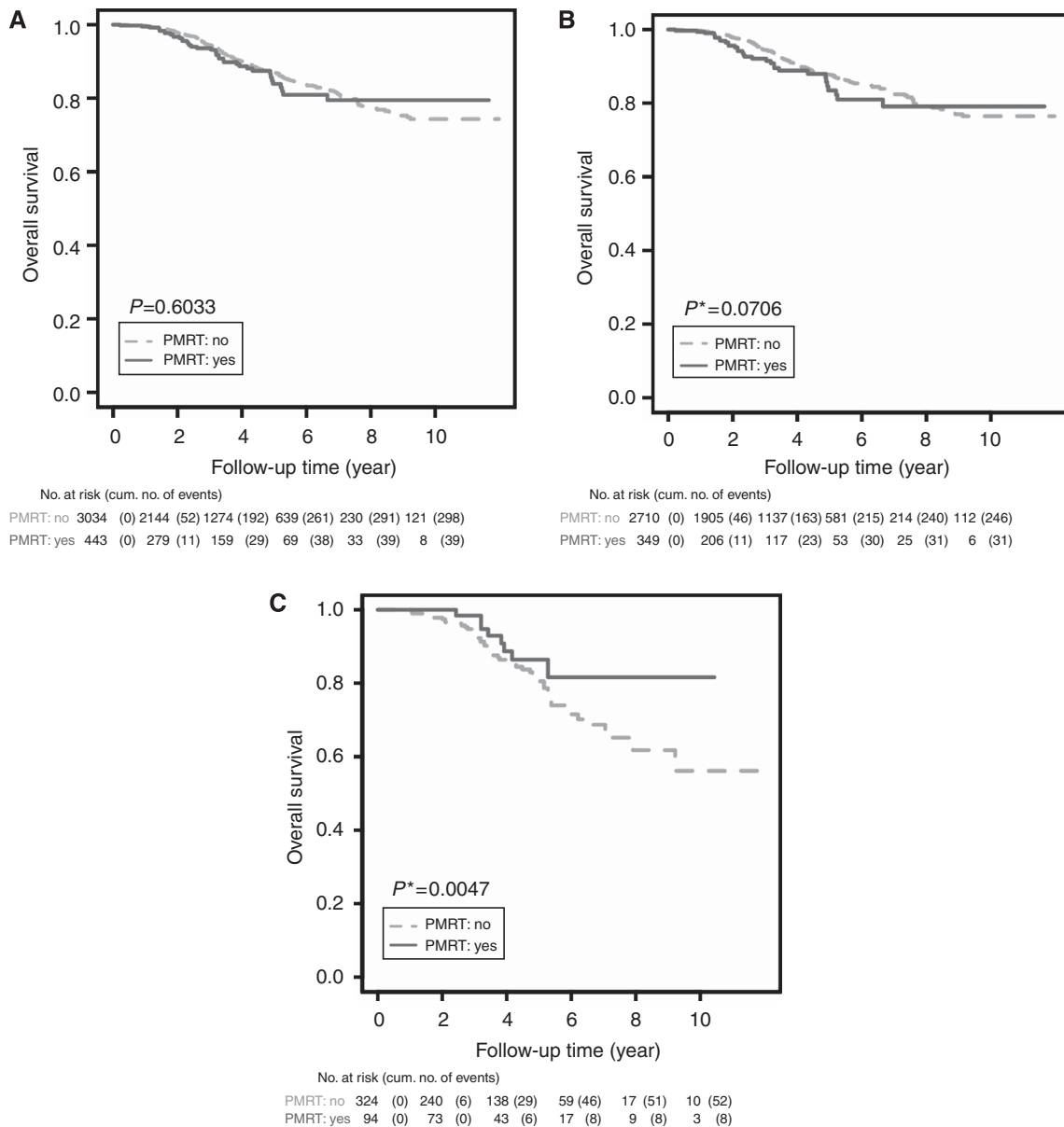


Figure 3. Kaplan–Meier OS estimates of breast cancer patients with pN1 disease according to PMRT: (A) all patients with pN1 disease; (B) patients with the low cLNR; and (C) patients with the intermediate cLNR. \*Indicates P-value adjusted for multiple comparisons using Tukey’s procedure.

disease who would respond better to PMRT. Provided appropriate axillary dissection is satisfied as a prerequisite, PMRT should be recommended for patients with two or three positive nodes who belong to the intermediate cLNR group.

**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

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