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Lymph node density in oral cavity cancer: results of the International Consortium for Outcomes Research

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Background: Lymph node density (LND) has previously been reported to reliably predict recurrence risk and survival in oral cavity squamous cell carcinoma (OSCC). This multicenter international study was designed to validate the concept of LND in OSCC.

Methods: The study included 4254 patients diagnosed as having OSCC. The median follow-up was 41 months. Five-year overall survival (OS), disease-specific survival (DSS), disease-free survival (DFS), locoregional control and distant metastasis rates were calculated using the Kaplan–Meier method. Lymph node density (number of positive lymph nodes/total number of excised lymph nodes) was subjected to multivariate analysis.

Results: The OS was 49% for patients with LND $\leqslant$ 0.07 compared with 35% for patients with LND $>$ 0.07 ($P<0.001$). Similarly, the DSS was 60% for patients with LND $\leqslant$ 0.07 compared with 41% for those with LND $>$ 0.07 ($P<0.001$). Lymph node density reliably stratified patients according to their risk of failure within the individual *N* subgroups ($P=0.03$). A modified TNM staging system based on LND ratio was consistently superior to the traditional system in estimating survival measures.

Conclusion: This multi-institutional study validates the reliability and applicability of LND as a predictor of outcomes in OSCC. Lymph node density can potentially assist in identifying patients with poor outcomes and therefore for whom more aggressive adjuvant treatment is needed.

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With an estimated 263 900 new cases and 128 000 deaths per year, squamous cell carcinoma of the oral cavity (OSCC) is among the most common malignant tumours and a significant source of morbidity (Shah and Gil, 2009). Although the incidence of OSCC has decreased in most developed countries over the past decades, it remains a common cancer for both male and female individuals in south–central Asia and in central and Eastern Europe (Yako-Suketomo and Marugame, 2008). The AJCC/UICC staging system for OSCC is based on primary tumour classification (T), on quantification of nodal metastases (N) according to size, number and distribution, and on the presence of distant metastases (M) (Patel and Shah, 2005). In this system, the presence of lymph node metastases has been associated with poor outcome. However, nodal stage by itself was not shown to reliably predict prognosis (Rudoltz *et al*, 1995; Parsons *et al*, 1997; Gavilan *et al*, 2000; Shingaki *et al*, 2003; Bernier *et al*, 2005). It is clear that identification of metastatic positive lymph nodes is based on the quality of neck dissection as well as on the sampling procedure (the level of histopathologic scrutiny). As such, the probability of identifying metastasis in lymph nodes relies on the technical performance of both surgeons and pathologists (Bhattacharyya, 1998; Agrama *et al*, 2003). As limited lymph node dissection may result in pathological understaging, lymph node density (LND) has emerged as an independent prognostic factor for carcinoma of the bladder as well as for OSCC (Stein *et al*, 2003; Gil *et al*, 2009). Lymph node density (Gil *et al*, 2009; Kim *et al*, 2011; Lee *et al*, 2012; Passoni *et al*, 2013), or lymph node ratio (LNR) (Attaallah *et al*, 2013; Sayed *et al*, 2013; Wu *et al*, 2013), equals the ratio of positive lymph nodes to the total number of excised lymph nodes. This ratio attempts to compensate for the potential bias of the sampling method by utilising two information components: the disease regional spread (number of positive nodes) and the surgical treatment (total number of nodes removed during surgery). In this study, which was undertaken by the *International Consortium for Outcome Research (ICOR) in Head and Neck Cancer*, we aimed to validate the utility of LND as a prognostic tool in patients with OSCC. We also compared the staging system based on LND with the conventional classification used by the American Joint Committee on Cancer (AJCC) (Edge SB).

MATERIALS AND METHODS

Patients and methods. Our study cohort included anonymised data on 4254 patients from 11 cancer centers worldwide. The study was approved by the local institutional review board (IRB) committees of the participating centres. Data were collected retrospectively on all patients by using uniform database templates to ensure consistent data collection. Criteria for patient inclusion were as follows: histopathological diagnosis of OSCC, surgical treatment with a neck dissection involving levels I–III, I–IV or I–V as described by the American Head and Neck Society, available pathological report and follow-up data and >6 months follow-up or earlier death or recurrence (Robbins *et al*, 2008). Table 1 presents the demographic and clinical data of these patients. Their follow-up ranged from 2 to 322 months (median 41 months); follow-up period for N+ patients was 4–322 (median 46 months).

Histopathological analysis. A total of 118 261 lymph nodes were evaluated, of which 6353 (5.3%) were positive. The tissues were evaluated at each centre by a certified head and neck pathologist. Specimen dissection, tissue sampling, fixing, cutting and microscopic examination of the primary tumour were carried out in a similar way according to the guidelines for the histopathological assessment (group, 2007). There were 1280 (30%) patients with 1391 lymph nodes, which had documented evidence of extracapsular spread (ECS).

Table 1. Demographic and clinical data of patients

Variable	No. of patients	%
Mean age, year		
52.63 ± 14. 6 (14–99)	4254	100
Gender		
Male	2815	60.1
Female	1439	39.9
Treatment		
Surgery	1297	22
Surgery + RT	2245	58
Surgery + CRT	553	15
Surgery + RT + Erbitux	159	5
Type of neck dissection		
Elective	2434	52
Therapeutic	1820	48
Extent of neck dissection		
I–III/IV	2746	60.7
I–V	525	13.2
Radical ND	327	9.9
Bilateral ND	656	16
T classification		
1	613	13
2	1374	30
3	623	15
4	1644	42
N classification		
N0	2268	43.3
N1	652	15.3
N2a	88	2
N2b	988	23.2
N2c	246	6
N3	12	0.2
Overall TNM stage		
I	464	9
II	799	13
III	668	16
IV	2323	62
Follow-up (months)		
Mean	49.6 ± 44	100
Median	41	
Range	2–322	

Statistical analysis. Five-year overall survival (OS), disease-specific survival (DSS), disease-free survival (DFS), locoregional control and distant metastasis rates were calculated using the Kaplan–Meier method, and the difference in survival rate was assessed by the log-rank test (Kaplan and Meier, 1958; Peto *et al*, 1977). OS was measured from the date of surgery to the date of death or last follow-up. The DSS was calculated from the time of diagnosis to death resulting from OSCC. The univariate association between individual clinical features and survival was determined with the log-rank test (Mantel, 1966). A multivariate analysis using the Cox proportional hazards regression model was performed to compare the factors with prognostic potential as indicated by univariate analyses (Cox, 1972; Gil *et al*, 2007). The limit of

significance for all analyses was defined as $P<0.05$; two-sided statistical tests were used in all calculations. All data were analysed using StatView 5.0 software package (SAS Institute Inc, Cary, NC, USA) and confirmed by an independent statistician (ES and CR) using the IBM SPSS Statistics package (IBM Corporation, Armonk, NY, USA). Variables used to stratify lymph node metastases included the total number of lymph nodes dissected (<20 or $\geqslant 20$), pathological N (pN) classification (pN0, pN1, pN2a, pN2b, pN2c or pN3), ECS (absent or present) of tumour and the ratio of the number of positive-to-total number of lymph nodes (the LND or LNR). Nodal yield of $<$, $\geqslant 20$ was selected because its prognostic implication was previously described (Ebrahimi *et al*, 2011). Previous studies showed that once 18–20 nodes are surgically removed and pathologically analysed, the neck is likely to be correctly staged and occult microscopic disease adequately treated (Ebrahimi *et al*, 2011). The seventh edition of the tumour-node-metastasis staging system for oral cavity SCC was used for TNM staging (Edge *et al*, 2010). Time-dependent receiver operating characteristic (ROC) curves, area under the curve (AUC) of the ROC curve, sensitivity, specificity, as well as likelihood ratios were calculated to determine which LND best defines different risk groups of OSCC subjects (Heagerty *et al*, 2000; Etzioni *et al*, 2003; Xiao *et al*, 2011; Espin *et al*, 2012). A cutoff of 0.07 was selected by time-dependent ROC curve analysis for disease-specific death (AUC (c-index) = 0.79, 95% CI 0.53–0.94, sensitivity and specificity for 5 years DSS 91% and 84%, respectively). To test the stability of the cutoff point, we also performed 1000 times bootstrapping (Chen and George, 1985; Efron, 1994). Each time, we generated a risk-score formula on 650 randomly selected participants from the data set. The average and standard deviation of the 1000 threshold values were 0.066 ± 0.012. On the basis of these cutoff points, the all-combined 1986 patients were classified into high-risk or low-risk groups. The mean with an empirical standard error using 1000 logHRs was 1.42 ± 0.34, and the empiric 95% CI was between 1.21 and 1.65. Correlation analysis was performed using the Pearson's coefficient of regression. We compared a modified TNM staging system based on LND with the traditional TNM staging system (based on standard pN classification) (Supplementary Table 1).

Investigation for the presence of between-centre heterogeneity was performed using a two-stage random effects model (Stukel *et al*, 2001). At the first stage of analysis, the difference in prognosis between LND >0.07 and LND <0.07 groups was determined for each centre. In the second stage, the centre-specific effect estimates were introduced into a random effects model as described by (DerSimonian and Laird, 1986), which allows for unexplained sources of heterogeneity between centres. Heterogeneity across centres was assessed using Cochran's Q test ($P<0.1$ was considered statistically significant, given the test has limited power) and quantified using the I^2 measure (the percentage of total variation across centres attributable to heterogeneity rather than chance) (Higgins and Thompson, 2002).

The reporting of this study conforms to Strengthening the Reporting of Observational Studies in Epidemiology guidelines for reporting of observational studies (flowchart not presented) (von Elm *et al*, 2007).

RESULTS

A total of 4254 OSCC patients treated at 11 tertiary cancer centres were eligible for inclusion into the study (Table 1). Elective neck dissection (neck dissection for clinically stage N0) was performed on 2435 patients (57%), and therapeutic neck dissection (neck dissection for clinically stage N+) was performed on 1819 patients (43%). Supplementary Figure 1 summarises the management and outcome of the study patients. Kaplan–Meier estimates of 5-year OS, DFS and DSS for all study patients were 56%, 55% and 64%, respectively.

Histopathological examination of the neck dissection specimens revealed 1986 (46.7%) patients with positive lymph nodes. There were 2268 patients with pN0 disease (53.3%), 652 patients with pN1 disease (15.3%), 1322 patients with pN2 disease (31.2%) and 12 patients with pN3 disease (0.2%). The overall rate of occult neck metastases was 21%. Supplementary Table 2 shows the rate of neck metastases for each T classification. The 5-year OS was 66% for patients with pathologically negative neck lymph nodes and 43% for those with positive nodes ($P<0.0001$). The 5-year DSS was 74% for patients with pathologically negative neck nodes and 52% for those with positive nodes ($P<0.0001$). Supplementary Figure 2 shows the Kaplan–Meier curves of OS and DSS according to the N status. ECS was present in 1280 patients and it also had a significant effect on OS and DSS on univariate analysis ($P<0.001$).

We further analysed the group of patients with N positive disease ($n=1986$). In each neck dissection specimen, there were 2–104 (mean ± s.d., 39 ± 23) lymph nodes and 1–34 (3.1 ± 4.6) of them were positive. The median LND was 0.064 (range, 0.009–1). Univariate analysis revealed that margin status (negative, <5 mm or positive), pathological T stage, pN stage, ECS, overall TNM stage and treatment group (surgery, surgery and radiation therapy or surgery and chemoradiation) were significant predictors of 5-year OS, DSS and DFS (Ambrosch *et al*, 1995; Fukano *et al*, 1997; Liao *et al*, 2012a,b). Most importantly, LND was also found to be a significant predictor of OS and DSS (Figure 1), as well as DFS, local control, locoregional control and distant metastasis rate (Figure 2). For patients with an LND $\leqslant 0.07$, the 5-year OS was 49% compared with 35% in patients with an LND >0.07 ($P<0.001$). Similarly, the 5-year DSS was 60% for patients with an LND $\leqslant 0.07$ compared with 41% in patients with an LND >0.07 ($P<0.001$). When the threshold value of 0.066 based on the bootstrapping results was applied to the analysis, comparable log-rank *P*-value and HR were observed (Supplementary Figure 3).

To further evaluate the impact of clinicopathological variables in a multivariate model, we first analysed the data without LND. The variables compared were gender, age, depth of invasion, margin status, T stage, pN stage, overall pathological stage, ECS, total number of lymph nodes excised and treatment group. Gender ($P<0.0001$), age ($P=0.0006$), margins status ($P<0.0001$), pathological T stage ($P<0.0001$), pN classification ($P<0.0001$) and treatment group ($P=0.0001$) were significant predictors of OS. The significant DSS predictors were gender ($P<0.0001$), age ($P=0.04$), margin status ($P<0.0001$), pathological T stage ($P<0.0001$), pN classification ($P=0.001$) and treatment group ($P=0.006$). Next, we added the LND variable to the multivariate model with a separation threshold of 0.07 (Table 2). The results showed that an LND >0.07 was independently associated with a poorer OS and DSS ($P=0.019$ and $P=0.004$, respectively). Other predictors that remained significant for both OS and DSS were margin status, T stage, pN classification and treatment group. An LND $\leqslant 0.07$ was associated with better local control, locoregional control and DFS in a multivariate analysis ($P<0.01$, Supplementary Table 3). Multivariate analysis showed that only treatment group, overall TNM stage and LND were significant predictors of distant metastasis ($P<0.05$, Supplementary Table 3). Most importantly, the proportional hazard fits ($-$Loglikelihood value) in all of the analyses (including OS, DSS, RFS, distant metastasis-free survival, local and locoregional control rates) were better for the model that included LND than the one without it (Supplementary Table 1). Similarly, when neck nodal status classified according to N1, N2 and N3 was added to the model as an independent variable instead of being subclassified according to pN1, pN2a, pN2b, pN2c and pN3, LND remained a significant predictor of outcome. Likewise, when patients with pN2 and pN3

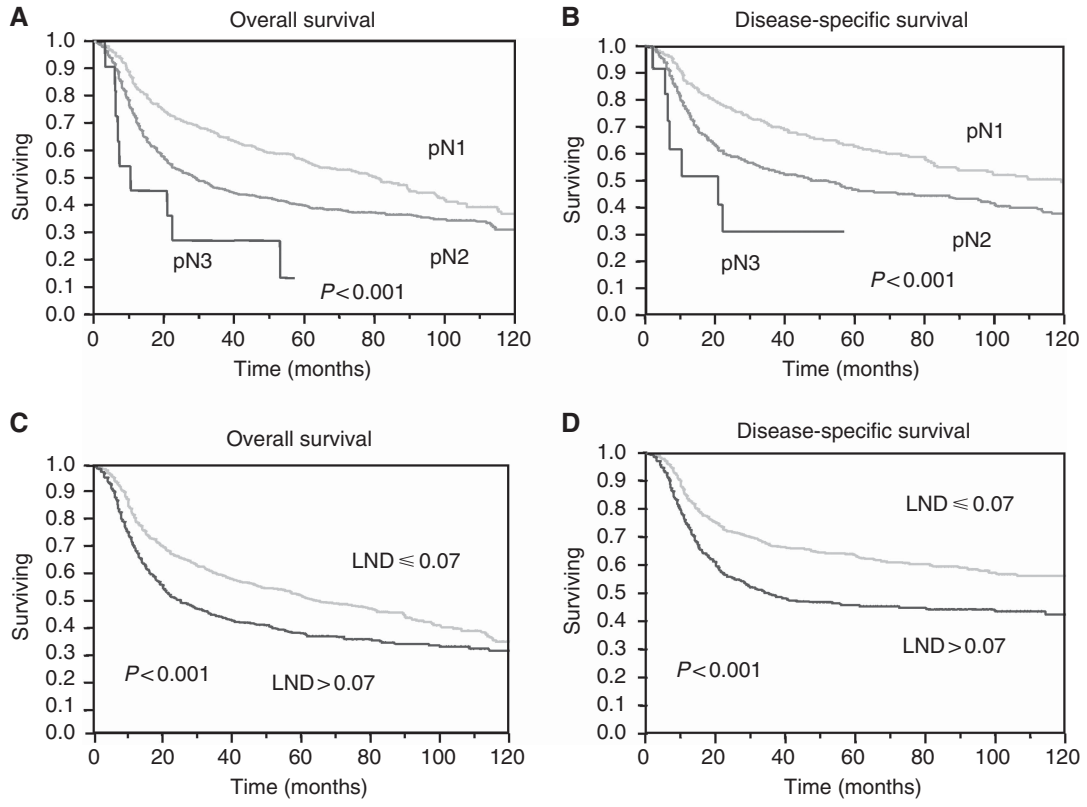

Figure 1. Five-year overall survival and disease-specific survival rates calculated using the Kaplan–Meier method in patients with positive neck nodes. (**A** and **B**) Using TNM nodal classification ($P<0.001$); (**C** and **D**) using LND with a cutoff point of 0.07 ($P<0.001$). An analysis using LND separation point of 0.066 (based on the bootstrapping analysis) yielded similar results.

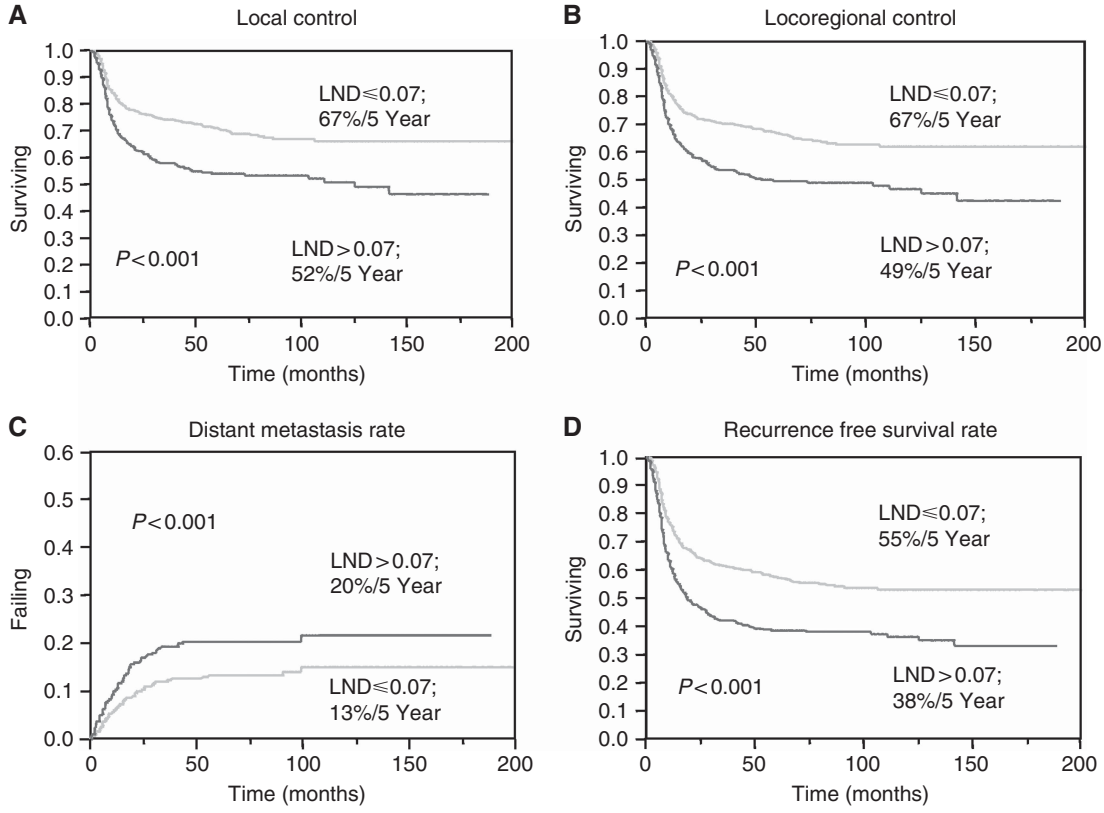

Figure 2. Five-year (**A**) local control, (**B**) locoregional control and (**C**) distant metastasis failure and (**D**) disease-free survival rates calculated by the Kaplan–Meier method in patients with positive neck nodes. The LND model had a cutoff point of 0.07 ($P<0.001$). Similar results were retrieved using LND cutoff point of 0.066.

Table 2. Multivariate analysis of prognostic factors for overall and disease-specific survival ($n = 1986$)

	Overall survival			Disease-specific survival		
Variable	***P***	**Adjusted HR**	**95% CI**	***P***	**Adjusted HR**	**95% CI**
Gender						
Male	<0.0001	1		0.0009	1	
Female		0.33	0.24–0.52		0.49	0.2–0.77
Age						
<65	0.0009	1		0.03	1	
⩾65		2.25	1.25–3.56		1.8	1.2–3.1
Depth of invasion						
<4	0.52	NA	NA	0.28	NA	NA
4–8						
⩾8						
Margins						
Negative	<0.0001	1		<0.0001	1	
Close		2.75	1.63–14.5		1.46	1.2–3.6
Positive		3.14	1.9–4.1		1.89	1.4–3.1
Pathologic T classification						
T1	<0.0001	1		<0.0001	1	
T2		2.05	1.3–3.6		1.9	1.1–3.9
T3		2.26	1.5–4.1		2.5	1.4–5.7
T4		3.33	2.3–6.1		3.1	1.7–4.7
Pathologic N classification						
N1	0.004	1		0.004	1	
N2a		1.3	1.03–1.9		1.6	1.2–3
N2b		2.2	1.5–2.8		1.9	1.3–4.1
N2c		3.1	1. 8–4.9		2.4	1.6–7.1
N3		3.9	1.2–7.1		3.2	1.6–5.2
Extracapsular spread						
No	0.2	NA	NA	0.25	NA	NA
Yes						
Total number of lymph nodes						
<20	0.83	NA	NA	0.56	NA	NA
⩾20						
Treatment group						
Surgery	0.0005	1		0.01	1	
Surgery + RT		0.59	0.44–0.73		0.7	0.5–0.9
Surgery + CRT		0.71	0.6–0.8		0.77	0.5–0.9
Lymph node density						
⩽0.07	0.019	1		0.004	1	
>0.07		1.7	1.2–1.9		1.62	1.4–1.9
Overall TNM stage						
I	0.69	NA	NA	0.8	NA	NA
II						
III						
IV						
LND-based TNM stage						
I	0.03	1		0.03	1	
II		1.5	1.2–2.2		2	1.6–4.2
III		2.4	1.3–5.4		4.1	3.1–8.1
IV		2.9	1.5–6.1		4.8	3.6–8.2

Abbreviations: 95% CI = 95% confidence interval, CRT = chemoradiation, HR = hazard ratio, RT = radiation therapy.

were combined, LND remained a significant independent predictor of outcome ($P=0.01$), whereas the pN classification did not. We also used the other separation point in this analysis, as suggested by the bootstrapping of the LND thresholds 0.066 (see Materials and methods); this analysis yielded similar results. Two-stage random effects analysis was used to investigate between-centre heterogeneity. We confirmed the absence of significant institutional heterogeneity for OS ($I^2=0\%$; $P=0.76$) and DSS ($I^2=0\%$; $P=0.4$). To rule out colinearity between LND and number of positive nodes, we repeated the multivariate analysis without total number of nodes and number of positive nodes. In this analysis, LND > 0.07 remained significant for OS ($P=0.008$, HR = 2.6) and DSS ($P=0.0006$, HR = 2.4). Furthermore, after removing patients with <20 lymph nodes from our analysis, LND > 0.07 remained a significant predictor for DSS, $P=0.0073$.

In order to further assess the ability of LND to predict treatment response in a more homogeneous population, and to account for the potential impact of adjuvant treatment, we performed a subgroup multivariate analysis on each of the following treatment groups: patients undergoing surgery alone ($n=183$, due to patients' refusal to radiotherapy or prior irradiation), patients undergoing postoperative radiotherapy ($n=1247$) and patients who received adjuvant chemoradiation ($n=556$). LND emerged as an independent predictor of both OS and DSS on multivariate analysis in patients receiving postoperative radiotherapy without chemotherapy ($P=0.02$ and $P=0.01$, respectively) and surgery alone ($P=0.005$ and $P=0.007$, respectively). In patients receiving postoperative chemoradiation, LND successfully predicted DSS ($P=0.03$) but not OS ($P=0.13$, Figure 3).

Similar survival analyses performed separately on patients undergoing elective neck dissections (cN−) and therapeutic neck dissections (cN+) revealed the same results (Supplementary Figure 1). Comparison of the neck dissection and LND variables between these groups is shown in Supplementary Table 4. Overall, LND was a significant predictor of OS and DSS on a multivariate analysis in both of these groups ($P<0.01$).

As previous studies had demonstrated the ability of LND to distinguish between individual pN subgroups, we further investigated whether LND could identify high- and low-risk patients within each pN1 or pN2 classification groups. Figure 4 demonstrates that LND at a cutoff of 0.07 could distinguish between high-risk- and low-risk patients within each pN1 and pN2 patients. The pN3 subgroup could not be similarly analysed, as it consisted of only 12 patients.

Finally, we compared a modified TNM staging system based on LND, to the traditional TNM staging system (based on standard pN classification, see Supplementary Table 1). Both the traditional and new staging systems were introduced into the multivariate model. Notably, the new TNM staging system that was based on the LND ratio was consistently superior to the traditional system in all of the selected survival measures (Table 2 and Supplementary Table 3 for the multivariate analysis). Supplementary Figure 4 shows the Kaplan–Meier curves of OS and DSS according to the disease stage in the TNM staging system based on LND and the traditional TNM staging.

DISCUSSION

The mainstay of treatment of patients with OSCC is surgical ablation of the primary tumour. Neck dissection is performed as an elective procedure or when the clinical or radiological examination shows evidence of lymph node metastases (Gil *et al*, 2009). Tumour stage, margin status, depth of invasion and the presence of neck metastases are significant prognostic factors in this

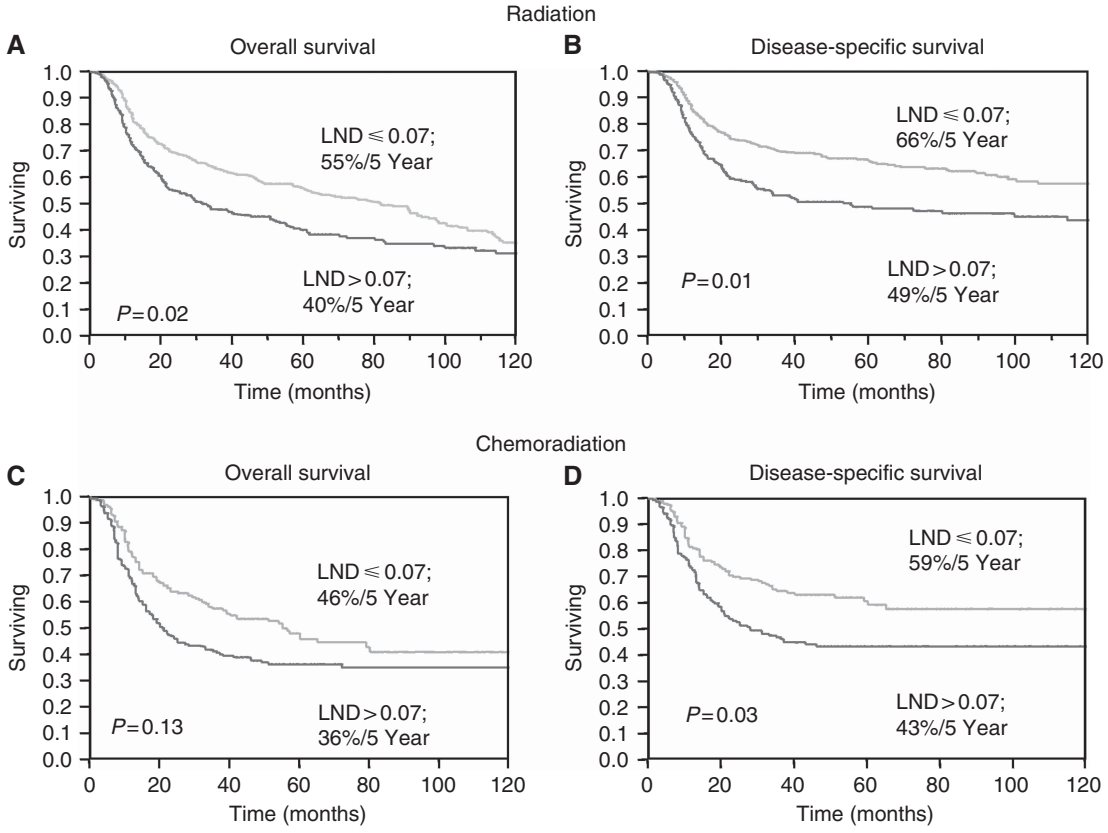

Figure 3. (**A–D**) Kaplan–Meier curves of overall and disease-specific survival according to the treatment modality. The difference in survival rate was assessed by the log-rank test.

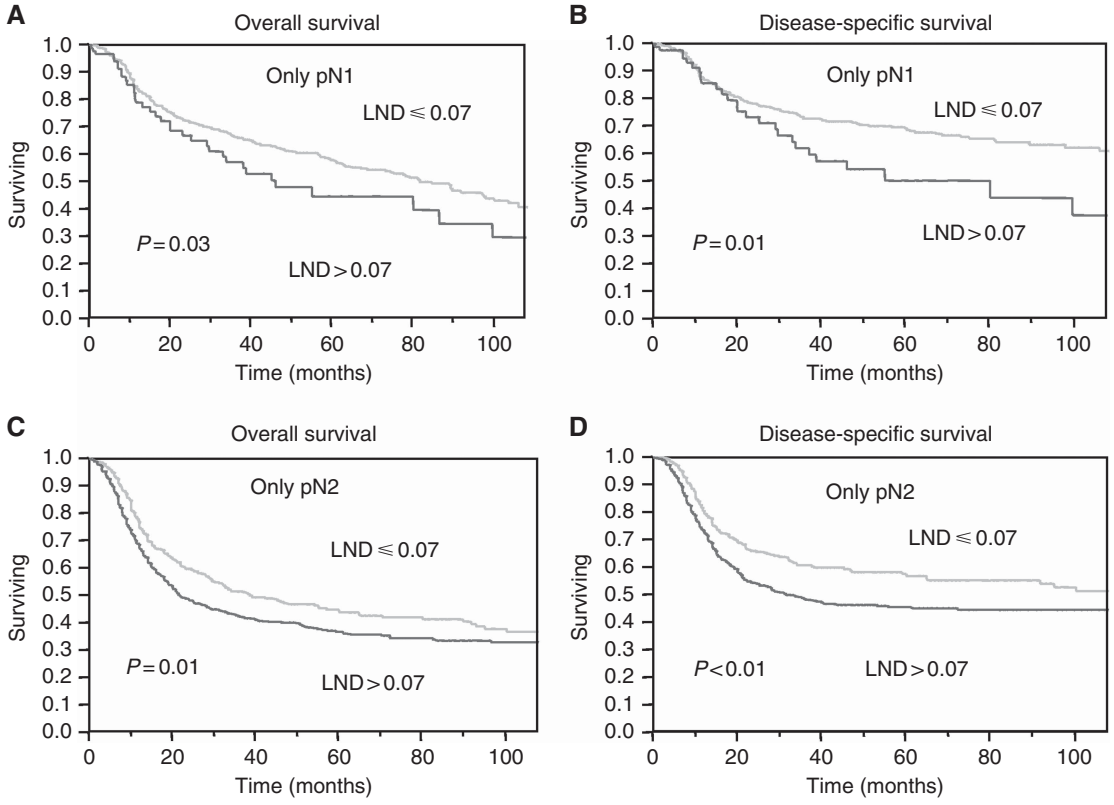

Figure 4. The ability of LND to distinguish between low-risk and high-risk patients within individual pN subgroups. Kaplan–Meier curves of overall and disease-specific survival in a subgroup of patients with pN1 nodal classification (**A** and **C**) and pN2 nodal classification (**B** and **D**). LND reliably distinguished between patients in each subgroup with a low risk and those with a high risk for treatment failure ($P<0.05$).

population (Mamelle *et al*, 1994; Pentenero *et al*, 2005). The single most important factor that determines the nodal staging is the nodal sampling procedure. The value of the number of positive nodes as a predictor of outcome for head and neck cancer patients was first suggested by Mamelle *et al* (1994). Fifteen years later, it was shown for OSCC patients that LND is superior to conventional nodal staging for predicting outcome (Roder *et al*, 1994; Stein *et al*, 2003; Kassouf *et al*, 2006; Herr, 2007; Liao *et al*, 2012a,b; Ooki *et al*, 2007; Gil *et al*, 2009; Kim and Cha, 2012; Kim *et al*, 2011; Amar *et al*, 2012).

LND is a mathematical derivation of the ratio between positive lymph nodes and the total number of excised lymph nodes. The cutoff ratio is applicable, for example, in a patient with one positive lymph node among 20 examined, which results in a LND ratio of 0.05. The ratio of LND weighs three factors that can potentially influence nodal staging: (1) tumour factors (the true number of positive lymph nodes), (2) surgical factors (the actual number of nodes removed during neck dissection) and (3) sampling factors (the completeness of the pathological analysis). We postulated that patients with a higher LND are expected to fare worse than patients with a lower ratio, even when they have a similar N classification. Previous studies investigated the utility of LND in small cohorts of patients, which were performed by single institutes mostly in the United States and Canada. In the current study, we aimed to investigate the clinical significance of LND in a large collaborative study of 11 cancer centres across the globe. This study provides the first large-scale analysis of LND in patients with OSCC. In the current study, we evaluated the predictive value of the LND compared with the conventional staging system in over 1986 patients from 11 medical centres across the globe. We aimed to determine the ability of the LND to predict OS, DSS and locoregional recurrence-free survival in patients undergoing neck dissection. The results of our multivariate analyses showed that LND is superior to the conventional N staging system in predicting OS, DSS and locoregional control. Interestingly, the LND was also a predictor of distance metastases. Most importantly, we were able to show that LND was sensitive enough to identify a subpopulation of patients who are at high risk for tumour recurrence within each pN classification. Our multivariate analysis showed that LND was a better predictor of outcome than conventional N1 and N2 classification in the following groups of patients: those undergoing elective neck dissections, those undergoing therapeutic neck dissections and those receiving adjuvant radiotherapy or chemoradiation. On the foundation of these results, we suggest a modification of the TNM staging classification that is based on LND instead of pN stage for patients with nodal metastases.

Recent studies have demonstrated slight improvement in 5-year survival rates after adjuvant-concurrent chemoradiation therapy compared with radiotherapy alone for advanced head and neck SCC (Bernier *et al*, 2004). However, because of the significant morbidity associated with intensification of adjuvant treatment – that is adding chemotherapy to radiotherapy – there is still considerable controversy over the pathological characteristics of the tumour that predict the need for more aggressive adjuvant treatment (Bernier *et al*, 2005). We hypothesise that LND can potentially assist in indentifying patients with poor outcomes and therefore for whom more aggressive adjuvant treatment is needed. Further studies are required to determine whether patients with a high LND will benefit from concurrent chemoradiation therapy. Although our data provide a strong argument in favour of nodal ratios to stratify risk of recurrence, other factors related to nodal status, such as the size and volume of the occupied lymph node, nodal site, presence of occult micrometastases discovered by molecular methods and extent of ECS may also be significant predictors of outcome. We recognise that their interplay needs elaboration.

We also realise that one of the limitations of this study is the potential of inconsistency in the surgical technique and processing of the pathological specimens that may introduce potential errors. The mean number of lymph nodes removed in our cohort was 33, with a standard deviation of 23 and a range of 2–104. However, fewer than 20 lymph nodes were found in only 771 (21%) patients, and almost all of them had selective neck dissection. The previously reported mean lymph node yield in a unilateral radical neck dissection ranged from 1 to 97 nodes (Bhattacharyya, 1998; Agrama *et al*, 2001; Jose *et al*, 2003). The variations in the number of lymph nodes retrieved from our specimens are, therefore, similar to other studies. Owing to the retrospective nature of the study data regarding ethnicity, primary tumour site, smoking status and alcohol exposure were not available. Yet two-stage random effects analysis revealed minimal heterogeneity between-centres, and even after we excluded cases with <20 lymph nodes from our analysis, LND remained the only significant independent predictor of outcome. Conversely, the significance of LND as a predictor of outcomes in our heterogenous cohort across multiple countries assure the broad applicability of research finding worldwide and might facilitate the uptake of LND as a prognosticator into standard practice in diverse patient populations (Trimble *et al*, 2009).

In conclusion, we have validated the importance of LND in a multi-institutional international study that represents the largest and most detailed cohort of OSCC to date. The results and detailed statistical analyses show that LND is a useful adjunct to the conventional TNM staging system and that LND may be used to identify patients at high risk of treatment failure and therefore for whom more aggressive adjuvant treatment may be needed.

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Novelty and Impact Statements: Squamous cell carcinoma of the oral cavity (OSCC) is the common malignant tumors of the head and neck. Recent data indicate that the conventional staging system does not necessarily predict prognosis in OSCC, especially after adjuvant radiotherapy. In this first multicenter international study, we show that lymph node density is superior to the conventional nodal staging system in predicting outcome.

These new data provide benefits that can advance management of head and neck carcinomas worldwide.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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