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Review

Lymph node ratio as prognostic variable in oral squamous cell carcinomas: Systematic review and meta-analysis

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ABSTRACT

Lymph node ratio (LNR) has been shown to be an independent prognostic factor for oral squamous cell carcinoma (OSCC) in various centre-based studies recently. A range of cut-off values have been suggested. A meta-analysis was performed to evaluate the prognostic effects of LNR and to investigate the cut-off value.

Electronic search on Pubmed, Embase and Cochrane library and manual search were performed for studies up to January 2018. The outcomes were overall survival (OS), disease specific survival (DSS), disease free survival (DFS), local recurrence free survival (LF), locoregional disease free survival (LRF), and distant metastasis disease free survival (DM).

19 studies between 2009 and 2017 were included. The total number of patients was 14,254 (range 19–3958). Data was grouped into Group A (with pathological nodal disease, pN+) and Group B (with and without pathological nodal disease, pN+ and pN−). In the meta-analysis, the high LNR was significantly related to short OS (A = HR 1.902; 95%CI: 1.453–2.488, B = HR 2.76; 95%CI: 2.13–3.59), DSS (A = HR 1.728; 95%CI: 1.159–2.579; B = HR 2.83; 95%CI: 1.8–4.44) and DFS (A = HR 2.27; 95%CI: 1.74–2.96; B = HR 2.01; 95%CI: 1.44–2.82) in both groups; and shorter LRF in Group B (HR 5.013; 95%CI: 3.584–7.011). In the analysis, all cut-off values were shown to be significant and there was no strong evidence to consider a possibility of a second significant value.

Based on our results, LNR is an independent prognostic factor in OSCC and may be considered in future oncologic staging systems.

Introduction

Head and neck cancer is the 6th most common cancer worldwide [1]. 30% of these are estimated to be oral cavity cancers with 95% of which is oral squamous cell carcinomas (OSCC) [1–3]. Management of OSCC remains surgical, with adjuvant radiotherapy or chemoradiation reserved for advanced stage tumours [4,5]. OSCC can be classified into different subsites: lips, buccal mucosa, retromolar trigone, alveolar ridge, tongue and floor of mouth [6]. About 30–50% of OSCC patients have metastatic lymph node (LN) during clinical examination and is associated with poor outcome [1,7–11]. The final pathological LN identification is dependent on the surgical neck dissection as well as the pathologists' specimen protocol [2,11], which have not been taken into account in the current American Joint Committee on Cancer (AJCC) Tumour Node Metastasis (TNM) classification. Some studies have shown that N stage was not significant in survival prediction [1,11], indicating the need for an improvement in the current staging system.

Lymph node ratio (LNR) or lymph node density (LND) is defined as the ratio of the positive LN to the total number of LN removed [11]. It was shown to be an independent prognostic factor in breast, bladder as well as colorectal cancers [12–15]. Its superiority to traditional TNM staging was attributed to its inclusion of information on the diseased nodes and extent of clearance control [2,16,17]. Centre-based studies on LNR in OSCC has been published recently and different cut-off values were proposed [2,18]. A multicentre study showed that LNR ≥ 0.07 was related to significant lower overall survival in OSCC patients [11]. Hence, it is time to assess the prognostic value of LNR in OSCC.

Methods

The analysis was performed adhering to Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [19].

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Search strategy

PubMed, EMBASE, and Cochrane library were searched with (node* or nodal*) and (density* or ratio*) and (oral cancer* or oral carcinoma*). References used in the articles were manually examined to find further relevant citations. All the searches and data collection were performed independently by two reviewers (A & B) in January 2018; Any disagreements in abstracting data were resolved by a third party (C).

Inclusion criteria and study selection

All published studies which evaluated the prognostic values of LNR in oral cancer patients were identified.

Studies with the following criteria were eligible for inclusion:

1. OSCC patients with positive LN were included
2. LND or LNR was calculated
3. The LNR and their associated clinical outcomes were measured
4. Full text articles were published regardless of language
5. No pre-operative radiation or chemotherapy was given
6. Adjusted HR is based on LNR or LND as a categorical variable

Studies that were abstracts, case reports, reviews or letters were excluded. To avoid duplication of data such as the overlapping of the same patient pool between studies, only the largest sample size or the most current paper was included. However, the publication was kept if a different clinical outcome was measured. When an adjusted hazard ratio (HR) was not reported, the study would be excluded. However, studies were included if their result was negative in their univariate analysis or only unadjusted HR value was reported, hence, LNR was not incorporated in the final multivariate analysis.

The outcomes were overall survival (OS), disease specific survival (DSS), disease free survival (DFS), locoregional disease free survival (LRF), local recurrence free survival (LF), and distant metastasis disease free survival (DM). OS is determined as the time lapsed from surgery to death or last follow-up [2,11,17,20–22]. DSS is determined as the time lapsed from time of diagnosis to death resulting from OSCC [11,17,21,23]. DFS is determined as the duration of survival without confirmed locoregional recurrence or distant metastases from the date of surgery [22].

Data abstraction and assessment of quality

Using a standardised data template, the following characteristics were identified and extracted: author, year of publication, age, patient pool and endpoints.

Adhering to the Reporting recommendations for tumour MARKer prognostic studies (REMARK) guidelines [24,25], quality assessment was done. The quality scale assessment was structured with the following framework:

1. Well-defined inclusion and exclusion criteria
2. Nature of study (Prospective or retrospective)
3. Patient characteristics described
4. Tumour characteristics described
5. LND or LNR measurements described
6. Study endpoints or outcomes described
7. Follow-up period described
8. Patients unavailable for statistical analysis identified (i.e. lost to follow-up)

Each study is given a score from 0 to 8, with 8 being the highest quality and 0 indicative of the lowest quality [13].

Data analysis

To assess the association of LNR with OSCC, the pooled HR with its 95% confidence interval (CI) was calculated. When more than two LNR categories were present, the lowest LNR was chosen for that study. Data was reorganised into two categories, and with fixed effect model, a new HR was calculated. If the 95% CI did not overlap one, a HR of > 1 would indicate a worse prognosis. If endpoints consisted more than two studies, a meta-analysis using the random effects model was conducted. Using the Cochran Q-static and I^2 tests, heterogeneity between studies was estimated. Substantial heterogeneity between studies was regarded when the Q-test has a p-value of < 0.05 or an I^2 value of 50%. A pooled adjusted HR from existing studies was compared with the final pooled HR values.

To identify any potential publication bias, the Funnel plots, the Egger linear regression test or the Begg rank correlation test were performed, and a p-value of < 0.05 was regarded as significant. When the publication bias was significant, a trim-and-fill method was used. Statistical significance was set as < 0.05 and all statistical tests were two-sided. Stata Version 13.1 (StataCorp, College Station, TX, 2013) was used in this study.

Results

Results of the literature search

The search strategy retrieved 2119 publications, comprising 635 hits in Pubmed, 1456 hits in Embase and 28 hits in Cochrane library. Following a systematic screening process (Fig. 1), 28 articles were reviewed for eligibility as full text and 19 studies were included in the final review. Nine studies were excluded and the reasons for exclusion were listed in Table 1. The quality scores ranged from 3 to 7. Most of the studies were moderately well designed (Table 2), with three out of the 19 studies having quality scores of < 5.

Study characteristics of included studies

The description of characteristics of the included studies were in Table 3. The total patient pooled from all the studies was 14,254 (range 19 [20] – 3958 [38]). The included articles were published between 2009 and 2017. Two studies were multicentre [11,38], eight studies originated from Asian countries [1,16,20,22,31,35,36,41], and the remaining nine studies were conducted in non-Asian countries. One study was prospective [16] and the rest were retrospective. The reported follow-up varied from 20.9 to 79 months.

There was heterogeneity of patients between studies (see Table 4). Eight studies [1,11,16,18,20,23,34,36] included patients with pathological lymph node metastases only (pN+, Group A). Another eight studies [16,17,21,37,39–42] analysed patients with and without nodal disease together (pN+ and pN−, Group B). Four studies [22,31,35,38] included patients with pN + and pN- and analysed them separately (Group C).

The mean total lymph node yield ranged from 22.8 to 41 and median ranged from 1 to 36.

The LNR cut-off points used in the studies ranged from 0.025 to 0.4. Most of them (16/19) used the range between 0.05 and 0.07 (Table 2). The methods of calculation of cut-off points differed among studies, including the median [17,31,39,40], ROC analysis [11,16,22,23], the minimum p value from the log-rank test [18], the maximally selected rank statistic method [34,37], a graphical derived value from a logarithmic change in data [21], or past published results [1,20,35,36,38,41].

While most studies included tumours from all sites of OSCC, five studies focused on tongue [18,40], floor of mouth [42] and buccal [20,39] carcinomas only. The endpoints included in the studies were OS (n = 14), DSS (n = 9), DFS (n = 5), LRF (n = 5), DM (n = 2), LF

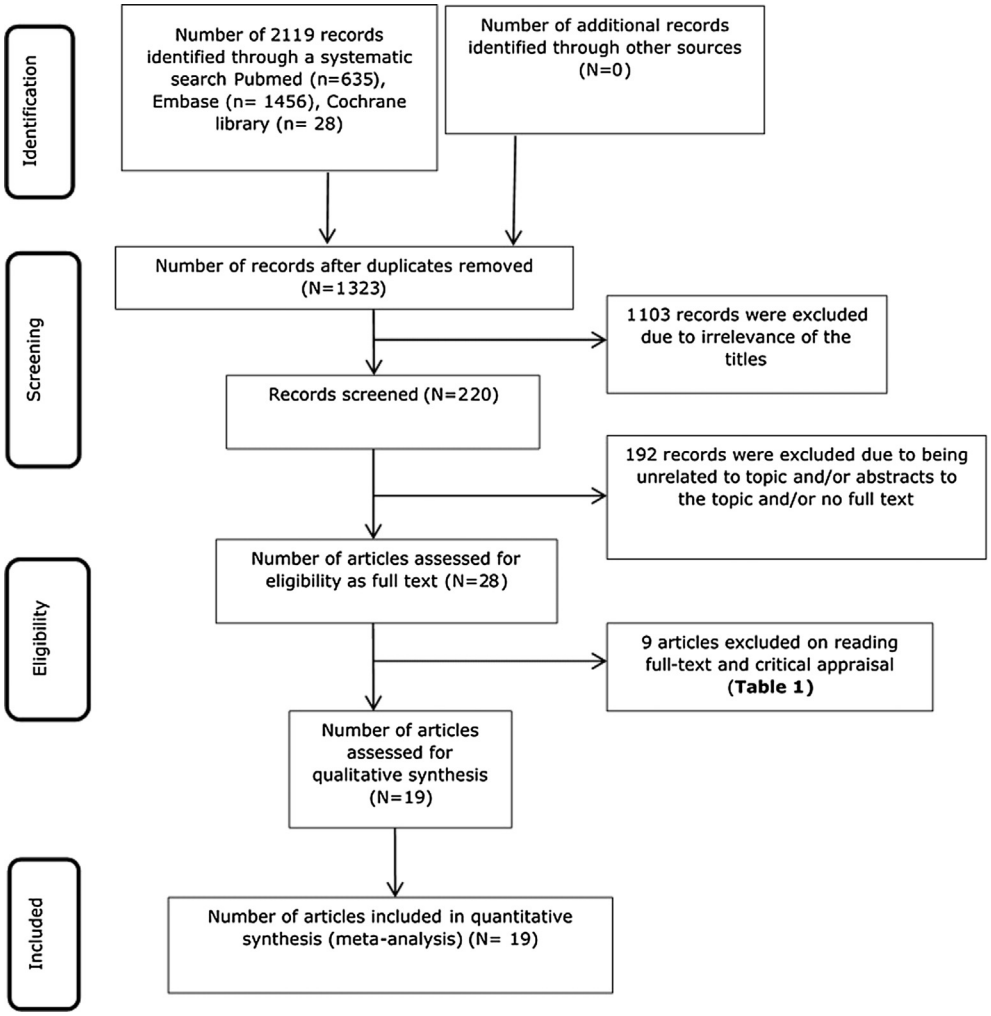

Fig. 1. PRISMA flow diagram [19].

Table 1
Excluded Studies.

Author	Year	Reason for exclusion
Ong [2]	2016	Insufficient data on HR associated with LNR groups
Yang [26]	2016	30% of the sample had undefined surgery
Yang [27]	2015	Review paper
Sayed [28]	2013	Data overlap with ICOR containing similar analysis [11]
Urban [29]	2013	Insufficient data on LNR groups associated with HR calculation
Kim KY [30]	2012	Data overlap with more recent paper by same author [31]
Liao [10]	2012	Data overlap with ICOR containing similar analysis [11]
Voos [32]	2010	Review paper
Shrime [33]	2009	Data includes preoperative radiation

(n = 1) and lung metastasis (n = 1).

Meta-analysis results

Incorporate studies from Group C into Group A and B

To calculate the pooled HR for Group A (pN+) as well as Group B (pN+ with pN−), Group C data was reorganised to approximate the largest possible standard error (SE) and its corresponding HR before incorporating into Groups A and B.

Group A: pN+

Eleven studies were included in the meta-analysis. Adel study [35] from Group C was excluded due to its overlapping patient pool with Patel et al.'s ICOR [11]. The new HRs for Shrime and Lee studies [34,38] used for the analysis in Group A were calculated using fixed effect models.

OS, DFS and DSS were the identified endpoints (Fig. 2). No significant heterogeneity existed among the studies for OS (I^2 = 16.5%, p = 0.296) and DFS (I^2 = 0%, p = 0.418), but moderate heterogeneity existed for DSS (I^2 = 58%, p = 0.036). The results showed that an increase in LNR may predict poor OS (pooled HR: 2.11; 95%CI: 1.68–2.66), DFS (pooled HR: 2.27; 95%CI: 1.74–2.96) and DSS (pooled HR: 2.61; 95%CI: 1.68–4.05).

Meta-regression analysis was performed for OS (p = 0.55), DFS (p = 0.42) and DSS (p = 0.664). It showed that LNR cut-off was not the source of heterogeneity and had no positive association with outcomes. Due to the retrospective and observational nature of studies, further analysis was unable to determine the source of heterogeneity in DSS.

To assess potential publication bias in the included studies, Funnel plots and Egger's test were conducted. Funnel plots for DFS display no obvious asymmetry, and the *p* value of Egger's test was 0.354. Studies of OS (*p* = 0.014) and DSS (*p* = 0.014) had statistically significant publication bias. Three potential missing studies were identified in both. The recalculated pooled HR for OS was 1.902 (95%CI: 1.453–2.488, p = 0) and DSS was 1.728 (95%CI: 1.159–2.579, p = 0.007). This indicated a similar outcome even though publication bias existed.

To compare with the final pooled HR results, adjusted HR values were pooled from six studies in the original Group A with the exception of Lieng [18] and Chow [20] which contained unadjusted HR values. Sufficient studies were available for OS and DSS. Similar results showed

Table 2
Quality assessment of the eligible studies.

Study	Inclusion and exclusion criteria	Prospective or retrospective	Patient characteristics	Tumour characteristics	LNR measurements	Endpoint	Follow-up period	Patients unavailable for statistical analysis	Quality scale
Gil [17]	1	1	1	?	?	1	1	1	6
Shrime [34]	1	1	?	?	1	?	1	?	4
Ebrahimi [21]	1	1	?	1	?	1	1	1	6
Kim SY [1]	1	1	1	1	1	?	1	?	6
Patel [11]	1	1	?	1	1	?	1	?	5
Kunzel [23]	1	1	1	1	1	?	1	?	6
Adel [35]	1	1	1	1	?	?	0	1	5
Lieng [18]	1	1	1	1	?	?	1	1	6
Suzuki [36]	1	1	?	?	?	1	1	1	5
Chang [22]	1	1	1	?	1	1	1	?	5
Chow [20]	1	1	1	1	1	?	1	?	6
Hosni [37]	1	1	1	1	?	?	1	?	5
Kim KY [31]	1	1	?	?	1	?	?	?	3
Lee [38]	1	1	?	1	?	?	?	?	3
Safi [39]	1	1	1	1	1	1	1	?	7
Safi [40]	1	1	1	1	?	1	1	?	6
Son [16]	1	1	1	1	?	1	1	1	7
Xu [41]	1	1	1	1	1	?	1	1	7
Zirk [42]	1	1	?	1	?	1	1	?	5

increase in LNR resulted in poor OS (pooled adjusted HR: 2.11; 95%CI: 1.51–2.95) and DSS (pooled adjusted HR: 2.67; 95%CI: 1.56–4.60).

Group B: pN- and pN+

Twelve studies were included in the analysis. OS, DFS, DSS and LRF were the identified endpoints (Fig. 3).

No significant heterogeneity existed among the studies for OS (I^2 = 37.4%, p = 0.12) and LRF (I^2 = 0%, p = 0.741), but moderate heterogeneity existed for DFS (I^2 = 50.7%, p = 0.132) and DSS (I^2 = 60.5%, p = 0.038). The results showed that an increase in LNR predicted poor OS (pooled HR: 2.76; 95%CI: 2.13–3.59), DFS (pooled HR: 2.01; 95%CI: 1.44–2.82), DSS (pooled HR: 2.83; 95%CI: 1.8–4.44) and LRF (pooled HR: 5.21; 95%CI: 3.69–7.35).

Meta-regression analysis performed for OS (p = 0.772), DFS (p = 0.845), DSS (p = 0.337) and LRF (p = 0.965) showed that LNR cut-off is not the source of heterogeneity among the studies. We were unable to perform further analysis to identify the source of heterogeneity in DFS and DSS.

Regarding the publication bias, OS, DFS and DSS had no obvious asymmetry in funnel plots, and the *p* values of Egger's test were 0.204, 0.482 and 0.267 respectively. Studies of LRF had statistically significant publication bias (p = 0.045). Upon filling with one potential missing study, the recalculated pooled HR was 5.013 (95%CI: 3.584–7.011, p = 0.000).

To compare with the final pooled HR results, adjusted HR values was pooled from all eight studies in the original Group B. Sufficient studies were available for OS, DSS and LRF. Similar results showed that increase in LNR resulted in poor OS (pooled adjusted HR: 2.76; 95%CI: 1.90–3.99), DSS (pooled adjusted HR: 3.02; 95%CI: 1.87–4.87) and LRF (pooled adjusted HR: 5.21; 95%CI: 3.69–7.35).

Discussion

LN metastases are the most important prognostic factor for OSCC patients [6,45,46] and results in almost half reduction in 5-year survival rate [47]. Various characteristics of LN were proposed as prognostic factors for OSCC. These include extracapsular spread (ECS) [48–50], number of positive lymph nodes [51], lymph node yield [52–55], micrometastasis [56,57], level of neck involvement [58,59] and size of lymph nodes [60], of which most are featured in the latest update of AJCC TNM staging system [6]. Recently, LNR is recognised as a strong independent prognostic factor for OSCC. LNR represents a mathematical formulation that involves two parameters: the number of positive LN and the total LN yield.

Positive lymph nodes

Positive LN yield reflects the tumour burden and the extent of disease spread. In Ho et al.'s study [51], they noted that the mortality risk was proportional to the number of metastatic nodes. However, prognosis based on the number of positive LN alone can be misleading. A low value might give a false impression of the actual disease given that the number of diseased node yielded is affected by the type of neck dissection performed.

Roberts et al. [52] shown in their multicentre study that the number of positive LN yield was a significant prognostic factor of OSCC but LNR was not. However, their analysis was based on the data from Surveillance, Epidemiology and End Results program (SEER) where information on the type of neck dissection, anatomical nodal levels removed and the protocol of pathologic review of dissection were missing [29,33,38]. Recurrence rate, an important endpoint [33], was also unavailable from SEER. SEER also lacked data on the adjuvant chemotherapy, extra-capsular spread and margin conditions which are important factors for multivariate analysis and eventual HR calculation [38]. Such limitations also existed in Lee et al study [38] which was included in our meta-analysis.

Ridder et al. [61] questioned the reliability of LNR in view of its vulnerability to total nodal yield. The total harvested nodes are influenced by various factors: differences in anatomy, surgical expertise, type of neck dissection and specimen processing [62]. They also illustrated that the change in specimen protocol affected LNR outcomes but not the total diseased nodes and they believed that the number of positive LN was a more reliable parameter than LNR [61]. However, the adequacies of disease eradication through neck dissections cannot be addressed by positive LN alone.

Clearance control

Total LN yield is important for staging and disease eradication and is dependent on the quality and type of neck dissections. First introduced by Crile [63] in 1906 and later by Martin et al. [64] in 1950s, radical neck dissection (RND) is the collective removal of the entire cervical lymphatic system. However, it brought significant morbidity such as chronic neck and shoulder pain, cosmetic deformity and facial

Table 3
Main characteristics of the eligible studies.

Study	Year	Database	Recruitment period	Prospective	Endpoints with HR	Total Nodal yield	LNR cut-off	Method of LNR determination
Gil [17]	2009	USA*	1986–1996	No	OS, DSS, LRF	Mean 35 ± 19	≤0.06, > 0.06	Median
Shrime [34]	2009	Canada	1994–2004	No	OS	Mean 41.6, Median 36	0.06–0.125, < 0.06, ≥0.125	Maximally selected rank statistic
Ebrahimi [21]	2011	Australia*	1987–2009	No	OS, DSS	Mean 27.4	≤0.025, 0.025 < x ≤ 0.075, 0.075 < x ≤ 0.2, > 0.2	Log scale
Kim SY [1]	2011	South Korea	1994–2006	No	DSS	Median 25	≤0.06, > 0.06	Based on Gil [17]
Patel [11]	2013	ICOR	DNS	No	OS, DSS, DFS, LF, LRF, DM	Mean 39 ± 23	≤0.07, > 0.07	ROC curve
Kunzel [23]	2014	Germany	1980–2010	No	DSS	Median 26, Mean 27.75	≤0.05, > 0.05, ≤0.07, > 0.07	ROC Curve, Median
Adel [35]	2016	Taiwan*	2008–2013	No	OS, DFS	DNS	0, < 0.06, ≥ 0.06	Based on Gil [17] & Ong [2]
Lieng [18]	2016	Australia	1980–2011	No	OS, DFS	Mean 22.8, Median 19	≤0.143, > 0.143	Log-rank test
Suzuki [36]	2016	Japan	2009–2013	No	OS, DM, Lung metastasis	DNS	< 0.07, ≥0.07	Based on Patel [11]
Chang [22]	2017	Taiwan	2002–2015	No	OS, DFS	DNS	0, ≤0.05, > 0.05	ROC Curve & Youden index
Chow [20]	2017	Hong Kong	2000–2016	No	OS, DSS	Median 23	≤0.07, > 0.07	Based on Patel [11] & Suzuki [36]
Hosni [37]	2017	Canada	1994–2012	No	OS	Median 36	≤0.06, > 0.06	Maximally selected rank statistic
Kim KY [31]	2017	South Korea	1990–2011	No	OS	Median 1	0, ≤0.06, > 0.06	Median
Lee [38]	2017	SEER	2007–2013	No	OS, DSS	Mean 33 ± 17	0, ≤0.2, 0.2 < x ≤ 0.4, 0.4 <	Based on Chen [43]
Safi [39]	2017	Germany*	2003–2013	No	LRF	DNS	< 0.07, ≥0.07	Median
Safi [40]	2017	Germany*	2003–2013	No	LRF	DNS	< 0.06, ≥0.06	Median
Son [16]	2017	South Korea	2010–2015	Yes	OS, DSS, LRF	DNS	≤0.05, > 0.05	ROC
Xu [41]	2017	China	1999–2011	No	DFS, DSS	Mean 23.5 ± 12.0, Median 22	≤0.06, > 0.06	Based on Reinisch [44]
Zirk [42]	2017	Germany*	2002–2013	No	OS	Median 21, Mean 26.7 ± 17.4	≤0.07, > 0.07	DNS

ICOR: International Consortium for Outcomes Research, OS: Overall survival, DFS: Disease free survival, DSS: Disease specific survival, LRF: Locoregional disease free survival, LF: Local recurrence free survival, DM: Distant metastasis disease free survival, DNS: Did not specify. *Centres contributing to ICOR database.

edema to patients due to the removal of the jugular vein, spinal accessory nerve and sternomastoid muscle. Modified radical neck dissection (MRND) was introduced as a more "conservative" attitude to preserve these structures while maximising regional control of disease [65]. Later on, Lindberg defined specific lymph node risk groups with reference to various primary sites of head and neck cancer [66]. This introduced the concept of selective neck dissection (SND) by preservation of low-risk nodal basins for selected patients, thus decreasing morbidity. In high risk areas such as tongue and floor of mouth where skip metastases could occur, SND might cause more harm than good [67–69]. Byers et al. [68] proposed an extended supraomohyoid neck dissection due to the inadequacies of SND in disease eradication. However, to date, there is no consensus nor guidelines for the anatomic limits for SND procedures and boundaries can vary among surgeons within an institution [70]. It is believed that LNR could provide a reference and answer to the adequacy of neck extension for each metastatic LN present.

Patients undergoing primary surgery for resection of the primary tumour are recommended to include RND, MRND or SND for the cN + neck, and SND for the cN0 neck [5]. The type of neck dissection (ND) impacts the total nodal yield grossly and the actual threshold continues to be investigated today. The latest AJCC manual [6] considers harvesting 15 or more lymph nodes in a previously untreated patient as an adequate neck dissection, while other recent studies showed a minimum of 18 to 26 nodes were required before the neck was staged accurately and occult microscopic disease was adequately treated [53,54]. In addition to this uncertain threshold, the issue of LN hypertrophy occurring differently among individuals put the reliability of using total LN yield alone into question. Friedman et al. [71] noted the number of LN in each nodal level and the total LN yield in human cadavers were lower than those in clinical neck dissections. He proposed that significant LN hypertrophy was related to the presence of primary SCC. Nevertheless, the lymph node yield is unable to mirror the true impact of positive LN on survival [38]. Hence the use of LNR merges the benefits of both parameters while addressing their shortcomings.

Lymph node ratio cut-off value

This paper is the first meta-analysis to evaluate LNR as a prognostic factor for OSCC. Pooled HR showed LNR is a strong independent prognostic factor of OSCC for endpoints OS, DFS and DSS, as well as LRF in Group B (pN + and pN −). In the analysis, all cut-off values were shown to be significant and there was no strong evidence to consider a possibility of a second significant value. Considering OS, the lowest available LNR identified in Group A and Group B were 0.05 and 0.025 respectively. Since Group A is a subset of Group B, 0.025 could be considered as the cut-off for OS in both groups.

To translate these findings to clinical practice, it requires a minimum of 40 lymph nodes harvested for each positive lymph node identified to ensure a similar overall survival to a negative neck. Hence for cN + patients undergoing ipsilateral ND surgery as a curative approach, it seems that RND or MRND should be performed to improve their overall prognosis. This echos to the NCCN guidelines [5] whereby patients with LN metastases have comprehensive neck dissections performed because of possible disease outside the bounds of SND. A RND yields an average of 31 to 42 lymph nodes [72–74], compared to MRND which yields 6 to 13 nodes less [75]. SND yields the least and is also dependent on the levels of neck harvested [76]. Man et al found an average nodal yield for level I through level V to be 6, 11, 12, 10, 12 respectively [72]. However, a large variation exists between studies. Not all patients who underwent RND or MRND would have LN yield above 40. Though Agrama et al. attributed the most likely reason for the variation to be surgical technique due to individual judgment and philosophy [75], physical difference among patients [71] and difference in specimen protocol among institutions may account for this

Table 4
Patient and pathologic characteristics of the eligible studies.

Study	No. of patients	Age	Treatment	Type of Neck Dissection (ND)	T stage	N stage	Sites	Specimen protocol	Follow up
Group A									
Shrime [34]	143	Mean 58.7 (14.8–89.4)	Surgery OR Surgery with (Radiotherapy OR Chemotherapy)	DNS	pT1 to T4	pN1 pN2	Tongue gum floor of mouth buccal mucosa hard palate Retromolar trigone	No	Mean 32.4mo (1.2 to 140.4mo)
Kim SY [1]	78	Mean 55 (21–88)	Surgery OR Surgery with (Radiotherapy OR Chemoradio therapy)	Selective, Modified Radical, Radical, Bilateral	pT1 to T4	pN0 pN1 pN2b pN2c	Tongue gum floor of mouth buccal mucosa hard palate Retromolar trigone	Yes (Centre based)	Median 58mo (4 to 180mo)
Patel [11]	1986	Mean 52.63 (14–99) ^	Surgery OR Surgery with (Radiotherapy OR Chemoradio therapy OR Radiotherapy with Erbitux)	Selective, Radical, Bilateral	pT1 to pT4	pN0 pN1 pN2a, 2b, 2c pN3	Based on AJCC definition	CAP protocol 2007	Median 46mo (4 to 322mo)
Kunzel [23]	147	Median 55 (26–85)	Surgery OR Surgery with (Radiotherapy OR Chemoradio therapy)	Elective unilateral, Bilateral	pT1 to pT4	pN1 pN2	Floor of mouth Tongue Gingiva Cheek	DNS	Mean 4.12 yr (0.01–23.17 yr)
Lieng [18]	72	Mean 22.8 (1–72)	Surgery with (Radiotherapy OR Chemoradio therapy)	DNS	pT1 to pT4	pN1 pN2 pN3	Tongue	DNS	Median 55mo (2.1 to 177mo)
Suzuki [36]	35	DNS	Surgery OR Surgery with (Radiotherapy OR Chemoradio therapy OR Chemotherapy)	Enbloc neck dissections: Unilateral, Bilateral (Japan Neck Dissection study group)	pT1 to pT4	pN1 pN2 pN3	Tongue gum floor of mouth buccal hard palate	DNS	Mean 20.9mo (SD 17.2mo)
Chow [20]	19	Median 70 (46–95)	Surgery OR Surgery with (Radiotherapy OR Chemoradio therapy OR Chemotherapy)	Selective, Modified Radical, Radical	pT1 to pT4	pN0 pN1 pN2 pN3	Buccal	DNS	Median 79mo (5-167mo)
Son [16]	65	Median 54 (24–87)	Surgery OR Surgery with (Radiotherapy OR Chemoradio therapy)	Elective, Therapeutic	pT1 to T4	pN0 pN1 pN2	Tongue gum floor of mouth buccal mucosa hard palate Retromolar trigone Lip	DNS	Median 46mo (14–74)
Group B									
Gil [17]	386	Mean 58 (14–88)	Surgery OR Surgery with Radiotherapy	Selective, Modified Radical, Radical, Bilateral	pT1 to T4	pN0 pN1 pN2a, 2b, 2c pN3	Tongue Mouth floor Buccal Upper & lower gum Hard palate Retromolar	Based on CAP protocol 2007	Median 67mo (4–184)
Ebrahimi [21]	313	Median 63.4 (28.5–91.5)	DNS	Selective, Radical, Bilateral	pT1 to T4	pN0 pN1 pN2a, pN2b, 2c	Based on AJCC definition	DNS	Median 32.3mo
Hosni [37]	914	Median 61 (18–92)	Surgery OR Surgery with (Radiotherapy OR Chemoradio therapy)	Selective, Modified Radical, Radical, Bilateral	pT1 to T4	pN0 pN1 pN2	Tongue gum floor of mouth buccal mucosa hard palate Retromolar trigone	DNS	Median 51mo (1-189mo)
Safi [39]	95	Median 66 (35–98) ^	Surgery OR Surgery with Radiotherapy	Selective, Modified Radical, Bilateral	pT1 to T4	pN0 pN1 pN2	Buccal	Yes (Centre based)	Median 29mo (3–100) ^
Safi [40]	130	Median 61.5 (25–92) ^	Surgery OR Surgery with Radiotherapy	Selective, Modified Radical, Bilateral	pT1 to T4	pN0 pN1 pN2	Tongue	DNS	Mean 41.51mo (3–92) ^
Son [16]	157	Median 54 (24–87)	Surgery OR Surgery with	Elective, Therapeutic	pT1 to T4		Tongue gum	DNS	Median 46mo (14–74)

(*continued on next page*)

Table 4 (*continued*)

Study	No. of patients	Age	Treatment	Type of Neck Dissection (ND)	T stage	N stage	Sites	Specimen protocol	Follow up
			(Radiotherapy OR Chemoradio therapy)			pN0 pN1 pN2	floor of mouth buccal mucosa hard palate Retromolar trigone Lip		
Xu [41]	2036	Mean 59 (+/- 12.2)	Surgery OR Surgery with (Radiotherapy OR Chemoradio therapy)	Elective unilateral, Bilateral	pT1 to pT4	pN0 pN1 pN2 pN3	Tongue Gingiva Buccal Floor of mouth Hard palate	Yes (Centre based)	Median 65mo (1-178mo)
Zirk [42]	155	Median 50 (33–90)	Surgery OR Surgery with (Radiotherapy OR Chemoradio therapy)	DNS	pT1 to T4	pN0 pN1 pN2a, 2b, 2c pN3	Floor of mouth	DNS	Median 38mo
Group C									
Adel [35]	277	Mean 51.9 (27–84)	Surgery OR Surgery with (Radiotherapy OR Chemoradio therapy)	Selective, Modified Radical, Bilateral	pT1 to pT4	pN0 pN1 pN2b, 2c pN3	Tongue Mouth floor Lip Buccal Alveolar ridge Hard palate Retromolar	DNS	DNS
Chang [22]	389	Mean 51.8 (23–84)	Surgery OR Surgery with (Radiotherapy OR Chemoradio therapy)	DNS	pT1 to pT4	pN0 pN1 pN2 pN3	Lip Retromolar trigone Gingiva Tongue Palate Buccal Floor of mouth	DNS	Median 42mo (0–152)
Kim KY [31]	316	Median 61 (19–86)	Surgery	DNS	pT1 to pT4	pN0 pN1 pN2	DNS	DNS	DNS
Lee [38]	3958	Mean 59 (+/-13)	Surgery OR Surgery with Radiotherapy	DNS	pT1-T4	pN0 pN2, but exclude 2c pN3	Tongue Lip Floor of mouth Gum Retromolar trigone Buccal Hard palate	DNS	DNS

DNS: Did not specify, CAP: College of American Pathologists.

variance as well [61].

However, current practice favours SND rather than RND [2]. The role of SND in cN + neck is contentious [77]. The concept of SND is the predictability of nodal spread in OSCC [77]. LNR emphasizes the importance of obtaining a threshold number of LN for better outcome. Hence SND, with a lower lymph node yield, might underestimate the true extent of disease and might increase the likelihood of having residual microscopic disease [34,78].

There is no doubt that there might be survival benefits associated with more extensive lymph node dissection [54]. Though our research on LNR applies regardless of subsequent adjuvant therapy received, it will be too hasty to disregard the researches in modern adjuvant therapies which set the decision on SND in a grey area. Historically, even with RND, locoregional failures was a dominant problem [79] and almost invariably proved fatal [80]. As the effectiveness of post-operative radiation was confirmed in 1970s by Fletcher et al. [81], it was believed that surgery and irradiation should be considered complementary with surgery removing the gross disease and irradiation eradicating the diffused microscopic portion [82]. Today, adjuvant radiotherapy (RT) is indicated when there is evidence of extra nodal extension, positive margin, pT3-4, pN2-3, pN+ at level IV and V, perineural and lymphatic invasion as well as vascular embolism [5]. A study by Kolli et al. [83] and a recent meta-analysis by Liang et al. [46] suggested that SND with adjunctive therapy may obtain acceptable clinical outcome in cN + OSCC patients compared to RND with RT. Hence this offers an alternative for centres where the average LN yield from ipsilateral MRND or RND falls below 40. Such patients could be offered SND instead of RND in view of possible subsequent RT as they fall into the poor prognostic group by having LNR > 0.025. This might avoid the morbidities related to the additional neck extension. On the other hand, in certain countries where RT facilities are unavailable or poorly accessible, RND and MRND might continue to remain the gold standard of treatment [84–86].

For pN + patients that had undergone SND in view of cN0, current NCCN guidelines suggest to consider RT [5]. Our study suggests extension of neck dissection to be offered for such patients in view of poor survival outcomes. However, our results were unable to identify a second significant cut-off value within Groups A and B. This cut-off would be important to stratify them into different risk groups and maybe useful in suggesting more aggressive adjunctive therapy to high risk patients Hence it is contrary to the belief that LNR can guide the use of adjuvant therapy [11], our analysis showed otherwise.

Limitations of the study

Our study is not without limitations. With only one prospective

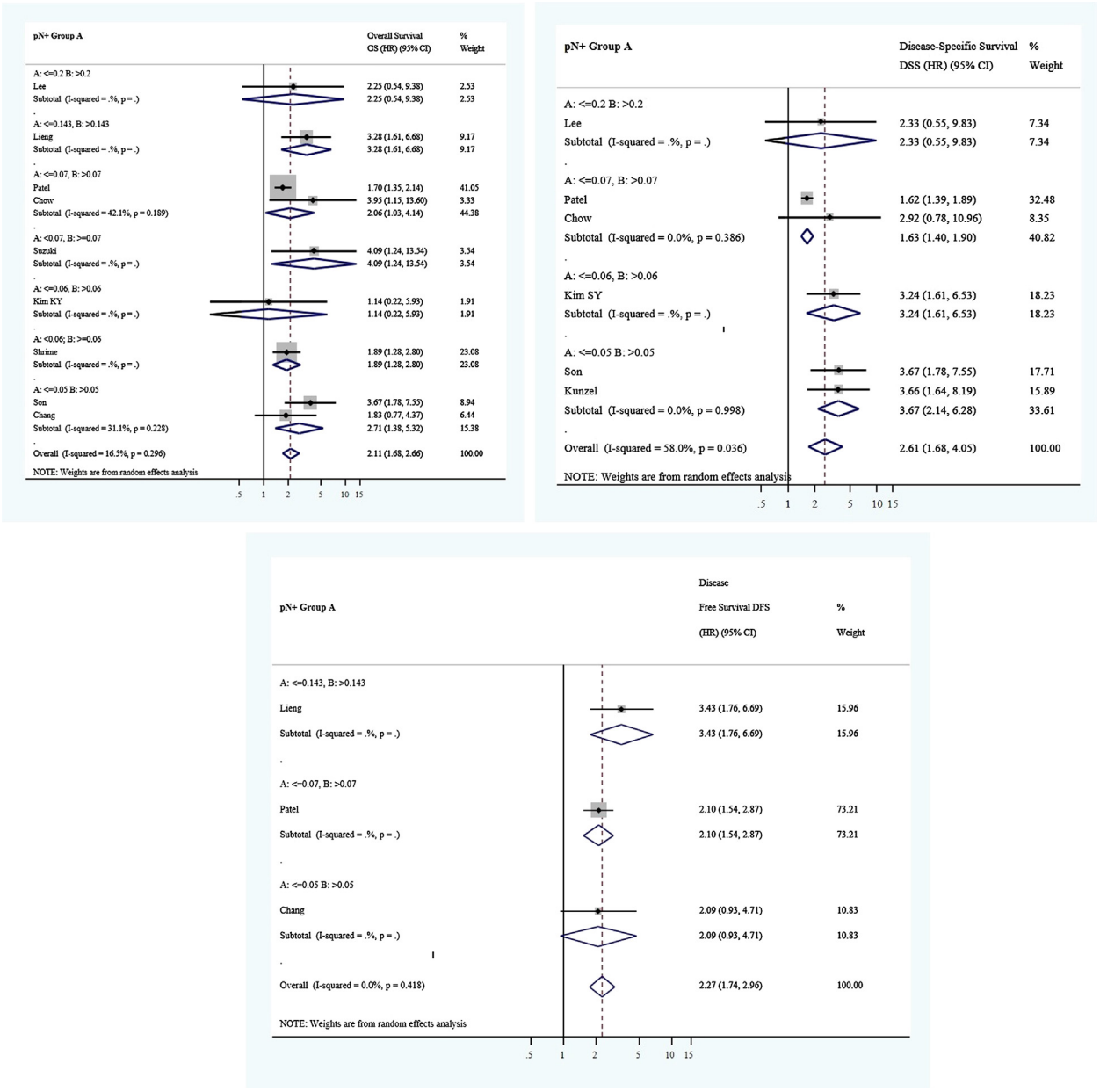

Fig. 2. Forest plots of the meta-analysis regarding the overall survival (OS), disease-specific survival (DSS) and disease-free survival (DFS) in Group A: pN+.

study [16], included studies are bounded by their retrospective design. Data regarding patient characteristics such as ethnicity, smoking and alcohol exposure were unavailable [11] and important tumour related factors such as extracapsular spread (ECS), primary site of tumour and postoperative adjuvantive theraoy were also excluded because of missing entries [31]. The varying follow-up time [31,35,38] and endpoint definitions [1,11,18,20,23,31,34,35,37,38,41] are also the fundamental weakness of all retrospective analyses. Three studies [31,34,38], despite having low quality grading due to unclear description of follow-up time and definitions of endpoints, were included in the meta-analysis. This is because the final data presented had implied such information. Types of neck dissections were not investigated in some studies [18,22,31,34,38,42]. Situations such as midline oral cavity tumours requiring bilateral neck dissection should be identified, as they would increase the total nodal yield and lower LNR into a more favourable ratio, thus introducing confusion [34]. One should be cautious when applying the 0.025 LNR cut-off in bilateral neck dissection. N3 patients were excluded from some studies due to technical difficulty in determining whether a metastatic LN larger than 6 cm is a single node or multiple, matted LN [23,34].Therefore, there was difficulty in performing subgroup analysis in group A and B.

Studies have used minimum p-values, time-dependent receiver operating characteristic curves analysis, median and mean value to identify LNR cut-off point. While the analysis calculated through median or mean of LNR are highly sensitive to individual data [18], HR calculated might be an overestimation or underestimation.

Future direction

Certainly, more prospective studies with better designed trials would be warranted for future LNR studies. There should be standardisation in areas such as specimen protocol. In our meta-analysis, only two studies include these descriptions [2,11]. The College of American Pathologist (CAP) [87] now recommends hospitals and laboratories to start using the CAP Cancer protocols containing tumour staging from the 8th edition of the AJCC Cancer Staging Manual. LNR should also be

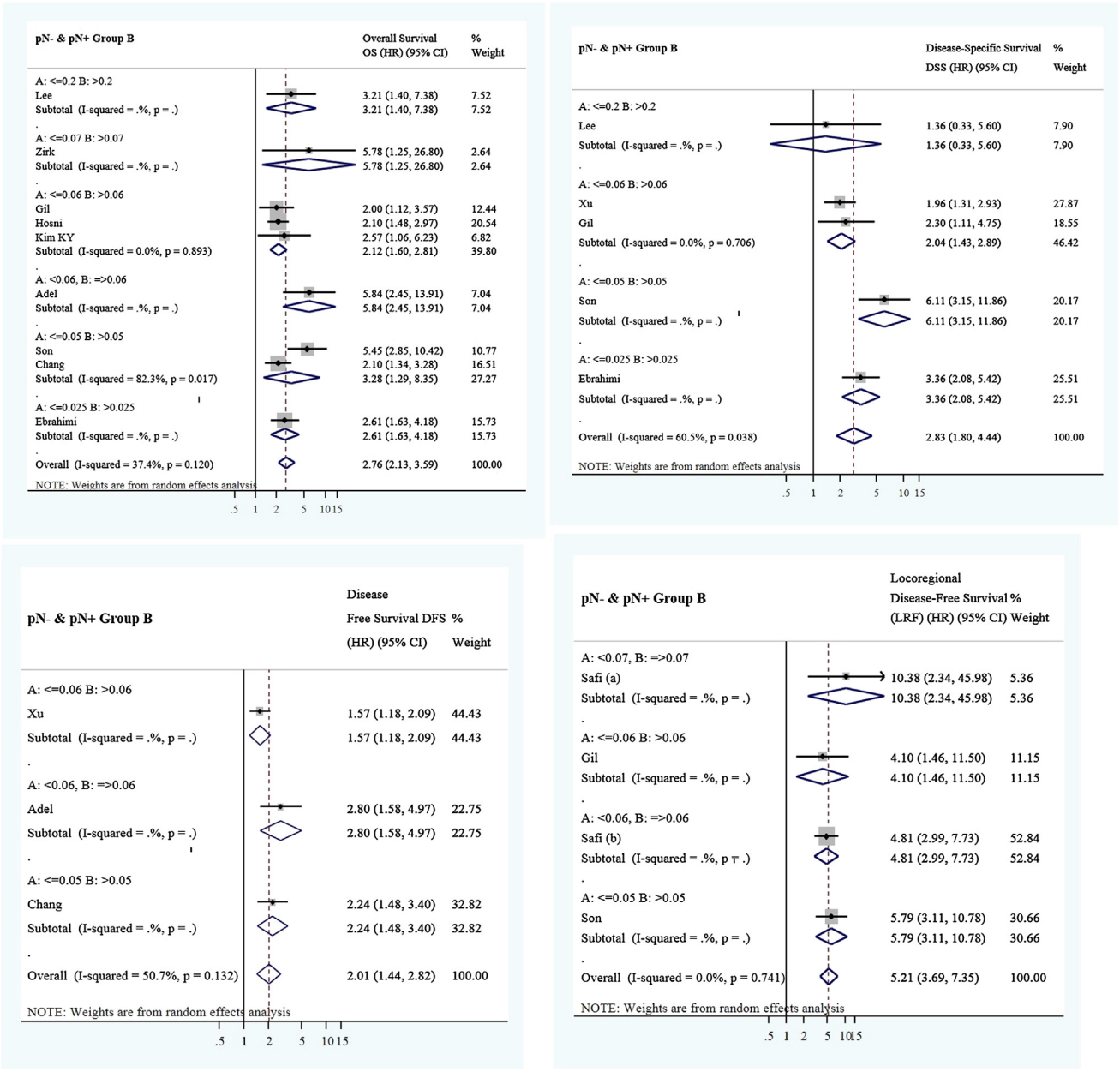

Fig. 3. Forest plots of the meta-analysis regarding the overall survival (OS), disease-specific survival (DSS), disease-free survival (DFS) and locoregional disease-free survival (LRF) in Group B: pN− and pN+.

derived from ipsilateral neck to prevent dilution or biased ratios and N3 could be excluded in view of technical difficulties [44]. Anatomic factors, such as adjaceny of tumour to bone, tumour accessibility and regional lymphatics are important parameters for considerations [2,88,89]. Due to the limited subsite studies, this study was unable to conclude its effect on LNR. Nevertheless, such subsite analysis may reduce possible confounding factors to LNR that may be present at different parts of the oral cavity.

Conclusion

In summary, the data from this meta-analysis showed that LNR is an independent prognostic factor in OSCC. However, more prospective validation would be needed to test the cut-off value we proposed. Lastly, it is important to acknowledge that LNR will be a continual evolving figure. The advances in radiotherapy, chemotherapy or target therapy will likely increase this ratio in the long term giving more leniency in the extent of neck dissection. It is the authors' belief that the shift towards SND for neck clearance will continue, but for now, option of RND and MRND remains.

Conflict of interest

All the authors declare that there is no conflict of interest related to this article.

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