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CLINICAL REVIEW

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Prognostic value of the nodal yield in head and neck squamous cell carcinoma: A systematic review

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Abstract

Objective: Literature analysis on the prognostic factor of the nodal yield (NY) in neck dissections (NDs), which in general surgical oncology is a strong prognosticator and quality-of-care marker.

Methods: We performed a systematic review of all PubMed and Embase publications until June 30, 2018 screening for data on NY as prognosticator and overall survival (OS) as outcome in patients with head and neck squamous cell carcinoma (HNSCC). Risk for bias was asserted by application of the Quality In Prognosis Studies tool.

Results: Of the 823 screened publications, 15 were included in this analysis. Five out of seven that compared NY ≥18 vs <18 as prognosticator, showed significantly improved survival if NY ≥18. Six studies used other cutoffs and three reported improved survival with each additionally harvested lymph node.

Conclusion: Increased NY in ND specimen for HNSCC, most commonly described as ≥18 lymph nodes, is associated with improved OS and could be used as a prognosticator and quality-of-care marker.

KEYWORDS

carcinoma, head and neck cancer, lymph node excision, neck dissection, nodal yield, oral cancer, prognosis, squamous cell

1 | INTRODUCTION

A neck dissection (ND) remains the gold standard for staging regional lymph node metastasis in patients with head and neck squamous cell carcinoma (HNSCC). Currently, the number of metastatic lymph nodes found in the ND specimen determines whether or not adjuvant therapy is applied. So far there is still debate concerning the clinical benefit, its extent and the preferred technique of the performed ND.[1] In patients with limited risk of metastasis, the traditionally performed radical ND is replaced by functional or selective NDs.[2] In oral and oropharyngeal SCC, no difference in overall survival (OS), recurrent disease (RD), or disease-free survival is reported when comparing patients that underwent either a radical or a selective ND.[3]

However, in other types of cancer, the number of lymph nodes removed during primary surgery is associated with

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improved survival.[4–10] In colorectal cancer, this even led to a minimal number of 12 LNs that have to be resected, to ensure high quality of care as included in the National Comprehensive Cancer Network evidence-based guidelines for CRC.[11] For lung and gastric cancer, comparable recommendations have been developed.[12] These kinds of recommendations do currently not exist for HNSCC. In the new T/N/M-8 classification, extranodal extension has been added as a prognostic factor, but so far the nodal yield (NY) has not.[13] In HNSCC, there is need for new quality metrics that correlate with long-time survival.[14,15] Several studies have investigated the potential for the NY as prognosticator or quality metric in HNSCC.[16–30] The aim of this study is to systematically review the current evidence on the prognostic value of NY in patients with HNSCC.

2 | METHODS

2.1 | Criteria for inclusion

A systematic search of PubMed and Embase database was performed on June 30, 2018. Articles were considered eligible for inclusion if they investigated the NY as a prognostic factor for OS. Any type of HNSCC investigated was eligible for inclusion. Studies had to be original articles, meaning the authors performed the investigation themselves and their results were not published elsewhere. Studies were excluded if they were not written in the English language, did not report the absolute number of LNs or only investigated the lymph node ratio (percentage of metastatic LNs of all harvested LNs). Animal studies, commentaries, and reviews were also excluded.

2.2 | Search strategy

The search terms were divided into three groups: domain, determinant, and outcome. The domain search terms were: carcinoma OR cancer AND oral OR oropharynx OR pharynx OR hypopharynx OR larynx OR head and neck. The determinant search terms were: neck AND node OR nodes AND count OR counts OR ratio OR ratios OR number OR numbers. The outcome search terms were: survival OR outcome OR outcomes OR predictor OR predictors OR metrics.

PubMed and Embase syntax: see appendix 1.

Two authors (WWBDK and SLNM) screened all articles on title and abstract. Predefined inclusion and exclusion criteria were used to select the eligible articles (see above). After selecting all eligible articles, cross-reference screening was done manually to prevent missing articles not identified at the initial search. Contradictions were discussed and resolved.

2.3 | Data collection

The following information was extracted from each study: Name of first author, year of publication, sources of data, sample size, head and neck site, number of lymph nodes, number of NDs, survival outcome measured in OS, statistical methods, and cutoff values.

2.4 | Quality In Prognosis Studies

To score the methodological quality of the eligible articles, the Quality In Prognosis Studies (QUIPS) tool was used.[31] As part of the QUIPS tool, risk of bias was scored in six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. For each domain risk of bias could score: low, moderate, or high. Studies scoring high risk of bias in three or more domains were considered to be of low methodological quality and studies scoring low risk of bias in three or more domains were considered to be of high methodological quality. All studies scoring in-between were considered to be of moderate methodological quality. Two reviewers (WWBDK and SLNM) independently assessed the studies using the QUIPS methodology. Disagreements were solved by discussion.

2.5 | Synthesis and analysis of results

Due to heterogeneity (ie, different cutoff values), the results from all studies were not quantitatively pooled and thus a true meta-analysis could not be performed. Alternatively, a forest plot was generated with DistillerSR Forest Plot Generator from Evidence Partners[32] (Figure 2).

For clinical relevance, the included studies were analyzed with attention to tumor site, cN0 or cN+ status, extend of the dissection, bilateral NDs, the reasoning behind the analyzed cutoff level, and the type of survival metric used.

3 | RESULTS

3.1 | Search

In total, the search yielded 823 articles after removal of duplicate articles. After screening titles and abstracts, 35 articles were subsequently full text screened for eligibility (Figure 1). Thirteen articles met the inclusion criteria and after addition of two articles identified by cross-reference screening, 15 articles were included in this review. The included studies describe data on patients with SCC in the oral cavity, larynx, oropharynx, and hypopharynx. Ten studies only included oral cavity SCC[16,17,20–23,27–30] whereas three studies included patients with tumors at all four

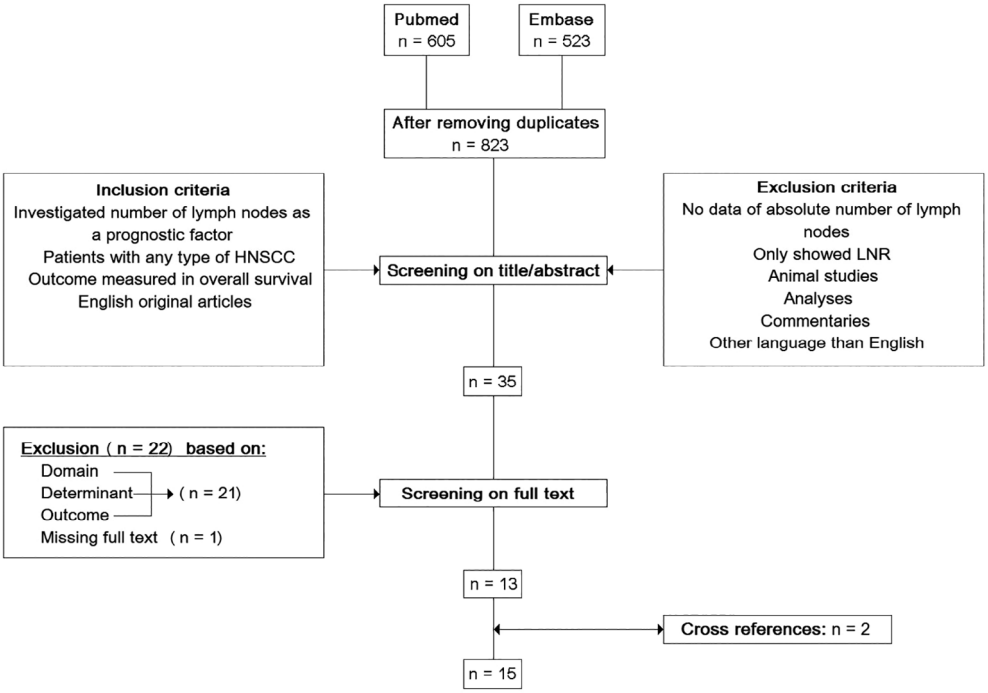

FIGURE 1 Flowchart of search, date of search 30th of June 2018. HNSCC, head and heck squamous cell carcinoma; LNR, lymph node ratio, that is, percentage of metastatic lymph nodes of total number of harvested lymph nodes in dissection

different sites.[18,24,25] Ho et al included both laryngeal and hypopharynx SCC,[19] and Böttcher et al only described laryngeal SCC[26] (Table 1). All studies reported OS as an outcome measurement. All studies used cox proportional hazard models to analyze survival.

Of the included articles, six studies used the National Cancer Data Base (NCDB) that contain data on all patients with cancer in the USA as their patient population.[18–22,24] Although sample sizes in these six studies are different, an overlap between the study populations may be expected.

TABLE 1 Study characteristics

Study	Sample size	Database	Head and neck site	cN0 / cN+ patients	Survival outcome	Statistical methods
Lee et al.[16]	78	Single-center retrospective	OC	Both	OS	CPH
Son et al.[17]	157	Single-center prospective	OC	Both	OS	CPH
Cramer et al.[18]	41 572	NCDB	OC, HP, L, OP	Both	OS	CPH
Ho et al.[19]	8351	NCDB	HP, L	Both	OS	CPH
Ho et al.[20]	14 554	NCDB	OC	Both	OS	CPH
Tsai et al.[21]	7811	NCDB	OC	cN0	OS	CPH
Kuo et al.[22]	4365	NCDB	OC	Both	OS	CPH
	4618	SEER				
Lemieux et al.[23]	4341	SEER	OC	cN0	OS	CPH
Divi et al.[24]	63 978	NCDB	OC, HP, L, OP	Both	OS	CPH
Divi et al.[25]	572	Multicenter retrospective	OC, HP, L, OP	Both	OS	CPH
Böttcher et al.[26]	54	Single-center retrospective	L	Both	OS	CPH
Ebrahimi et al.[27]	1567	Multicenter retrospective	OC	cN0	OS	CPH
Jaber et al.[28]	162	Multicenter retrospective	OC	cN0	OS	CPH
Sayed et al.[29]	1408	Double-center retrospective	OC	Both	OS	CPH
Ebrahimi et al.[30]	225	Single-center retrospective	OC	Both	OS	CPH

Abbreviations: CPH, cox proportional hazard regression; HP, hypopharynx; HN, head and neck, no distinction; L, larynx; NCDB, National Cancer Database (USA); N0, no regional lymph node metastasis; N+, lymph node metastasis are present; OC, oral cavity; OP, oropharynx; OS, overall survival; SEER, (Surveillance, Epidemiology and End Results program) National Cancer Institute USA.

Kuo et al and Lemieux et al used data form the Surveillance, Epidemiology and End Results (SEER) database, also from the USA.[22,23] The SEER database contains information on patients with cancer and is designed to be representative for the total population.[33] Thus, overlap between the SEER and NCDB databases is also plausible.

Of the non-nationwide database studies, three studies performed a retrospective multicenter analysis,[25,27,28] three studies a retrospective single-center analysis,[19,26,30] Sayed et al a retrospective double-center analysis[29] and Son et al a prospective single center analysis.[17]

3.2 | Quality assessment

We used the QUIPS-analysis to assess the methodological quality and subsequent risk of bias. The quality of the reported studies, varied from moderate to high (Table 2).[31] Most studies (92%) were retrospective of nature where bias is unavoidable. Eight of the 15 studies were of high methodological quality according to our QUIPS analysis.[16,17,25–30] The seven other studies are of moderate methodological quality.[18–24] No studies were determined to be of low methodological quality.

3.3 | Selection of cutoff values

In the studied publications, several different cutoff values were used. Ebrahimi et al. (2011) calculated the cutoff value of 18 LNs, based on the creation of four categorical variables <18, 18-24, >24-32, and >32 LNs.[30] Böttcher et al also had a median of 18 LNs harvested that they used as cutoff.[26] Five studies did not calculate their own cutoff and referred to the value determined by Ebrahimi et al. (2011).[17,18,24,25,27] Three studies calculated a survival "per harvested LN".[19,20,28] Lemieux et al created four categorical variables 1-11, 12-21, 22-35, and 36-98 based on the median number of all harvested LNs, in a similar fashion as performed in the Ebrahimi et al. (2011) study.[23] Only four studies calculated their cutoff value after a forward regression and receiver operating characteristic curve analysis, which were 19, 22, 24, and 16/26 LN's respectively.[16,21,22,29] Kuo et al calculated two cutoffs: 16 LNs for cN0 patients and 26 LNs for cN+ patients.

3.4 | Combined cN0 and cN+ analysis

Ten studies did not discriminate between cN0 and cN+ patients (Table 3).[16–20,24–26,29,30] Of these, eight studies evaluated a cutoff value varying from 18 to 25 LNs and compared survival with ≥(18-25) LNs and <(18-25) LNs in the ND specimen (Table 3). In six out of eight studies, a NY ≥(18-25) was significantly associated with improved OS (Table 3). The hazard ratios of these studies varied from 0.19 to 0.93 (Table 3). For most studies, the outcome measurements were displayed as hazard ratios. However, Sayed et al only reported the percentage of the population that survived.[29] Son et al and Böttcher et al failed to determine a significant difference in OS.[17,26] Ho et al. (2018) and

TABLE 2 QUIPS

Study	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting	Quality
Lee et al.[16]	◖	○	○	○	◖	○	***
Son et al.[17]	○	○	○	○	◖	◖	***
Cramer et al.[18]	◖	◖	●	◖	●	○	***
Ho et al.[19]	◖	◖	●	◖	●	○	**
Ho et al.[20]	◖	◖	●	◖	●	○	**
Tsai et al.[21]	◖	◖	●	◖	●	○	**
Kuo et al.[22]	◖	◖	◖	◖	●	◖	**
Lemieux et al.[23]	◖	◖	●	◖	●	○	**
Divi et al.[24]	◖	◖	◖	◖	●	○	**
Divi et al.[25]	○	◖	◖	○	◖	○	***
Böttcher et al.[26]	○	◖	○	○	◖	◖	***
Ebrahimi et al.[27]	○	◖	◖	○	◖	○	***
Jaber et al.[28]	○	◖	○	○	◖	○	***
Sayed et al.[29]	○	◖	○	○	◖	◖	***
Ebrahimi et al.[30]	○	◖	○	○	◖	○	***

Quality assessment with QUIPS-tool (Quality In Prognosis Studies) to score the risk of bias in prognosis studies. ○, low risk at bias; ◖, moderate risk of bias; ●, high risk of bias; ***, high methodological quality; **, moderate methodological quality; *, low methodological quality.

TABLE 3 Results of cN0 and cN+ analysis together

Study	Cutoff number of lymph nodes examined	Value with 95% confidence interval	*P*-value	Univariate (U)/multivariate (M)
Lee et al.[16]	≥19 vs <19	HR 0.19 (0.05-0.72)	.014	U
Son et al.[17]	≥18 vs <18	HR 0.88 (0.12-6.25)	.898	U
Cramer et al.[18]*	≥18 vs <18	HR 0.93 (0.89-0.96)	<.001	M (age, sex, race, comorbidities, subsite, tumor classification, lymph node status, human papillomavirus status, extracapsular extension, adjuvant therapy, insurance status, hospital type, and hospital volume)
Ho et al.[19]*	Per 10 LNs	HR 0.97 (0.96-0.98)	<.001	M (nodal size, laterality, extranodal extension, margin status, and adjuvant treatment)
Ho et al.[20]*	Each additional LN from 10-35	HR 0.98 (0.98-0.99)	<.001	M (nodal size, laterality, extranodal extension, margin status, and adjuvant treatment)
Divi et al.[24]*	≥18 vs <18	HR 0.85 (0.82-0.88)	<.001	M (sex, age group, race, comorbidities, site, pathologic stage, extracapsular extension, adjuvant therapy, insurance, income, education, volume, and hospital type)
Divi et al.[25]	≥18 vs <18	HR 0.71 (0.57-0.90)	.005	U
	≥18 vs <18	HR 0.72 (0.57-0.92	.007	M (age, race, Zubrod performance status, smoking history, primary site, pathologic T stage, extracapsular nodal extension, and number of positive nodes)
Böttcher et al.[26]	≥18 vs <18	HR 1.11 (0.40-3.14)	.837	U
	≥18 vs <18	HR 4.74 (0.66-34.48)	.122	M (AJCC stage + Adjuvant treatment)
	≥25 vs <25	HR 0.66 (0.22-1.96)	.456	U
	≥25 vs <25	HR 0.32 (0.08-1.28)	.108	M (AJCC stage + Adjuvant treatment)
Sayed et al.[29]	≥22 vs <22	85% vs 68%	.032	U
Ebrahimi et al.[30]	≥18 vs <18	HR 0.45 (0.26-0.83)	.009	U
	≥18 vs <18	HR 0.50 (0.28-0.91)	.020	M (age, nodal status, T stage, and adjuvant, radiotherapy)

Abbreviations: AJCC, American Joint Committee on Cancer; HR, hazard ratio; LN, lymph node; N0, no regional lymph node metastasis; N+, lymph node metastases are present. *, study used NCDB (National Cancer Database (USA)).

Ho et al. (2017) investigated survival per harvested LN. Both studies showed that after 10 LNs, every additionally harvested node was associated with significantly improved survival.[19,20] For the study of Ho et al. (2017), however, this effect was only observed until 35 harvested nodes (Table 3).

3.5 | cN0 separately

Nine studies analyzed a cohort with only cN0-patients (Table 4).[16,21–24,26–28,30] Seven of these nine studies evaluated a cutoff value varying from 16 to 25 LNs and compared survival with ≥(16-25) LNs and <(16-25) LNs in the ND specimen (Table 4).[16,21,22,24,26,27,30] In six out of seven studies, a NY ≥(16-25) was significantly associated with improved OS (Table 4). The hazard ratios of these studies vary from 0.16 to 0.82 (Table 4). Böttcher et al failed to determine a significant difference in OS.[26] Jaber et al looked at survival per harvested LN and showed a significantly improved OS per harvested LN (OS, RR 0.98; 95% CI 0.97-1.0 $P = .01$).[28] Lemieux et al divided patients into four NY groups, with group 1 (1-11 LNs) as the reference set. This study found a significantly improved OS for group 4 (36-98 LNs) and group 3 (22-35 LNs) vs 1, but not for group 2 (12-21 LNs) vs 1 (Table 4).[23]

3.6 | Site and relationship with survival

Four studies lumped different sites of HNSCC together[18,19,24,25] and 10 studies discussed the oral cavity separately.[16,17,20–23,27–30] In these studies, the OS improved with a greater NY. Adversely, in laryngeal carcinoma, separately investigated in only one study, NY did not improve survival.[26] However, these results were not statistically significant and the sample size of this study, with 54 participants, was small compared to the other studies. Oropharyngeal and hypopharyngeal sites could not be investigated separately.

3.7 | Extend of ND

Only seven of the 15 studies described the type of ND performed (Table 5).[16,17,26–30] Six studies contained more selective

TABLE 4 Results of cN0 analysis

Study	Cutoff number of lymph nodes examined	Value with 95% confidence interval	*P*-value	Univariate (U)/multivariate (M)
Lee et al.[16]	≥19 vs <19	HR 0.16 (0.03-0.78)	.023	U
Tsai et al.[21]*	≥24 vs <24	HR 0.82 (0.75-0.88)	<.001	M (unclear where was adjusted for)
Kuo et al.[22]*∞	≥16 vs <16	HR 0.817 (0.694-0.962)	.015	M (patient age, sex, ethnicity, insurance status, year of diagnosis, facility variables (annual case volume, facility type, geographic location), and clinical variables (pathologic tumor [pT] and lymph node [pN] classification, tumor grade, surgical margin status, radiation status, chemotherapy status)
Lemieux et al.[23]∞	12–21 vs 1-11	HR 0.91 (0.79-1.05)	.192	M (unclear where was adjusted for)
	22-35 vs 1-11	HR 0.85 (0.74-0.99)	.031	
	36–98 vs 1-11	HR 0.82 (0.72-0.95)	.010	
Divi et al.[24]*	≥18 vs <18	HR 0.81 (0.76-0.85)	<.001	M (sex, age group, race, comorbidities, site, pathologic stage, extracapsular extension, adjuvant therapy, insurance, income, education, volume, and hospital type)
Böttcher et al.[26]	≥18 vs <18	HR 0.83 (0.22-3.10)	.782	U
	≥25 vs <25	HR 0.31 (0.04-4.39)	.278	U
Ebrahimi et al.[27]	≥18 vs <18	HR 0.68 (0.48-0.95)	.024	M (age in years, sex, pathological T stage, pathological N stage, surgical margin status, extracapsular nodal spread, period of primary treatment (1970-1979, 1980-1989, 1990-1999, 2000-2011), and adjuvant therapy
Jaber et al.[28]	Per LN	RR 0.98 (0.97-1.0)	.01	U
	Per LN	RR 0.98 (0.97-1.0)	.014	M (unclear where was adjusted for)

Abbreviations: HR, hazard ratio; LN, lymph node; N0, no regional lymph node metastasis; N+, lymph node metastases are present. *, study used NCDB (National Cancer Database (USA)); ∞, study used SEER (Surveillance, Epidemiology and End Results program) National Cancer Institute USA.

NDs than comprehensive/radical NDs (Table 5).[16,17,26–28,30] Böttcher et al listed also a level V dissection as selective for laryngectomy, however this should be considered as comprehensive.[26] Sayed et al. included more radical than selective NDs.[29] Four studies demonstrated that the extension of the ND is related to a higher NY.[22,28–30]

3.8 | Bilateral NDs

Five studies corrected for bilateral NDs by taking the mean number of LNs of both sides.[25–28,30] Kuo et al and Divi et al excluded patients who underwent a bilateral ND.[22,24] Lee et al included only the ipsilateral tumor side of neck in case of bilateral NDs.[16] Sayed et al did show the exact number of bilateral NDs but did not state if and what kind of correction was applied.[29] Six studies did not provide any information about bilaterality of the ND.[17–21,23]

TABLE 5 Information neck dissections

	Selective level I-III/IV	Radical level I-V
Lee et al.[16]	78	–
Son et al.[17]	102	55
Böttcher et al.[26]	54 (I-V)	–
Ebrahimi et al.[27]	1484	275
Jaber et al.[28]	111	51
Sayed et al.[29]	528	1152
Ebrahimi et al.[30]	270	13

4 | DISCUSSION

This systematic analysis of the literature suggests evidence that also for HNSCC patients increased NY is associated with improved survival. Although different patient populations and NY (cutoffs) were analyzed, the overall findings show an improved survival with higher NYs. The cutoff value of ≥18 nodes resulted in a significant improvement of OS in five out of seven studies. Other significant cutoffs reported, range from 11 to 25 LNs or describe improvement of OS with each additional node removed. Most studies conclude that a higher NY results in improvement of OS. However, two studies did not find a significant OS with higher NY. The studies of Böttcher et al and Son et al, both single center cohort studies that scored well on

TABLE 6 Results of cN+ analysis

Study	Cut-off number of lymph nodes examined	Value with 95% confidence interval	*P*-value	Univariate (U)/multivariate (M)
Kuo et al.[22]	≥26 vs <26	HR 0.791 (0.692-0.903)	.001	M (patient age, sex, ethnicity, insurance status, year of diagnosis, facility variables (annual case volume, facility type, geographic location), and clinical variables (pathologic tumor [pT] and lymph node [pN] classification, tumor grade, surgical margin status, radiation status, chemotherapy status)
Divi et al.[24]*	≥ 18 vs <18	HR 0.89 (0.84-0.95)	<.001	M (sex, age group, race, comorbidities, site, pathologic stage, extracapsular extension, adjuvant therapy, insurance, income, education, volume, and hospital type)

Abbreviations: HR, hazard ratio; N+, lymph node metastases are present. *, study used NCDB (National Cancer Database (USA)).

methodological quality, had small sample sizes of only 54 and 157 participants, respectively. Moreover, Böttcher et al only included laryngectomy cases, for which the NY may be less applicable. Lemieux et al. only failed to determine a significantly better OS with higher NY in the analysis between the groups of 12-21 LNs vs 1-11LNs, whereas the two groups >21LNs did show a better OS. The failed significance vs this 12-21LN group may be explained by the inclusion of patients with less than 18 LNs, a critical threshold employed by others.

The studies included in this review are descriptive by nature. There are no studies available that investigate the biological explanation for the observed improvement of OS after increased NYs. One possible explanation could simply be that a higher NY results in fewer nodes left behind in the patient. The nodes left behind, even if relatively small in diameter, could still harbor tumor deposits that could give rise to recurrent metastatic disease. Second, the NY could also be related to the skill of the surgeon. In colorectal surgery, for example, NY is associated with level of experience of the surgeon.[34] If extrapolated to HNSCC, this could imply that more skilled head-neck surgeons may be more successful in a meticulous dissection of all neck levels.

Our findings are in line with a recently published review by Cheraghlou et al,[35] which pooled the results from some of the currently discussed studies and found a significantly increased survival with increased NY. This review investigated also the "nodal density," defined as the ratio of positive lymph nodes to the total nodes harvested, and found a significant reduction in patient survival if the nodal density increased. Together these results support and underscore the results from our independent literature review. In the Cheraghlou publication however, the manuscripts of Lee et al, Son et al, Cramer et al, Ho et al (2018), Ho et al (2017), Tsai et al, Jaber et al, and Sayed et al. incorporated in the current review were not included.

5 | LIMITATIONS

The studies discussed in this review must be interpreted with caution. All studies extracted data from databases that not always provided information on the extent of the NDs. Eight of the 15 studies did not provide any information about the type of ND.[18–25] Obviously more extensive NDs generally yield more LNs and therefore it seems logical that the type of ND influences the number of LNs found. Only four studies investigated this aspect and indeed demonstrated a positive association of the extend of ND and the NY.[22,28–30] On the other hand, Kuo et al found no difference in OS if patients were stratified by number of levels dissected, which suggests that the influence may be limited.[22]

Correction for bilateral NDs is a second item often unreported in the discussed studies. Six studies did not provide any information about bilaterality of the ND.[17–21,23] As it is expected that bilateral NDs yield more nodes, inadequate correction for bilateral NDs can bias the analysis.

Apart from the extension of the ND and surgical skill, the number of LNs found can depend on other factors too. One factor to take into consideration is the protocol used by the pathologist as this may also induce differences in the NY[36]: Differences in NY are observed per pathology department and depend on different techniques applied. When tissue is fixed in formalin for an additional 24 hours, for example, the NY is higher as determined in a study in the south of the Netherlands for colorectal cancer comparing six pathology departments.[37] Other factors that influence the NY in colorectal cancer, that may be applicable in HNSCC, are patient characteristics such as immunological response and the age of the patients.[6,38,39] Finally, prior radiation therapy to the neck is a known factor to result in a decreased NY.[40] In the studies described in this review, these (technical) details are most often missing. If information on these potential confounders was available, we listed them in Tables 3–4, and 6. In fact, for most studies, it was clear what

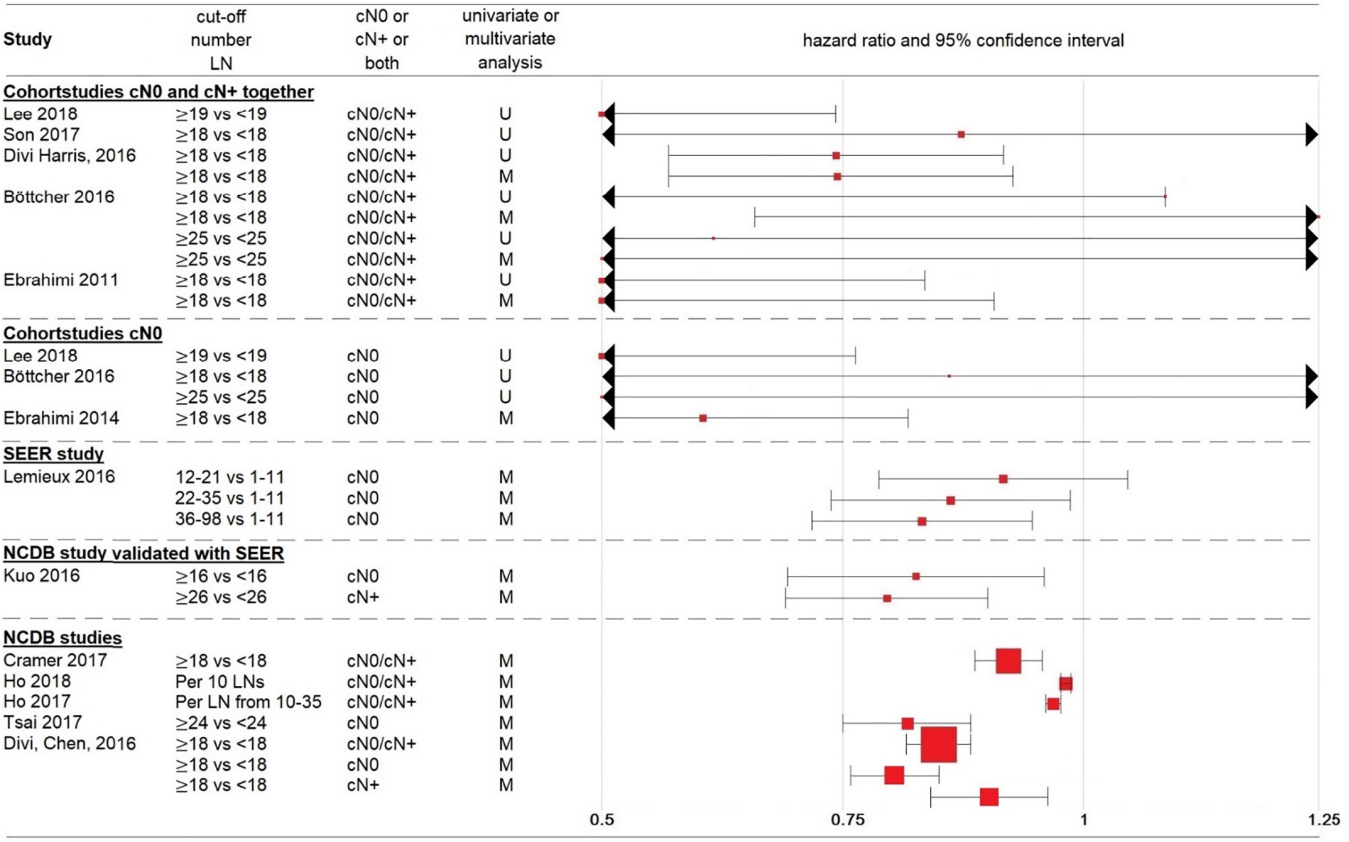

FIGURE 2 Forest plot of hazard ratios of death in group A compared to B. Hazard ratio <1 means, decreased chance of death in group A compared to group B thus better survival. Two studies were not included in this forest plot because they did not use hazard ratios.[28,29] A, Group of lymph nodes from cutoff till upper limit; B, group of lymph nodes from 0 till cutoff; 95% CI, 95% confidence interval; M, multivariate; N0, no regional lymph node metastasis; N+, lymph node metastases are present; OS, overall survival; U, univariate [Color figure can be viewed at wileyonlinelibrary.com]

factors were used in the multivariable analysis. In three studies though, it was unclear for what factors was corrected in multivariable analysis.[21,23,28]

As mentioned before, six studies used the same NCDB as their primary data source, which might result in overlapping samples and thus bias in our findings. The same accounts for Kuo et al and Lemieux et al that used the SEER database. Therefore, these six NCDB studies and two SEER studies should not be interpreted as independent confirmation studies but rather as one finding. We have therefore listed these studies separately in the overall forest plot (Figure 2). Although these nationwide registries may have significant internal overlap, their general conclusions are in line with the independently performed cohort studies included in this review.

6 | CONCLUSION AND PERSPECTIVES

Even though the evidence discussed in this review suggests that for HNSCC patients increased NY is associated with improved survival, it is too early to suggest the implementation of the lymph node count as a quality metric in daily practice. This is mainly because the exact influence of the variables involved is currently not yet known. To our opinion, future studies should ideally provide and address explicitly the following both preoperative clinical, surgical and pathological data:

- Site and location of the primary tumor
- Comorbidity and previous irradiation status
- Clinical N status
- Type of ND, whether diagnostic (in cN0) or therapeutic (in cN+)
- Number of levels dissected, in any case either selective or comprehensive
- For bilateral dissections, cN0 and/or cN+ status per side
- Method of determining the NY cutoff used
- Pathology processing protocol used.

Implementation of a NY criterium may help to underscore the centralization of HNSCC treatment, in line with treatment of colorectal cancer and may stimulate both

surgical and pathological partners to an optimal performance in their head and neck cancer care.

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APPENDIX 1. SEARCH SYNTAX

PubMed: ((((((carcinoma[tiab] or cancer[tiab]) AND (oral [tiab] OR oropharynx[tiab] OR pharynx[tiab] OR hypopharynx[tiab] OR larynx[tiab] OR "head and neck"[tiab])))) AND (((neck[tiab] AND (node[tiab] OR nodes[tiab])) AND (count[tiab] OR counts[tiab] OR ratio[tiab] OR ratios[tiab] OR number[tiab] OR numbers[tiab])))) AND (((survival [tiab] OR outcome[tiab] OR outcomes[tiab] OR predictor [tiab] OR predictors[tiab] OR metrics[tiab]))).

Embase: ((('carcinoma'/exp OR 'carcinoma':ab,ti OR "malignant neoplasm"/exp OR 'malignant neoplasm':ab,ti) AND ('oral':ab,ti OR 'oropharynx'/exp OR 'oropharynx': ab,ti OR 'pharynx'/exp OR 'pharynx':ab,ti OR 'hypopharynx'/exp OR 'hypopharynx':ab,ti OR 'larynx'/exp OR 'larynx':ab,ti)) AND ((('neck'/exp OR 'neck':ab,ti) AND ("lymph node"/exp OR 'node':ab,ti OR 'nodes':ab,ti)) AND ('count':ab,ti OR 'counts':ab,ti OR 'ratio':ab,ti OR 'ratios': ab,ti OR 'number':ab,ti OR 'numbers':ab,ti))) AND ('survival'/exp OR 'survival':ab,ti OR 'outcome':ab,ti OR 'outcomes':ab,ti OR 'predictor':ab,ti OR 'predictors':ab,ti OR 'metrics':ab,ti).