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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Metastatic lymph node burden predictive of survival in patients undergoing primary surgery for laryngeal and hypopharyngeal cancer

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Abstract

Purpose Metastatic lymph node (LN) burden is one of the most important prognosticators in human solid cancers, but has rarely been examined in laryngeal and hypopharyngeal cancers (LHC). We evaluated the nodal factors predictive of recurrence and survival in patients with LHC.

Methods This study included 141 consecutive patients who underwent primary surgery and neck dissection for previously untreated LHC at our tertiary referral centre. Nodal factors included the presence of pathological LN metastasis, number of positive LNs, LN ratio, and extra-nodal extension (ENE). Our proposed N classification was analysed by recursive partitioning analysis and compared with the AJCC and other N classifications using the c-index. Univariate and multivariate Cox proportional hazard regression analyses were used to define significant predictors of post-treatment disease-free survival (DFS) and overall survival (OS).

Results Of the 141 patients, 66 (46.8%) had positive LNs, and 27 (19.1%) had ENE. In multivariate analyses, the number of positive LNs was strongly associated with DFS and OS outcomes ($P < 0.01$). Our new N classification was proposed with four categories, such as N0 (0 LN+), N1 (1 LN+), N2 (2–4 LN+ or ENE) and N3 (≥ 5 LN+). The C-index of our new N classification improved the OS prediction (0.718) compared with the AJCC and the other N classifications (0.704–0.713).

Conclusion Metastatic LN burden is an important predictor of survival in patients with LHC. A proposed N classification using the number of positive LNs and ENE might improve the LHC survival prediction.

Keywords Laryngohypopharyngeal cancer · Lymph node · Metastatic burden · N classification · Survival

Introduction

Laryngohypopharyngeal cancer (LHC) is commonly treated with primary radiotherapy or concurrent chemoradiotherapy as potential organ preservation strategy (Forastiere et al. 2015; Bonomi et al. 2018). Surgery has become generally used as a salvage option after disease failure following a non-surgical treatment approach (Koch 2000). Function-preserving surgery has also evolved along with maintaining a functional larynx with acceptable oncological results compared to a non-surgical approach (Qian et al. 2014; Ahn et al. 2017; Kim et al. 2018). The primary surgical approach is still the standard of care for resectable tumours with extra-laryngeal extension, coexisting chronic disease and prelaryngeal function (Colevas et al. 2018).

The tumour-node-metastasis (TNM) staging manual proposed by the American Joint Committee on Cancer (AJCC) generally guides the prognosis of patients with cancer. The nodal (N) classification for head and neck cancer, the AJCC 7th edition staging system published in 2010, was categorised along with the presence of size (≤ 3 cm and > 3 cm), laterality (ipsilateral and bilateral/contralateral) and number (one and more) of lymph node (LN) metastases to the

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neck (Edge and Compton 2010). The N classification of the AJCC 8th edition staging recently proposed in 2017 involved extra-nodal extension (ENE) in addition to previous factors by allocating single positive LN (LN+) ≤ 3 cm with ENE to the N2a category and 1 LN+ > 3 cm with ENE or ≥ 2 any LN+ with ENE to the N3b category (Amin et al. 2017). However, the AJCC N classifications (7th and 8th editions) do not include the metastatic LN burden that has been increasingly suggested as an important prognostic factor in head and neck cancer (Ebrahimi et al. 2014; Ho et al. 2017, 2018).

Recent studies have shown that overall mortality escalates continuously along with the increased number of LN+ (Ho et al. 2018) and is also associated with a decrease in the number of LNs retrieved from neck dissection in patients with head and neck cancer (Divi et al. 2016a). However, the nodal factors associated with metastatic tumour burden and ENE need to be examined further in patients with LHC undergoing primary surgery. Therefore, we evaluated the nodal factors predictive of recurrence and survival in a LHC cohort of patients who underwent primary surgery involving thorough pathological examinations of cervical LNs from neck dissection. We also examined the role of our proposed N classification including metastatic LN burden and ENE compared with the AJCC and the other N classifications.

Materials and methods

Study patients

Electronic records were used to identify patients who were diagnosed with LHC at our tertiary referral centre from January 2006 to December 2016. Primary surgery versus primary radiation or chemoradiation for each patient was determined by the consensus of our tumour board team. Inclusion criteria were patients with previously untreated LHC who underwent curative primary tumour extirpation and neck dissection, regardless of clinical LN metastasis. Exclusion criteria included patients who underwent primary non-surgical treatments, such as radiotherapy, chemoradiotherapy or induction chemotherapy; referral patients with recurrent tumours, patients with distant metastases at initial staging or palliative treatment and patients with other pathology except squamous cell carcinoma, and those who were lost to follow-up < 2 years after surgery. Patients with early glottic cancer were also excluded because of unnecessary elective neck dissection from a very low rate of occult metastasis (Jakobsen et al. 1998). Finally, 141 consecutive patients were included in this study. Tumours were staged with the AJCC TNM staging manual (7th and 8th editions). This study was reviewed and approved by our institutional review board, and informed consent from each patient was waived.

All patients underwent surgery combined with or without postoperative radiotherapy or chemoradiotherapy. Surgery involved complete resection of loco-regional disease and therapeutic or elective neck dissection. Therapeutic neck dissection was performed at cervical levels I–V or I–VI of patients with a preoperative diagnosis, imaging workups and high-resolution ultrasonography-guided fine-needle aspiration biopsy. The elective neck dissection was performed at cervical levels II–IV of patients at risk of occult metastasis depending on the tumour site and extent, histological grade and invasion. Patients with bilateral or contralateral neck involvement or potential involvement underwent bilateral neck dissection. The neck dissection samples were divided according to neck side and the levels and were sent for pathological examination. Tumour pathology, extent, invasion and margin status were examined. The numbers of total harvested LNs and positive LNs and ENE were carefully and consistently examined in each patient by a board-certified pathologist who had clinical experience > 25 years. In addition, the positive LNs were examined with number of positive LNs at each cervical level, the largest diameter of the metastatic LNs, and the presence of ENE in each patient. ENE was defined as extension of the tumour through the LN capsule as indicated by the finding of cancer cells or an associated peritumoural reaction to extracapsular keratin extension (Apisarnthanarax et al. 2006).

Patients with adverse pathological findings, such as involved margin, perineural or lymphovascular invasion and nodal metastasis (Colevas et al. 2018), underwent postoperative intensity-modulated radiotherapy of median 64 Gy total irradiation dose at 1.8–2 Gy/daily fraction with or without simultaneous platinum-based chemotherapy. The patients were followed up at the outpatient clinic every 1–3 months in the first year, 2–4 months in the second year, every 6 months in the third to fifth years and annually thereafter (Ahn et al. 2017; Joo et al. 2019). Any lesion suspicious of relapse was confirmed by biopsy or serial imaging follow-up if a biopsy was not available. Patients who relapsed underwent salvage or palliative treatments.

Variables

Clinical and pathological variables were included: age (≥ 65 years), sex, smoking (pack-years), alcohol (≥ 1 drinks/day), Eastern Cooperative Oncology Group performance status (≥ 1), tumour site (larynx vs. hypopharynx), histological grade, perineural invasion, lymphovascular invasion and surgical margin status. Nodal factors, including the presence of pathological LN metastasis, number of total harvested and metastatic LNs, LN ratio and ENE were evaluated. T and N classifications and overall TNM stage were assessed.

Statistical analysis

Continuous variables are expressed as mean and standard deviation or median and range, while categorical variables are presented as numbers and percentages. Continuous and categorical variables were compared between the groups with and without regional metastasis at presentation using the *t* test and χ^2 or Fisher's exact test, respectively. Univariate and multivariate Cox proportional hazard regression analyses were used to define significant predictors of overall survival (OS), disease-specific survival (DSS) and disease-free survival (DFS). Variables with multi-collinearity were separately fit (Vatcheva et al. 2016). The cut-off values for the optimal number of positive LNs or the LN ratio were determined using time-dependent receiver operating characteristics (ROC) curve analyses and the area under the ROC curve (AUC) estimates (Heagerty et al. 2000). Hazard ratios and 95% confidence intervals (CIs) were estimated. The Kaplan–Meier and log-rank tests were used to determine survival and statistical significance, respectively.

A new N classification was proposed by binary recursive partitioning analysis (RPA), using significant nodal factors of the number of LNs and ENE that predict survival (Hothorn et al. 2006). The optimised binary RPA estimated a conditional interference tree, based on a permutation test using log-rank statistics with Bonferroni-adjusted *P* values for multiple comparisons. The comparison of survival predictors between the newly proposed N and AJCC 7th and 8th N classifications were assessed by the c-index. The N classification proposed by Ho et al. (2018) was also compared. The 5-year OS and DSS were also compared among the different N classifications.

A *P* value < 0.05 was considered significant, and all statistical tests were two-tailed. The statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

This study included 141 patients [132 male (93.6%) and 9 females (6.4%); median age, 65 years; range 33–78 years]. Table 1 summarises the characteristics of the patients. Laryngeal and hypopharyngeal cancers were found in 98 (69.5%) and 43 (30.5%) patients, respectively. All study patients underwent primary surgery and neck dissection. Ipsilateral and bilateral neck dissection was performed in 44 (31.2%) and 97 (68.8%) patients, respectively, of whom 66 (46.8%) had pathologically positive LNs, and 27 (19.1%) had ENE. The one, two (median) and three quartile numbers of LNs harvested were 42, 60 and 84, respectively: ≤ 18 LNs were observed in only three (0.9%) patients. The median (range) number of LNs examined was 51 (11–128) in the N0 patients and 69 (12–161) in the N + patients. The median (range) number of positive LNs was 1 (0–21) in all study patients and 2 (1–21) in the N + patients. The one, two (median) and three quartile numbers of positive LNs in the N + patients were 1, 2 and 4, respectively: ≥ 5 LN + were observed in 15 (10.6%) patients. At the last follow-up at a median of 60 months (range 24–134), 82 (58.2%) patients were alive without disease; 32 (22.7%) patients died of disease; 23 (16.3%) patients died of other causes and 4 (2.8%) were alive with disease. Site relapses were found in 38 (27.0%) patients. The clinical and pathological characteristics of the patients were compared between the absence and presence of pathological LN metastasis in Supplementary Table S1. Most clinical and pathological variables were comparable between the two groups. Lymphovascular invasion, numbers of harvested and involved LNs, ENE, T

Table 1 Patient characteristics (*N* = 141)

Variable	*N* (%)
Age (years), median (range)	65 (33–78)
Sex	
Male	132 (93.6)
Female	9 (6.4)
Smoking, ≥ 20 pack-years	107 (75.9)
Alcohol, ≥ 1 drink/day	105 (74.5)
ECOG performance scale, ≥ 1	23 (16.3)
Charlson comorbidity index, ≥ 1	60 (42.6)
Tumour site, larynx/hypopharynx	
Larynx	98 (69.5)
Hypopharynx	43 (30.5)
Histologic grade, poorly differentiated	18 (12.8)
Treatment	
Surgery alone	60 (42.6)
Surgery plus RT/CRT	67/14 (47.5/9.9)
Neck dissection, ipsilateral/bilateral	44/97 (31.2/68.8)
No. of patients with positive LNs	66 (46.8)
No. of LNs harvested, median (range)	60 (11–161)
No. of positive LNs, median (range)	1 (0–21)
Extra-nodal extension	27 (19.1)
Follow-up information	
Duration, median (range)	60 (24–134)
Last status	
NED	82 (58.2)
DOD/DOC	32/23 (22.7/16.3)
AD	4 (2.8)
Recurrence, any site	38 (27.0)

AD alive with disease, *CRT* concurrent chemoradiotherapy, *DOC*, died of other cause, *DOD*, died of disease, *ECOG* Eastern Cooperative Oncology Group, *LN* cervical lymph node, *NED* no evidence of disease, *RT* radiotherapy and N classifications, postoperative radiotherapy/chemoradiotherapy and recurrence and deaths were more frequently found in the N + patients than the N0 patients (all $P<0.05$). Five-year OS, DSS and DFS rates of all study patients were 65.5% (95% CI, 61.1–69.9%), 76.3% (72.3–80.3%) and 74.3 (70.4–78.2%), respectively.

Association between clinical/pathological factors and survival

Univariate analyses revealed that tumour differentiation, number of positive LNs, LN ratio, bilateral and lowest neck level involvement, and pN classification were significant factors for all OS, DSS and DFS outcomes (all $P<0.05$) (Supplementary Table S2). Age (≥ 65 years) was a significant variable for OS; tumour site (hypopharynx), perineural and lymphovascular invasion were significant factors for DSS and DFS (all $P<0.05$). In multivariate analyses, tumour differentiation, number of positive LNs and N classification were independent factors for OS, DSS and DFS ($P<0.05$) (Supplementary Table S3). The ENE was not a significant variable for OS and DFS but only for DSS in a univariate analysis. The time-dependent ROC curve analyses showed that the cut-off values for the optimal number of examined and positive LNs and the LN ratio were 80, 4 and 0.03, respectively. The cut-off of positive LNs (≥ 5) had an AUC of 0.719 (95% CI 0.615–0.823), with sensitivity and specificity of 88.3% and 80.5%, respectively, for 5-year OS. The number of positive LNs and LN ratios had significantly higher AUCs than the number of examined LNs ($P<0.05$).

Our proposed N classifications versus the AJCC and other N classifications

Our proposed N classification included the number of positive LNs at cut-offs of 0, 1, 2 and 5. The presence of all pathological ENE was considered the N2 classification. Therefore, the newly proposed N classification was: N0 (0 LN +), N1 (1 LN +), N2 (2–4 LN + or ENE), and N3 (≥ 5 LN +). Table 2 compares the 5-year OS and DSS rates

Table 2 Overall and disease-free survival for the proposed and AJCC TNM nodal staging systems for laryngohypopharyngeal cancer

N category	Criteria	*N* (%)	5-year OS % (95% CI)	5-year DS % (95% CI)
Proposed N staging system				
N0	0 LN+	66 (46.8)	78.5 (72.9–84.1)	89.4 (85.3–93.5)
N1	1 LN+	21 (14.9)	65.5 (54.8–76.2)	79.4 (70.2–88.6)
N2	2–4 LN + or ENE	39 (27.7)	53.4 (44.2–62.6)	66.9 (58.4–75.4)
N3	≥ 5 LN+	15 (10.6)	31.0 (18.2–43.8)	37.8 (23.1–52.5)
Other N staging system proposed by Ho et al. (2018)				
N0	0 LN+	66 (46.8)	78.5 (72.9–84.1)	89.4 (85.3–93.5)
N1	1 LN+	21 (14.9)	65.5 (54.8–76.2)	79.4 (70.2–88.6)
N2	2–3 LN + or ENE	35 (24.8)	59.9 (50.7–69.1)	70.2 (61.6–78.8)
N3a	4–6 LN+	8 (5.7)	46.9 (28.2–65.6)	46.9 (28.2–65.6)
N3b	≥ 7 LN+	11 (7.8)	22.5 (8.5–36.5)	30.0 (12.4–47.6)
AJCC 7th edition N staging system				
N0	0 LN+	66 (46.8)	78.5 (72.9–84.1)	89.4 (85.3–93.5)
N1	1 LN + , ≤ 3 cm	27 (19.1)	63.8 (54.0–73.6)	75.1 (66.3–83.9)
N2a	1 LN + , > 3 cm but ≤ 6 cm	0	–	–
N2b	≥ 2 ipsilateral LN + , ≤ 6 cm	33 (23.4)	60.8 (51.3–70.3)	73.7 (64.8–82.6)
N2c	Bilateral or contralateral ≥ 1 LN + , ≤ 6 cm	15 (10.6)	28.5 (11.5–32.5)	31.9 (18.9–44.9)
N3	≥ 1 LN + > 6 cm	0	–	–
AJCC 8th edition N staging system				
N0	0 LN+	66 (46.8)	78.5 (72.9–84.1)	89.4 (85.3–93.5)
N1	1 LN + , ≤ 3 cm	21 (14.9)	65.5 (54.8–76.2)	79.4 (70.2–88.6)
N2a	1 any side LN + ≤ 3 cm with ENE, or 1 ipsilateral LN + 3–6 cm	8 (5.7)	71.4 (54.3–91.2)	71.4 (54.3–88.5)
N2b	≥ 2 ipsilateral LN + , ≤ 6 cm	20 (14.2)	58.2 (46.0–70.4)	75.5 (64.6–86.4)
N2c	≥ 2 bilateral or contralateral LN + , ≤ 6 cm	7 (5.0)	33.3 (14.1–52.5)	41.7 (19.5–63.9)
N3a	≥ 1 LN, > 6 cm	0	–	–
N3b	1 LN + > 3 cm with ENE or ≥ 2 any LN + with ENE	19 (13.5)	41.6 (29.0–54.2)	44.5 (31.3–57.7)

AJCC American Joint Committee on Cancer, *CI* confidence interval, *DSS* disease-specific survival, *ENE* extra-nodal extension, *LN* lymph node, *OS* overall survival among ours and the other proposed N classifications. Our proposed N classification appeared to discriminate survival rates better than the N staging system proposed by Ho et al. and the AJCC 7th and 8th edition N staging systems. The recently proposed AJCC 8th edition N staging system included the ENE as well as number, size and laterality of LN+: 1 LN+ ≤ 3 cm with ENE is allocated to N2a and 1 LN+ > 3 cm with ENE or ≥ 2 any LN+ with ENE is allocated N3b. However, N3b was not well differentiated from N2c. Figure 1 shows the Kaplan–Meier curves estimating OS according to the differently proposed N classifications. Our proposed N classification appeared to be more discriminating than the other N classifications. In addition, the N classification was more discriminated in the previous AJCC version (7th edition) than the recent version (8th edition). These results might be more supported by the C-index analyses shown in Table 3. Our proposed N staging system appeared to improve the C-index value (0.718) compared to

Table 3 The C-indices of the proposed and AJCC TNM nodal staging systems on overall survival

N category	C-index (95% CI)
Proposed N staging system	0.718 (0.613–0.824)
Other N staging system proposed by Ho et al.	0.706 (0.601–0.811)
AJCC 7th edition N staging system	0.713 (0.607–0.819)
AJCC 8th edition N staging system	0.704 (0.599–0.811)

CI confidence interval, *DSS* disease-specific survival, *OS* overall survival

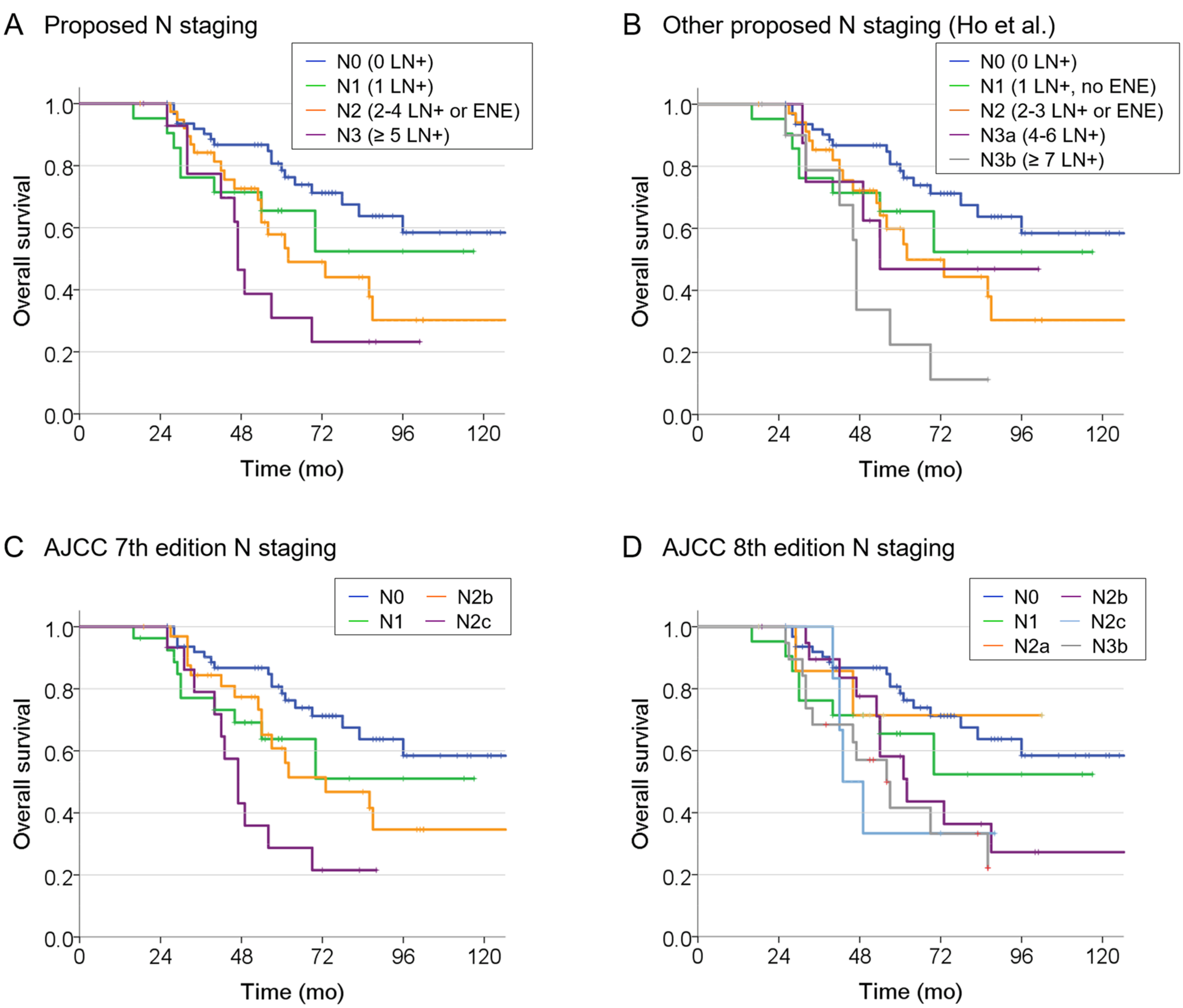

Fig. 1 Kaplan–Meier curves estimating overall survival according to the proposed and AJCC TNM nodal staging systems for laryngohypopharyngeal cancer. Log-rank test, $P < 0.05$. *ENE* extra-nodal extension, *LN* lymph node

the AJCC and the other N classifications (0.704–0.713) in OS predictions. Improved survival discrimination of the proposed N staging system was found for both primary tumour locations of larynx and hypopharynx (see the Supplementary Table S4 and Figure S1).

Discussion

The present study showed the prognostic role of metastatic LN burden in patients with LHC. The incidence rates of pathologically positive LNs and ENE were 46.8% and 19.1%, respectively. This observation might reflect on the high proportion of locally advanced tumours (60.3%) and the inclusion of hypopharyngeal cancer (30.5%) in our cohort. Previous studies showed incidence rates of 32.9% for positive LNs from neck dissection in the patients with laryngeal cancer, 70.8% for locally advanced tumours (Tomik et al. 2001) and 30% for occult LN metastasis even in clinically N0 T3–T4 laryngeal cancer patients, particularly those with a supraglottic location (Kligerman et al. 1995). Hypopharyngeal cancer generally metastasizes more frequently to the regional neck area than laryngeal cancer with an incidence of 80% in patients undergoing primary surgery and neck dissection (Joo et al. 2015; Suzuki et al. 2016). Regional metastasis of LHC is an ominous factor associated with increased recurrence and mortality (Jakobsen et al. 1998; Jover-Espla et al. 2018). Furthermore, the number of LNs involved and examined has been suggested as a better measure of prognosis in patients with head and neck cancer (Divi et al. 2016b; Kuo et al. 2016; Roberts et al. 2016).

Metastatic LN burden was initially calculated using the volumetric measurement of positive LNs, with a larger burden indicating poor survival of patients with LHC (Jakobsen et al. 1998). Later, the quantitative measurement of metastatic tumour burden was simply considered the number of positive LNs (Ho et al. 2018). Previous studies have shown that the number of positive LNs is a critical predictor of mortality from head and neck cancer, eclipsing other features of LN + size and laterality including the AJCC N classifications (Ebrahimi et al. 2014; Ho et al. 2017, 2018). One study examined the prognostic role of metastatic LN burden in 14,554 patients with oral cavity cancer identified in the National Cancer Data Base (NCDB) (Ho et al. 2017). Overall mortality escalated continuously with an increase in the number of LN + and decreased along with an increasing number of total LNs examined (Ho et al. 2017). Another international multicentre study of 3704 patients with oral cavity cancer also showed the prognostic value of the number of LN + regardless of unilateral or bilateral cervical metastasis (Ebrahimi et al. 2014). The number of LN + was better for discriminating patient survival of N2b and N2c in the category of ≤ 2, 3–4 and ≥ 5 than the LN laterality itself in terms of OS and DSS outcomes in patients with oral cavity cancer (Ebrahimi et al. 2014). The prognostic role of metastatic LN burden has also been suggested in patients with LHC undergoing surgery and neck dissection (Ho et al. 2018). As shown for oral cavity cancer, an increasing number of LN + continuously escalates overall mortality of LHC patients without a plateau, while other nodal factors of LN size, laterality and lower neck involvement are not associated with mortality (Ho et al. 2018). The present study also supports these previous findings of the relationship between metastatic LN burden and post-treatment survival. Metastasis via the lymphatic system decreases antitumor immunity, promotes tumour growth, and disseminates to systemic tumour burden, which might have impact on ultimate patient survival (Jones et al. 2018). Quantitative nodal burden might be considered as a very-high-risk in head and neck cancer patients benefiting from adjuvant therapy including intensification with chemoradiotherapy and immunotherapy (Denaro and Merlano 2018; Zumsteg et al. 2019), which warrants additional investigations.

Previous studies have suggested that the number of LNs examined is associated with survival from head and neck cancer as shown for the number of LN + (Divi et al. 2016a, b; Kuo et al. 2016; Ho et al. 2017, 2018). The identification of < 18 LNs examined in neck dissection samples was associated with increased overall mortality (HR 1.24–1.38) compared with ≥ 18 LNs in a large cohort of patients with mucosal head and neck cancer (Divi et al. 2016a, b). Another study showed the same results with a cut-off of 16 LNs for clinical N0 and 26 LNs for clinical N + examined in oral cavity cancer patients identified from the NCDB (Kuo et al. 2016). These findings suggest that more extensive neck dissection is required to improve survival of patients with head and neck cancer. However, the number of LNs examined was not associated with DFS, DSS or OS outcomes in our study. This may have been caused by a limitation in the number of patients included and the high yield of LNs from neck dissection (≥ 18 LNs in 99.1% of study patients). The LN ratio, numbers of LN + divided by numbers of LN examined (Zheng et al. 2018), has also been suggested as an important prognostic factor of recurrence and survival in patients with LHC (Joo et al. 2015; Suzuki et al. 2016). This was not supported by the NCDB study that included a large cohort of 12,437 patients with head and neck cancer, showing inferiority of the LN ratio compared to the number of LN + (Roberts et al. 2016).

The size, number, laterality and ENE included in the AJCC N classification remain poorly defined among different anatomical sites and pathological types of head and neck cancers. Recent studies from the NCDB and international multicentres have shown that size and laterality are not strong prognostic indicators in head and neck cancer (Ebrahimi et al. 2014; Divi et al. 2016a; Ho et al. 2017, 2018). ENE remains a significant factor for mortality after surgery for head and neck cancer (Ebrahimi et al. 2014; Ho et al. 2017, 2018). The modest significance of ENE in our study may have resulted from the limited number of patients included. Therefore, the recently proposed N classification included only two nodal factors, such as the number of LN + and ENE in a LHC cohort (Ho et al. 2018). The study included 1 LN + with ENE in the N2 category, as in the AJCC 8th edition N classification, and the N3 category regardless of ENE. The newly proposed N classification improved the predictive capacity of post-treatment OS compared to the AJCC 8th edition. In the present study, the ENE was included only in the N2 category. Greater than or equal to 5 LN + was allocated to the N3 category without subdividing N3a and N3b along with an increasing number of LN + because of the poor discrimination between N2 and N3a (4–6 LN +) proposed previously (Ho et al. 2018). Instead, the N3 category included an increased number of LN + compared with the previous report. Along with this revision, our proposed N staging appeared to improve survival predictability compared with the AJCC 8th edition and the other N classifications. Our proposed N classification is simple but needs to be validated in prospective cohort and multicentre/nationwide studies. Therefore, identifying the metastatic LN burden might improve the prognostic stratification and the selection of patients with additional benefits from postoperative chemoradiotherapy (Zumsteg et al. 2019).

In conclusion, the present study suggests the prognostic role of metastatic LN burden in patients with LHC who undergo surgery and neck dissection. Our newly proposed N classification includes the number of LN + and ENE and allocates patients to one of four categories of N0 (0 LN +), N1 (1 LN +), N2 (2–4 LN + or ENE) and N3 (≥ 5 LN +). The new N staging system might improve the predictive capability of survival in patients with LHC, but needs to be further validated in a large multicentre cohort.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to disclose.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. Informed consent from all individual participants was waived because of the retrospective nature of this study.

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