

Scientific Article

The Number of Radiographically Positive Lymph Nodes Further Stratifies Patient Survival Among Clinical N1 Patients With Human Papillomavirus –Associated Oropharyngeal Cancer



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Received November 7, 2021; accepted January 30, 2022

Abstract

Purpose: Human papillomavirus–associated oropharyngeal squamous cell carcinoma (HPV[+]OPSCC) requires further study to optimize the existing clinical staging system and guide treatment selection. We hypothesize that incorporation of the number of radiographically positive lymph nodes will further stratify patients with clinical N1 (cN1) HPV(+)OPSCC.

Methods and Materials: A post hoc analysis from 2 prospective clinical trials at a high-volume referral center was conducted. Patients underwent primary tumor resection and lymphadenectomy, followed by either standard-of-care radiation therapy (60 Gy in 30 fractions) with or without cisplatin (40 mg/m² weekly) or de-escalated radiation therapy (30 Gy in 20 twice-daily fractions) with concomitant 15 mg/m² docetaxel once weekly. Imaging studies were independently reviewed by a blinded neuroradiologist classifying radiographic extranodal extension (rENE) and the number and maximal size of involved lymph nodes. Patients without pathologic data available for assessment were excluded.

Results: A total of 260 patients were included. Of these, 216 (83%) were cN1. Patients had a median of 2 radiographically positive lymph nodes (range, 0–12), and 107 (41%) had rENE. For cN1 patients, stratifying by radiographically positive lymph nodes (1–2 vs 3–4 vs >4) was predictive of progression-free survival (PFS) ($P = .017$), with 2-year PFS rates of 96%, 88%, and 81%, respectively. More than 2 radiographically positive lymph nodes was identified as a significant threshold for PFS ($P = .0055$) and overall survival ($P = .029$). Radiographic ENE and lymph node size were not predictive of PFS among cN1 patients.

Sources of support: This work had no specific funding.

Disclosures: The wife of Dr Kowalchuk is a senior technical product manager for GE Healthcare. All other authors have no disclosures to declare.

Data sharing statement: Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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<https://doi.org/10.1016/j.adro.2022.100926>

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Conclusions: The number of radiographically positive lymph nodes is predictive of PFS and overall survival and could be used to meaningfully subcategorize cN1 patients with HPV(+)OPSCC. We recommend further validation of our proposal that cN1 patients with 1 to 2 radiologically positive lymph nodes be categorized as cN1a, patients with 3 to 4 radiologically positive lymph nodes categorized as cN1b, and patients with >4 radiographically positive lymph nodes categorized as cN1c.

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Introduction

Human papillomavirus (HPV)–associated oropharyngeal squamous cell carcinoma (HPV[+]OPSCC) remains an active area of research in the setting of favorable patient outcomes compared with other cancers of the head and neck,¹ and corresponding efforts to refine or de-escalate therapy are ongoing.^{2,3} However, such studies have demonstrated that further stratification of patient-specific disease is required.^{4,5} Pathologic extranodal extension (pENE), radiographic ENE (rENE), the number of involved lymph nodes, and many other factors have been analyzed in this context.¹ Some authors have reported on the prognostic value of ENE,^{6,7} but others have focused on the number of involved lymph nodes as the principle prognostic factor.^{8–10}

Two staging systems are commonly used for HPV(+) OPSCC: clinical staging and pathologic staging.¹¹ Although these systems effectively stratify patients, many analyses have identified additional factors which may improve risk categorization. The number of radiographically positive lymph nodes has not been thoroughly explored in this context, despite some suggestions that this factor could be more predictive of outcomes than ENE.^{12,13} One particular area of need involves the clinical N1 (cN1) designation. Patients remain cN1 if at least 1 ipsilateral involved lymph node is identified as ≤ 6 cm; however, an increasing number of ipsilateral involved lymph nodes does not increase a patient's risk to cN2 or cN3. This definition is in direct contrast to the pathologic nodal category, which simply relies on the number of pathologically involved lymph nodes.

As imaging studies continue to improve and more accurately assess a patient's disease characteristics, we hypothesize that incorporating the number of radiographically positive lymph nodes within clinical staging paradigms may further stratify cN1 patients.¹⁴ One group previously showed that patients with up to 4 radiographically positive lymph nodes had a 93% to 94% chance of remaining pathologic N0-1 (pN0-1) after surgical resection, demonstrating strong concordance between radiologic and pathologic lymph node involvement.¹⁵ These results suggest that patient stratification by radiographic assessment of the number of involved nodes should be further explored.

Accordingly, we conducted a post hoc analysis of patients enrolled in 2 prospective clinical trials to evaluate whether the cN1 categorization is improved by

incorporation of the number of radiographically positive lymph nodes, nodal size, or rENE.

Methods

Patient inclusion

A set of 262 patients was selected for this analysis, consisting of a post hoc analysis of patients previously enrolled in 2 prospective clinical trials: MC1273 (ClinicalTrials.gov identifier: NCT00606294) and MC1675 (ClinicalTrials.gov Identifier: NCT02908477). These trials included patients with HPV(+)OPSCC, ≤ 10 pack-year smoking history, and negative margins after surgical resection. Patients all had at least 1 of the following criteria: a lymph node > 3 cm, at least 2 positive lymph nodes, perineural invasion, lymphovascular space invasion, T3 or T4 primary disease, or ENE. A small fraction of patients enrolled in the second trial were not included in this database because the trial was still enrolling at the time of this project's initiation. These trials analyzed outcomes of de-escalated adjuvant radiation therapy for HPV(+)OPSCC after surgical resection and lymphadenectomy. The experimental arm consisted of docetaxel 15 mg/m² on days 1 and 8, with radiation therapy prescribed to 30 Gy in 20 1.5-Gy fractions delivered twice daily over 2 weeks. The radiation therapy dose was also escalated to 36 Gy in cases of pENE, with a 1-cm margin from preoperative imaging. The standard-of-care arm involved adjuvant radiation therapy: 60 Gy in 30 daily fractions to the ipsilateral neck and primary and 54 Gy in 30 fractions to the uninvolved, undissected neck, with or without concurrent cisplatin chemotherapy based on the presence or absence of ENE. The final delineation of pENE was made by the pathologist and was recorded as present if any ENE was identified. Institutional review board approval was obtained, and the study was conducted using best ethical and research practices.

Data acquisition

Head and neck computed tomography with contrast and positron emission tomography /computed tomography images were collected and independently reviewed by a radiologist who specializes in head and neck radiology and metabolic imaging (A.A.N.). The radiologist was blinded to both pathologic data and clinical outcomes. Important imaging findings assessed included the

maximal primary tumor size, number of involved lymph nodes, laterality of involved nodes, maximal size of the largest node in any dimension, and the presence of rENE. Features concerning for radiographic ENE included indistinct nodal margins, frank extension of the tumor into perinodal soft tissue, matted nodes, and/or evidence of tethering to adjacent structures with loss of the intervening fat plane. Not all imaging was performed at our institution, but all imaging studies were of sufficient quality for consideration in clinical trial enrollment. If an imaging study was repeated before trial enrollment, the repeated study was used for the analysis.

Imaging findings were correlated with pathologic findings obtained after robotic surgical resection. Surgical resection involved primary tumor resection and neck dissection. All patients were required to have pathologic results available for review for inclusion in the study. Key results included the maximal primary tumor size, number of involved lymph nodes, maximal size of the largest node in any dimension, presence of pENE, and extent of lymph node dissection. Per institutional practice, ipsilateral levels II–IV were almost universally dissected, whereas ipsilateral levels I and V, retropharyngeal nodes, and contralateral nodal levels were generally dissected only if indicated by disease-specific characteristics (eg, clinical concern for pathologically involved lymph nodes or a midline base of tongue tumor). Patient outcomes and recurrence information were updated from the initial prospective outcomes via retrospective chart review performed by the study investigators.

Endpoints

We analyzed the association of clinical staging factors, lymph node characteristics, and rENE with outcomes of loco-regional control, distant metastasis-free survival, progression-free survival (PFS), and overall survival (OS). Clinical and pathologic staging categories were both reported, and the number of radiographically involved lymph nodes was assessed as a stratifying factor for cN1 patients, as well as for the entire cohort. Clinical and pathologic staging used American Joint Committee on Cancer 8th edition staging for HPV(+)OPSCC. Furthermore, a threshold the number of radiographically positive lymph nodes predictive of PFS was sought within this group of cN1 patients. The predictive values of rENE and pENE were also considered. Finally, the potential predictive and prognostic value of a threshold of >4 radiographically involved lymph nodes was assessed because this directly correlates with the pN2 staging group.

Statistics

Statistical analysis involved the use of the Kaplan-Meier method to estimate and analyze the primary

endpoint of PFS, with use of the univariate log-rank test to determine statistical significance. In all cases, a threshold of $P < .05$ was used for statistical significance. Univariate Cox proportional hazards regression analyses were also performed to consider the hazard ratios of potential predictive factors for PFS, including cN2, pN2, and the number of radiographically positive lymph nodes; 95% confidence intervals (CIs) were presented for each hazard ratio.

Results

Patient cohort

From an initial data set of 262 patients, 260 were included after the exclusion of 2 patients owing to insufficient pathologic data. The majority of patients were male (90%) and all patients presented with pathologically confirmed squamous cell carcinoma of the tonsil or base of tongue. In each case, the HPV status of the tumor was verified by p16 immunohistochemistry (>70% diffuse nuclear and cytoplasmic staining) and/or HPV DNA in situ hybridization (HPV16, 18, 31, 33, or 51).

Patients had a median of 2 radiographically positive lymph nodes (range, 0–12; interquartile range [IQR], 1–4), and the median maximal dimension of the radiographically identified involved lymph nodes was 3.5 cm (IQR, 2.8–4.2 cm). On preoperative imaging, 107 patients (41%) had rENE and 152 (58%) were identified after surgical resection as having pENE. A median of 2 pathologically involved lymph nodes were found after surgery (range, 0–15; IQR, 1–3), and the median maximal dimension of the pathologically identified involved nodes was 4 cm (IQR, 3.03–4.78 cm).

After a median 33 months of follow-up (IQR, 22–53 months), 16 patients (6%) died. Of these, 9 (56%) died secondary to progressive disease. Overall, 10 (63%) had evidence of disease progression before death. Eighteen total patients (7%) were diagnosed with locoregional recurrence, and 18 (7%) developed distant metastatic disease.

The frequencies of each clinical and pathologic staging category are shown in Table 1. Whereas the number of clinically (radiologically) involved lymph nodes generally corresponded to the number of pathologically involved lymph nodes, rENE only demonstrated sensitivity and specificity of 54% and 71%, respectively, for pENE, as previously reported.¹⁵

Clinical staging

Patients with cN1 disease had 2-year PFS of 93%, whereas patients with cN2–3 disease had 2-year PFS of

Table 1 Characteristics of patients by clinical and pathologic staging categories

TNM stage	cT category	pT category	cN category	pN category	cTNM stage	pTNM stage
0	32	0	7	3	0	0
1	98	107	216	219	207	198
2	114	117	31	38	38	53
3	8	25	6	N/A	15	9
4	8	11	0	N/A	0	0

Abbreviations: c = clinical; N/A = not applicable; p = pathologic; TNM = tumor, node, metastases.

75%. Similarly, patients with pN1 had 2-year PFS of 94%, compared with 67% for pN2.

Radiographically identified involved lymph nodes

The number of radiographically positive lymph nodes was a strong predictor of PFS (hazard ratio [HR], 3.29; 95% CI, 1.70-6.38). When analyzing only cN1 patients (ie, only clinical evidence of ipsilateral neck involvement), the number of radiographically positive nodes, categorized as 1 to 2 versus 3 to 4 versus >4, demonstrated a statistically significant difference in PFS ($P = .02$) between the groups (Fig. 1). Patients with 1 or 2 radiographically involved lymph nodes had comparable 2-year PFS of 97% and 96%, respectively. Accordingly, this discretization was chosen to split 1 to 2 versus 3 to 4 radiographically involved lymph nodes as well as >4 radiographically involved lymph nodes (owing to the correlation with pN2 staging category). The 2-year PFS rates for these 3 groups of cN1 patients were 96% (1-2 radiographically positive

nodes), 88% (3-4 radiographically positive nodes), and 81% (>4 radiographically positive nodes), but wide CIs for PFS were demonstrated for the group with >4 radiographically positive nodes, owing to a small subset of such patients. Radiographic ENE was predictive of decreased PFS for the entire cohort (HR, 2.81; 95% CI, 1.45-5.43), as shown in Figure 2. However, when restricting the analysis to only cN1 patients, rENE was no longer a statistically significant predictor of PFS ($P = .13$). Maximal lymph node size was also not predictive of decreased PFS for the full cohort or specifically for cN1 patients. No relationship was found using different thresholds for maximal lymph node size or via assessment of lymph node size as a continuous variable.

Owing to the potentially confounding influence of the cT category, the relationship of the number of radiologic positive nodes to outcomes was reassessed after exclusion of cT3 and cT4 patients. More than 2 radiographically positive lymph nodes still demonstrated a statistically significant reduction in PFS ($P = .02$). These findings were consistent with the results of the Cox hazards analysis, which also showed decreased PFS with >2

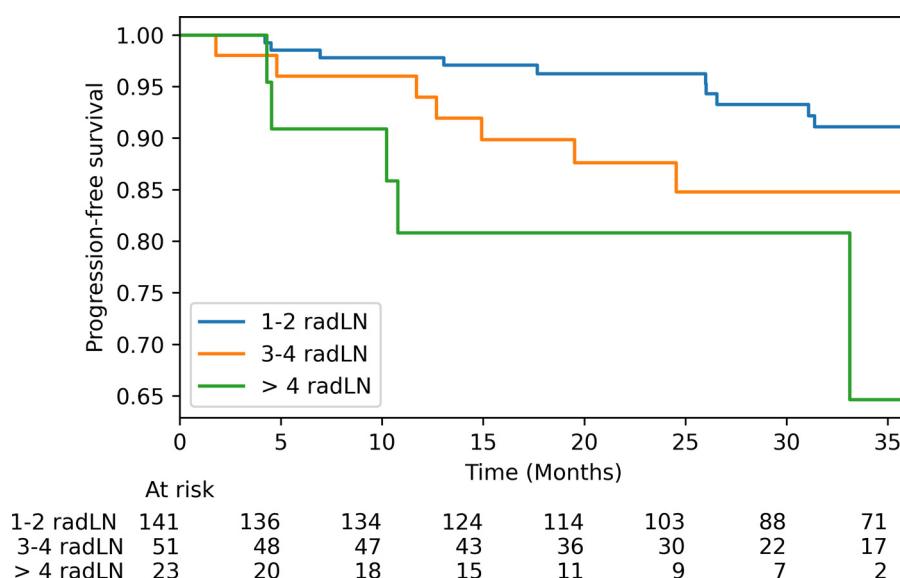


Fig. 1 Stratification of clinical N1 patients by radiographically identified involved lymph nodes (radLN) demonstrated a statistically significant association with progression-free survival ($P = .02$).

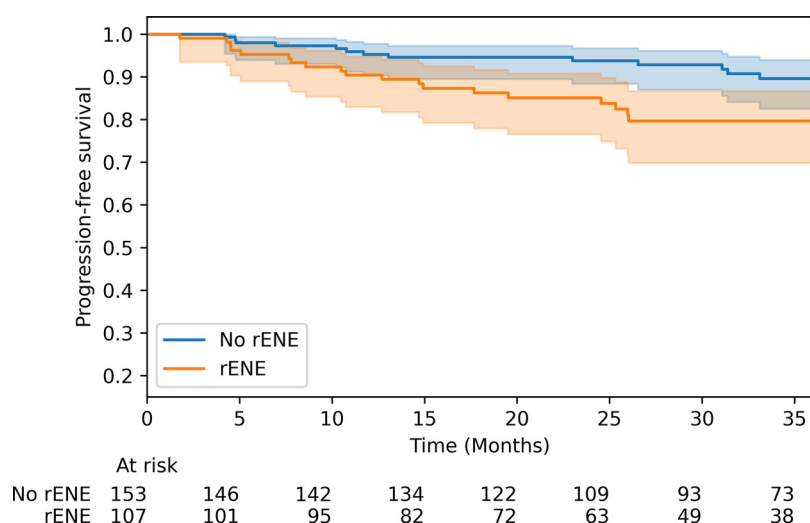


Fig. 2 Radiographically identified extranodal extension (rENE) was predictive of decreased progression-free survival (d , $P = .001$).

radiographically involved lymph nodes (HR, 2.93; 95% CI, 1.32-6.48). On Kaplan-Meier analysis, >2 radiographically positive lymph nodes was identified as a significant threshold for PFS ($P = .006$) as well as OS ($P = .03$) (Fig. 3). Furthermore, >2 radiographically positive lymph nodes was also predictive of both decreased and loco-regional tumor control ($P = .02$) and distant metastasis-free survival ($P = .01$). A univariate Cox hazards analysis for clinical and pathologic categorizations is presented in Table 2.

These findings suggest that the number of radiographic nodes (and not rENE or maximum nodal size) could be used to further categorize cN1 patients. This proposed reclassification of cN1 patients using the number of radiographically positive lymph nodes (1-2 = cN1a, 3-4 = cN1b, and >4 = cN1c) is portrayed in Figure 4.

Discussion

Our findings suggest that the number of radiographically positive lymph nodes is a significant predictor of PFS and OS in clinical N1 patients with HPV(+)OPSCC treated with surgery and de-escalated chemoradiotherapy. Importantly, although the number of positive lymph nodes was predictive of PFS for cN1 patients, rENE was not. In addition, lymph node size was not a significant predictor of PFS. A combined category system incorporating both the existing clinical staging system and the number of radiographically involved lymph nodes would stratify patients initially staged as cN1 into cN1a (1-2 radiographically positive lymph nodes), cN1b (3-4 lymph nodes), and cN1c (>4 lymph nodes), with 2-year PFS of 96%, 88%, and 81%, respectively. A vital threshold of >2

radiographically positive lymph nodes was identified, which predicted reduced PFS and OS. After further validation, this stratification may serve to better select patients for appropriate therapy by further refining the existing clinical staging system.

These results directly address a potential limitation of the American Joint Committee on Cancer 8th edition clinical staging system, as the number of clinically involved nodes (≤ 6 cm) does not alter the nodal category unless there are contralateral or bilateral lymph nodes. This fact remains in direct contrast to pathologic nodal categories, generally considered to be the “gold standard,” which simply stratify by the number of pathologically involved nodes. Our proposed expansion of the cN1 category directly addresses this dichotomy. Indeed, clinical decision-making already indirectly incorporates the number of involved lymph nodes, because the extent of radiation therapy fields and the need for chemotherapy are influenced by the number and location of involved lymph nodes.¹⁶ Patients in this study with >2 radiographically involved lymph nodes also had reduced loco-regional tumor control and distant metastasis-free survival, demonstrating that an increasing number of radiographically positive lymph nodes is predictive of both loco-regional recurrence and development of distant metastasis. One application of this system could be to refine enrollment criteria for future de-escalation studies. It may be that cN1b (and especially cN1c) patients are suboptimal candidates for de-escalation of radiation therapy and/or chemotherapy. For example, we found that a patient with our cN1c classification had 2-year PFS of 81%, whereas cN2 patients had a similar 2-year PFS of 75%. We encourage future studies to report outcomes as stratified by the number of radiographically involved lymph nodes to verify this finding.

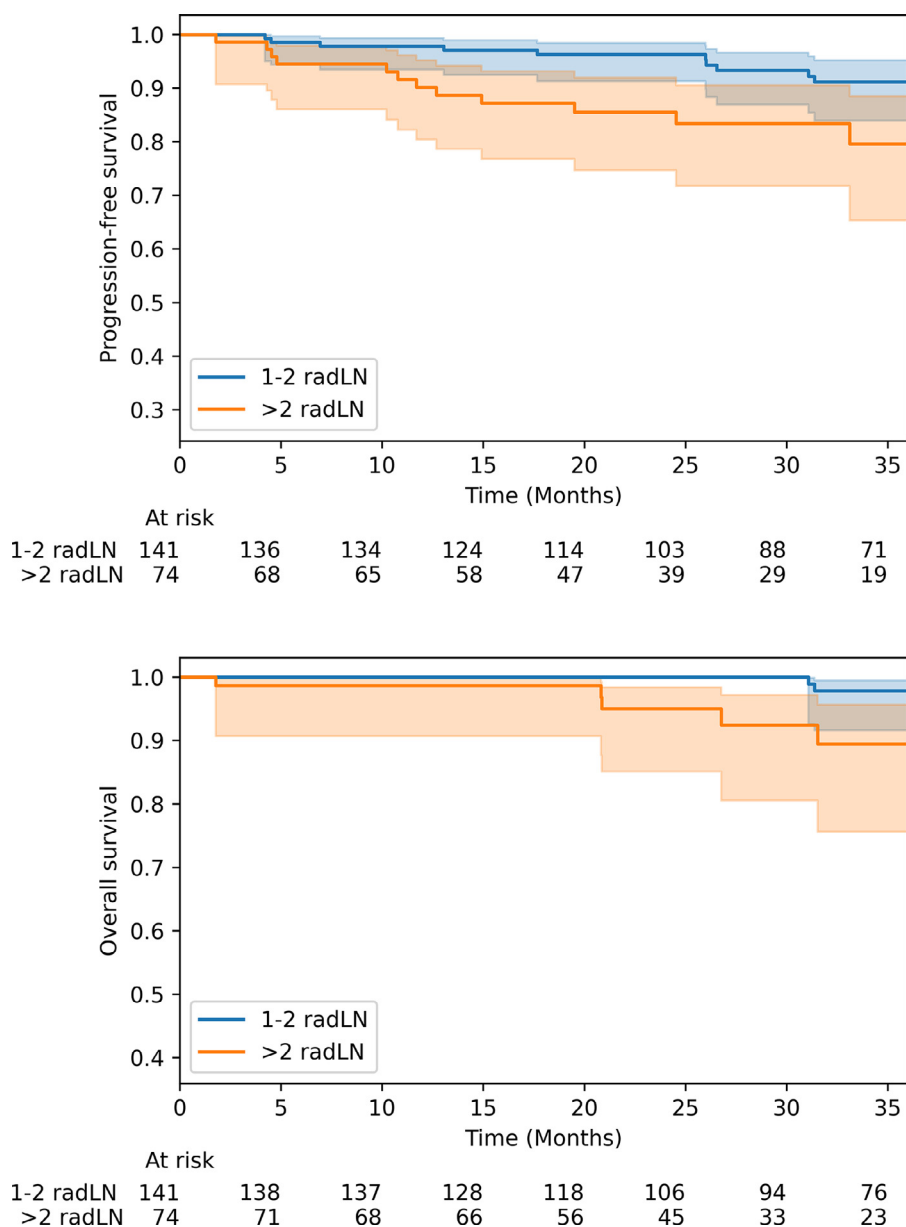


Fig. 3 Among clinical N1 patients, having >2 radiographically identified involved lymph nodes (radLNs) was predictive of decreased progression-free survival (A, $P = .006$) and decreased overall survival (B, $P = .03$).

Table 2 Predictors of progression-free survival for the entire cohort and for only clinical N1 patients*

Comparison	Entire cohort, HR (95% CI)	cN1 only, HR (95% CI)
pN2 vs pN0-1	6.33 (3.33-12.03), $P < .001$	5.95 (2.43-14.55), $P < .001$
cN2 vs cN0-1	3.17 (1.62-6.20), $P = .001$	†
rENE vs no rENE	2.81 (1.45-5.43), $P = .002$	1.83 (0.83-4.01), $P = .13$
pENE vs no pENE	3.64 (1.60-8.31), $P = .002$	2.41 (1.001-5.78), $P = .05$
cT3-4 vs cT0-2	1.97 (0.77-5.09), $P = .16$	1.29 (0.30-5.58), $P = .74$
>2 radLNs vs ≤2 radLNs	3.29 (1.70-6.38), $P < .001$	2.93 (1.32-6.48), $P = .008$
Maximum size LN, per 1 cm	1.14 (0.86-1.52), $P = .37$	1.09 (0.74-1.61), $P = .66$
Maximum LN size >3 cm	0.95 (0.49-1.83), $P = .87$	0.91 (0.40-2.06), $P = .82$

Abbreviations: c = clinical; ENE = extranodal extension; HR = hazard ratio; LN = lymph node; p = pathologic; r = radiographically predicted; radLN = radiographically identified involved lymph node.

* Results were based on univariate Cox hazards analyses. The hazard ratio is presented with the 95% confidence interval for each factor analyzed.

† Not conducted because this was a cN1 subset.

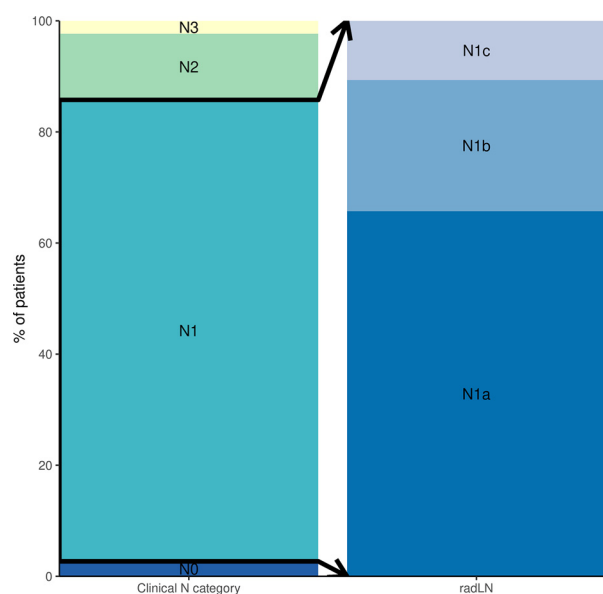


Fig. 4 The proposed subcategorization of the clinical N1 category is portrayed.

A widely accepted practice in both operative and non-operative paradigms is to recommend the addition of chemotherapy, most commonly cisplatin, to a treatment regimen when there is evidence of ENE. There is currently debate about what degree of ENE should merit the addition of chemotherapy and whether ENE should be included in the cN and pN staging systems for HPV(+) OPSCC.^{17,18} In our study, both rENE and pENE were predictive of PFS for all patients. Within the cN1 cohort, however, only the number of radiographically positive lymph nodes and pENE were predictive of patient outcomes. The inability of rENE to discriminate outcomes for cN1 patients supports the inconclusive findings noted in the literature concerning its predictive power.^{14,19} In contrast, multiple studies support the prognostic value of pENE, and reduced OS in patients with HPV(+)OPSCC with pENE has been demonstrated.^{20,21} This distinction underscores the critical importance of separately verifying the predictive power of radiographically identified and pathologically identified predictors of patient outcomes. Although our results support the use of pENE when available, further study is required regarding whether rENE should be used to guide patient treatment.

Our analysis also considered lymph node size as a predictor of PFS, but it failed to demonstrate even a statistical trend for all patients or for cN1 patients. Because our study population included patients enrolled in 2 de-escalation trials, there may have been insufficient cases of large lymph node size (only 6 cN3 patients) to analyze it as a predictor of outcomes; however, neither node size as a continuous variable nor a node size >3 cm (n = 167) predicted for PFS. Although there have been some reports that lymph node size is associated with ENE in HPV(+)

OPSCC, our results are not consistent with further stratification by this variable.²²

A key limitation of this analysis is that the data are derived from a single institutional experience. However, this is balanced by the rigorous criteria required for clinical trial enrollment and the fairly uniform treatment of patients on these protocols that allows for direct comparison with other de-escalation protocols. Because these patients were treated in an operative fashion, further validation of this stratification is necessary in a patient cohort treated with nonoperative paradigms. Additionally, a single radiologist reviewed the imaging, so future analyses could assess the interrater reliability of radiographically positive lymph nodes among radiologists to reveal the reproducibility of this variable. External validation would also be beneficial to verify the conclusions reported in this study. Another limitation of this analysis is the relatively few patients with >4 radiologically identified lymph nodes available for assessment. This was an inherent limitation of our study, as we studied patients who were candidates for de-escalated radiation therapy.

Conclusion

The number of radiographically positive lymph nodes is predictive of PFS and OS and could be used to meaningfully subcategorize cN1 patients with HPV(+)OPSCC. We recommend further validation of our proposal that cN1 patients with 1 to 2 radiologically positive lymph nodes be categorized as cN1a, patients with 3 to 4 radiologically positive lymph nodes categorized as cN1b, and patients with >4 radiologically positive lymph nodes categorized as cN1c.

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