Patterns of nodal metastasis and prognosis in human papillomavirus–positive oropharyngeal squamous cell carcinoma

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ABSTRACT: *Background.* The current American Joint Committee on Cancer (AJCC) staging system may not accurately reflect survival in patients with human papillomavirus (HPV)-positive oropharyngeal squamous cell carcinoma (SCC). The purpose of this study was to develop a system that more precisely predicts survival.

Methods. CT scans from 156 patients who underwent chemoradiation for advanced-stage oropharyngeal SCC with >2 years follow-up were reviewed. We modeled patterns of nodal metastasis associated with different survival rates. We defined $_{HPV+}$N1 as a single node <6 cm, ipsilaterally, contralaterally, or bilaterally. $_{HPV+}$N2 was defined as a single node ≥6 cm or ≥2 nodes ipsilaterally/contralaterally or ≥3 nodes bilaterally. $_{HPV+}$N3 was defined as matted nodes.

Results. There was no significant difference in disease-specific survival (DSS; $p = .14$) or overall survival (OS; $p = .16$) by AJCC classification. In patients grouped by $_{HPV+}$N1, $_{HPV+}$N2, and $_{HPV+}$N3 nodal classification, significant differences in DSS (100%, 92%, and 55%, respectively; $p = .0001$) and OS (100%, 96%, and 55%, respectively; $p = .0001$) were found.

Conclusion. A staging system with reclassification of size, bilaterality, and matted nodes more accurately reflects survival differences in this cohort of patients. Review of the AJCC staging system with these criteria should be considered for HPV-positive oropharyngeal SCC. © 2014 Wiley Periodicals, Inc. *Head Neck* **36:** 1233–1240, 2014

KEY WORDS: oropharyngeal squamous cell carcinoma, human papillomavirus, American Joint Committee on Cancer Staging System, matted nodes, nodal metastasis

INTRODUCTION

Patients with oropharyngeal squamous cell carcinoma (SCC) that are human papillomavirus (HPV)-positive have a good prognosis despite most patients presenting with advanced stage III and IV disease. In a recent review of 2 clinical trials examining HPV status and survival in oropharyngeal SCC, the Radiation Therapy Oncology Group reported that over 66% of patients (478 of 721) presented with advanced classification (N2 or N3) nodal disease.[1] Despite the advanced nodal classification at presentation, the strongest predictor of survival was HPV status, with a 3-year overall survival (OS) of 83.6% in this cohort.[1]

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The American Joint Committee on Cancer (AJCC) 2010 guidelines currently stage regional metastasis in oropharyngeal SCC based on size, number, and laterally of lymph nodes involved with cancer.[2] Although the staging system is continually updated every 5 years, the nodal staging system for oropharyngeal SCC has not been modified since its inception in 1977. With the improved survival in patients with oropharyngeal SCC who are HPV-positive, the AJCC staging system may not accurately reflect survival in this virally associated disease.

Currently, there are a number of clinical trials evaluating de-escalation in patients who are HPV positive. The logic around de-escalation is to treat patients less aggressively who present with more-advanced-stage disease. What if these patients are presenting at a more advanced stage because we are staging them with a system that does not apply to patients who are HPV positive? As we learn more about the molecular biology of cancers, one could imagine that we need to stage patients with a particular biology by 1 set of TNM criteria differently than another group of patients with a different biology, despite the fact that the disease is arising from the same site.

These types of adjustments have been made in other sites, such as breast cancer with the *BRCA* gene. If the disease is biologically different, perhaps at certain disease sites the disease will present differently based on TNM criteria.

Reconsideration of the staging system could refine risk stratification for oropharyngeal SCC that may facilitate a return to the design of clinical trials based on risk stratification rather than the gross approach of de-escalation for patients who are presenting with a virally associated disease. We hypothesize that there are patterns of nodal metastasis in HPV-positive oropharyngeal SCC that are associated with varied survival outcomes more predictive than the current AJCC system.

MATERIALS AND METHODS

Study population

All patients underwent a uniform clinical protocol consisting of weekly concomitant carboplatin, paclitaxel, and intensity-modulated radiation therapy for advanced-stage (III and IV) oropharyngeal SCC between 2003 and 2010. Patients were eligible for this study if they presented with previously untreated, AJCC nodal classification N1, N2, or N3, pathologically confirmed SCC of the oropharynx who were HPV-positive. Staging was performed in accordance with the 2010 American Joint Committee on Cancer staging system with a clinical examination, direct laryngoscopy in the operating room, and CT scan and/or CT/positron emission tomography. Patients were excluded if they had previous surgery or radiation therapy to the upper aerodigestive tract or neck imaging was not performed within 4 weeks of the initiation of treatment.

Population characteristics

One hundred fifty-six patients who met all inclusion criteria were identified, and baseline characteristics are shown in Table 1. There were 215 patients who were initially screened for enrollment in this study. Ten patients were excluded because pretreatment imaging was unavailable for review and 19 patients were excluded because inadequate tissue was available for analysis. There were 17 HPV-negative patients and 13 patients classified as AJCC N0 were also excluded. There were 143 male patients and the mean age of the cohort was 56.1 years. The frequencies of involved subsites were 45% (70 of 156) base of tongue, 54% (84 of 156) tonsil, and 1% (2 of 156) posterior pharyngeal wall. There were 30% (47 of 156) who had T4 tumors. Tobacco status was defined categorically as never, prior (quit >6 months before diagnosis), or current use of cigarettes, cigars, pipe, chewing tobacco, snuff, or snus. There were 50 never tobacco users, 56 prior tobacco users, and 50 current tobacco users.

TABLE 1. Baseline characteristics of the entire cohort.

Characteristics	Entire cohort $n = 156$ (number)
Age	
Mean	56.3
Subsite	
Base of tongue	45% (70)
Tonsil	54% (84)
Posterior pharyngeal wall	1% (2)
Overall stage	
III	7% (11)
IV	93% (145)
T classification	
T1	20% (31)
T2	37% (57)
T3	13% (21)
T4	30% (47)
N classification	
N1	9% (14)
N2a	8% (13)
N2b	42% (66)
N2c	25% (39)
N3	15% (24)
Tobacco status	
Never	32% (50)
Prior	36% (56)
Current	32% (50)

Tissue microarray and immunostaining

A tissue microarray (TMA) was constructed for 146 of 156 patients from pretreatment biopsies of the primary tumor by a previously described method.[3] There were 10 patients who did not have adequate tissue for TMA construction, therefore, single slides were made from paraffin-embedded tissue samples and stained concurrently with the TMA. Separate cores were taken for DNA extraction and polymerase chain reaction (PCR) analysis.

Staining for p16 was performed per protocol supplied by the kit (CINtec ^{p16INK4a} Histology Kit; MTM Laboratories, Westborough, MA). Antibody binding was scored by a pathologist (J.B.M.), using a continuous scale (ie, 10%, 30%, 90%, etc.) for the proportion of p16-positive tumor cells in each core or slide and the percentage scored was broken down into a quartile scale of 1 to 4: 1 was <5%; 2 was 5% to 20%; 3 was 21% to 50%; and 4 was 51% to 100% tumor staining. Intensity was scored as 1 equal to no staining; 2, low intensity; 3, moderate; and 4, high intensity. Scores for multiple cores from each patient were averaged. Staining for p16 was considered positive when >75% of tumor cells demonstrated strong nuclear and cytoplasmic staining or >2 intensity.

Isolation of DNA from cored tissue samples was performed using the QIAamp DNA FFPE Tissue Kit (Qiagen, Valencia, CA). DNA concentration and purity were confirmed via NanoDrop spectrophotometer (Thermo Scientific, Waltham, MA). HPV status was determined by an ultra-sensitive method using real-time competitive PCR and matrix-assisted laser desorption/ionization time-of-flight mass spectroscopy with separation of products on a matrix-loaded silicon chip array, as described by Tang et al.[4]

HPV status was determined by the combination of immunohistochemistry, and/or PCR, and was considered positive if p16 staining was positive or when p16 staining was unavailable, then PCR assay was positive. Table 2 shows the 5 patients with discordances between p16 staining and PCR assay results. The 2 patients who were p16 negative but PCR assay positive were considered HPV

TABLE 2. Patients with discordances between p16 staining and polymerase chain reaction assay results.

Patient #	PCR assay results	p16 immunostain proportion	HPV status for analysis
1	Negative	4	Positive
2	Negative	4	Positive
3	HPV16	0	Negative
4	Negative	4	Positive
5	HPV16	0	Negative

Abbreviations: PCR, polymerase chain reaction; HPV, human papillomavirus.
Note: p16 immunostain proportions: 1 = <5%; 2 = 5% to 20%; 3 = 21% to 50%; 4 = 51% to 100%.

negative and excluded. The pathologist was blinded to the clinical outcome.

Treatment protocol

Radiation was given 5 days per week. The prescribed doses were 70 Gy at 2.0 Gy per fraction to gross disease and 59 to 63 Gy at 1.7 to 1.8 Gy per fraction to low-risk and high-risk subclinical regions, respectively, delivered concomitantly according to published methods.[5,6] Chemotherapy consisted of weekly carboplatin (area under the curve 1) intravenously over 30 minutes and paclitaxel 30 mg/m^2 intravenously over 1 hour. Hydration and antiemetics were administered according to the standard of care.

Pretreatment imaging

Pretreatment CT or CT/positron emission tomography scans obtained within 4 weeks of starting therapy were reviewed by a neuroradiologist (M.I.). Primary tumor site and size, distance of the primary tumor from the midline, and encasement of the carotid artery by the primary tumor were recorded. The size (largest 2 dimensions) and distribution (level I–V) of each lymph node was recorded for each level of the neck. AJCC N3 disease was defined clinically as a lymph node or group of lymph nodes >6 centimeters. Matted nodes were defined as 3 nodes abutting one another with loss of intervening fat plane that is replaced with evidence of extracapsular spread (ECS) with imaging. We have previously reported that matted nodes are predictive of a poor prognosis independent of age, T classification, HPV, epidermal growth factor receptor, and smoking status.[7] ECS was defined with imaging as loss of the sharp plane between the capsule of the lymph node and the surrounding fat.

Modeling process

The first model we selected was a known model of poor prognosis in nasopharyngeal SCC defined by the seventh edition AJCC. Briefly, $_{Naso}$N1 was defined as unilateral regional metastasis, all <6 cm and above the supraclavicular fossa. $_{Naso}$N2 was defined as bilateral regional metastasis, all <6 cm and above the supraclavicular fossa. $_{Naso}$N3 was defined as node(s) >6 cm or regional metastasis in the supraclavicular fossa.

The second modeling approach selected patients with the worst prognosis. This group was defined by patients with matted nodes, as our previous work has shown, this cohort has a poor prognosis because of the development of distant metastasis.[7] We then determined that patients with single nodal metastasis, despite the conventional size criteria or laterality (ipsilateral, contralateral, or bilateral) seemed to have an improved prognosis. This included patients previously determined to have AJCC N1, N2a, or N2c with only a single node on each side of the neck. Finally, there was a group of patients that had a node >6 cm, or had >2 nodes ipsilaterally/contralaterally, or >3 nodes bilaterally that were not matted who had an intermediate prognosis as compared with patients with matted nodes or those with a single nodal metastasis. Therefore, we defined $_{HPV+}$N1 as patients who had a single node <6 cm, ipsilaterally, contralaterally, or bilaterally (AJCC N1, N2a, or N2c with a single node bilaterally). We defined $_{HPV+}$N2 as patients who had a single node ≥6 cm, or ≥2 nodes ipsilaterally or contralaterally, or ≥3 nodes bilaterally (AJCC N2b, N2c with ≥3 nodes, or N3, without matted nodes). We defined $_{HPV+}$N3 as patients with matted nodes. Table 3 summarizes the nodal classifications for each of the different systems. Radiographic examples for each of the HPV-positive N classifications are displayed in Figure 1.

Statistical analysis

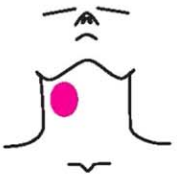
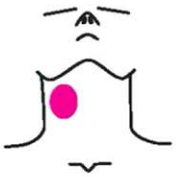
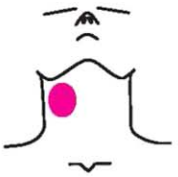
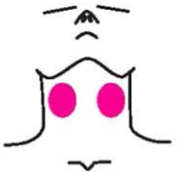
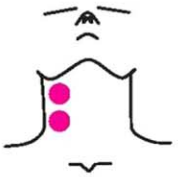
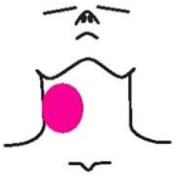
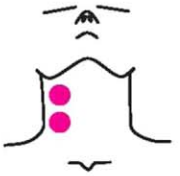
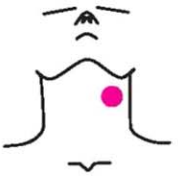
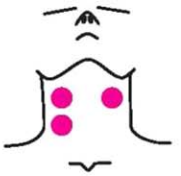
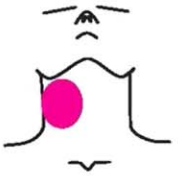
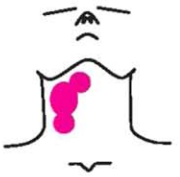
The outcomes of interest were OS and disease-specific survival (DSS). The start point for survival estimates was defined as the date of diagnosis. An OS event was defined as death from any cause; DSS events were defined as death from cancer, deaths from other causes were censored at the date of death. Variables studied included age, sex, disease subsite, AJCC T classification, AJCC N classification, AJCC nasopharyngeal N classification, tobacco status, and the HPV-positive N classification system presented above. Tobacco status was defined categorically as never, prior (quit >6 months ago), or current use. The 3 different staging systems were also compared based on their performance in a Cox proportional hazards model using the Akaike information criterion (AIC), in which smaller values are considered better. Written informed consent was obtained from all patients, and this research was approved by the Institutional Review Board of the University of Michigan.

RESULTS

The 3-year OS, DSS, and disease-free survival (DFS) for the entire cohort were 85%, 88%, and 77%, respectively, with a median follow-up of 42 months. The proportion of patients in the AJCC staging system, the $_{Naso}$N staging system and the $_{HPV+}$N staging system are stratified by T classification and shown in Table 4.

There were a total of 34 recurrences in the cohort. There were 3 patients with local recurrences with 1 of 3 successfully salvaged and 4 patients with isolated regional recurrences with 3 of 4 successfully salvaged. There was 1 patient with a local and regional recurrence who was successfully salvaged, but later died of other

TABLE 3. Summarization of the nodal classifications for each of the different systems.

AJCC Oropharynx	AJCC Nasopharynx	Proposed Oropharynx HPV+
 **N_1** Metastasis in single node < 3 cm in greatest dimension	 **N_1** Metastasis in supraclavicular node < 6 cm in greatest dimension	 **N_1** Metastasis in single ipsilateral node < 6 cm in greatest dimension
 **N_{2a}** Metastasis in ipsilateral node ≥ 3 cm and < 6 cm in greatest dimension	 **N_2** Metastasis in bilateral supraclavicular nodes < 6 cm in greatest dimension	 **N_1** Metastasis in bilateral nodes < 6 cm in greatest dimension
 **N_{2b}** Metastasis in ≥ 2 ipsilateral nodes < 6 cm in greatest dimension	 **N_3** Metastasis in supraclavicular node ≥ 6 cm in greatest dimension	 **N_2** Metastasis in ≥ 2 ipsilateral nodes
 **N_{2c}** Metastasis in contralateral node < 6 cm in greatest dimension	 **N_3** Metastasis in infraclavicular node	 **N_2** Metastasis in > 2 bilateral nodes
 **N_3** Metastasis in any node ≥ 6 cm in greatest dimension		 **N_3** Metastasis in ≥ 3 nodes abutting one another with loss of intervening fat plane that is replaced with evidence of extracapsular spread

Abbreviations: AJCC, American Joint Committee on Cancer; HPV, human papillomavirus.

causes. There were 20 patients who developed distant metastasis, 15 died of disease, 4 are alive with disease, and 1 patient who underwent wedge resection of the lung who is free of disease. There were 4 patients with a local recurrence and distant metastasis, 1 patient with a regional recurrence and distant metastasis, and 1 patient with a local, regional, and distant recurrence, all of whom died of disease.

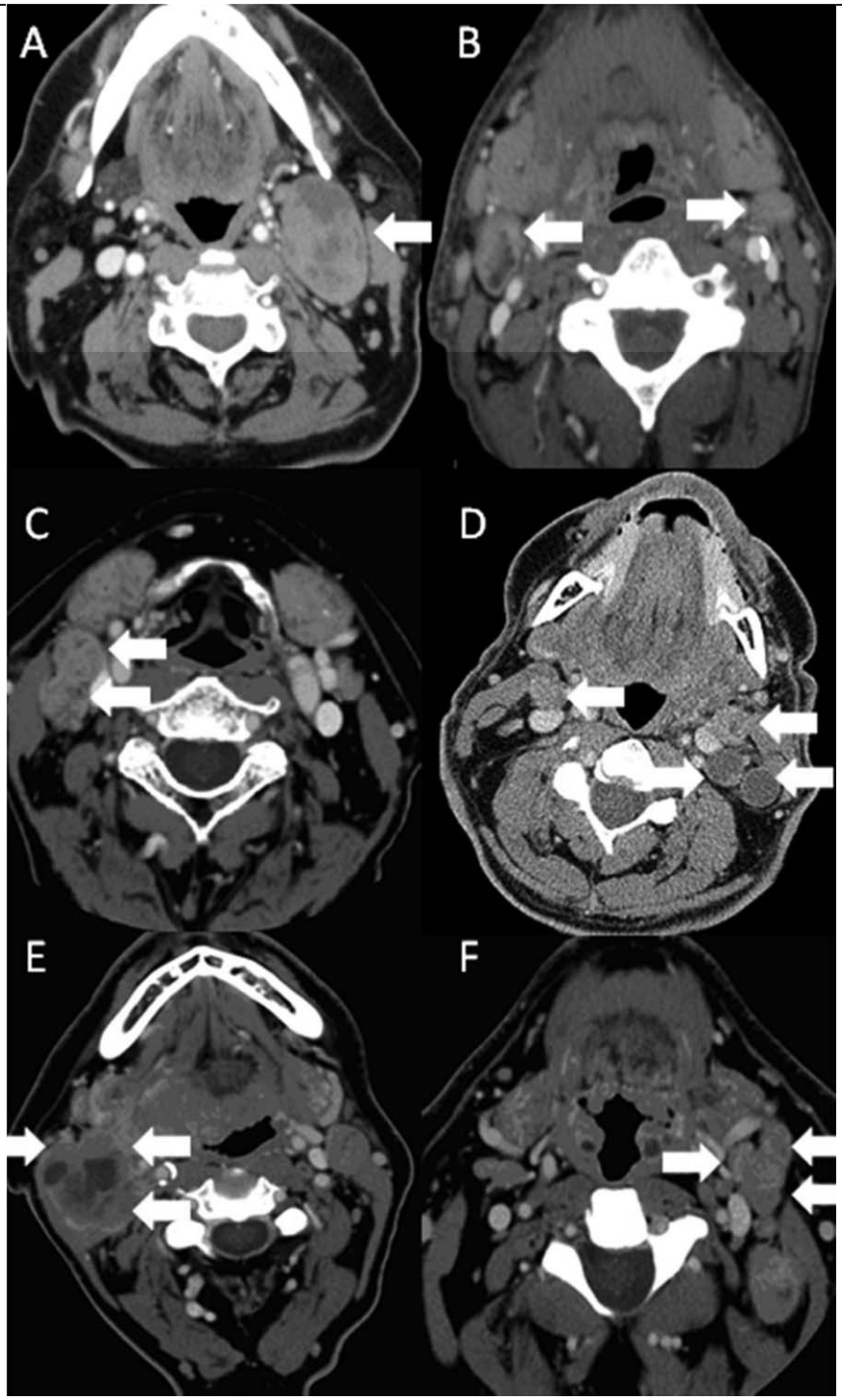


FIGURE 1. CT scans demonstrating examples of human papillomavirus (HPV)-positive N staging system. (A and B) Examples of patients who were categorized as $_{HPV+}$N1. (A) A single metastatic node <6 cm in level II of the left neck (arrow). (B) Bilateral level 2 nodal metastasis without other node involvement (arrows). (C and D) Examples of patients who were categorized as $_{HPV+}$N2. (C) Two metastatic nodes in level II of the right neck (arrows). (D) Bilateral level 2 nodal metastasis with more than 1 metastatic node on the left (arrows). (E and F) Examples of patients who were categorized as $_{HPV+}$N3. (E and F) Three nodes (arrows) with loss of intervening fat plane that is replaced with extracapsular spread (matted nodes).

TABLE 4. Number of patients within each nodal system stratified by T classification.

	$_{AJCC}$N1	$_{AJCC}$N2	$_{AJCC}$N3	$_{Naso}$N1	$_{Naso}$N2	$_{Naso}$N3	$_{HPV+}$N1	$_{HPV+}$N2	$_{HPV+}$N3	Total
T1	5	22	4	21	2	8	11	14	6	31
T2	4	43	10	37	8	12	12	37	8	57
T3	1	18	2	11	8	2	6	11	4	21
T4	4	35	8	19	16	12	13	17	17	47
Total	14	118	24	88	34	34	42	79	35	156

Abbreviations: AJCC, American Joint Committee on Cancer; Naso, nasopharyngeal; HPV, human papillomavirus.

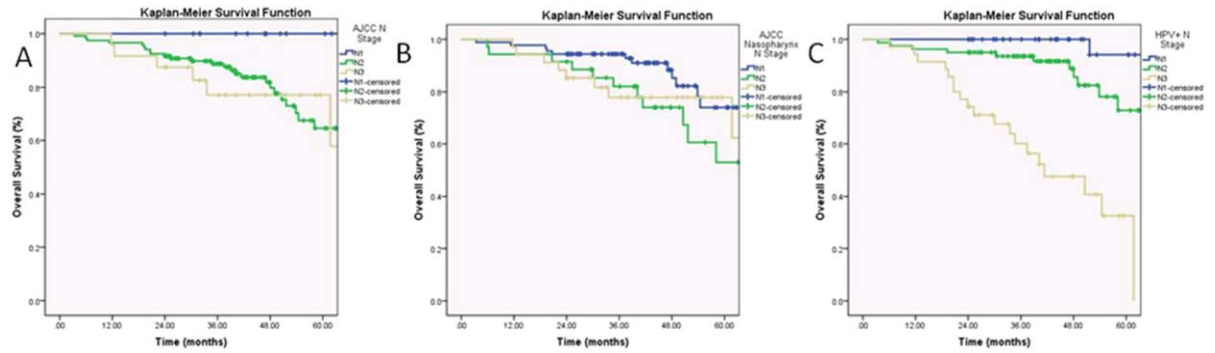


FIGURE 2. Overall survival (OS) curves of the entire cohort stratified by the American Joint Committee on Cancer (AJCC) oropharyngeal staging system, nasopharyngeal ($_{Naso}$N) staging system, and the human papillomavirus (HPV)-positive N ($_{HPV+}$N) staging system. (A) OS of the entire cohort stratified by the AJCC staging system. There were no significant differences in OS when comparing patients with N1 and N2 ($p = .063$) as well as N2 and N3 nodal disease ($p = .12$). (B) OS of the entire cohort stratified by the $_{Naso}$N staging system. There was no significant difference in OS when comparing $_{Naso}$N2 and $_{Naso}$N3 nodal disease ($p = .61$). (C) OS of the entire cohort stratified by the $_{HPV+}$N staging system. There were significant differences in OS when comparing patients with $_{HPV+}$N1 and $_{HPV+}$N2 ($p = .03$) as well as $_{HPV+}$N2 and $_{HPV+}$N3 nodal disease ($p = .0001$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

N classification by the current American Joint Committee on Cancer staging system

When stratifying by the current AJCC nodal classification system, there was no difference in the OS by the log-rank test ($p = .16$; Figure 2A). The 3-year OS stratified by the current AJCC nodal classification system for N1, N2, and N3 nodal disease was 100%, 86%, and 74%, respectively. The log-rank detects differences when comparing all 3 (N1, N2, and N3) survival curves and does not detect differences between individual groups. Therefore, N classifications were compared in a pair-wise fashion. There were no significant differences in OS when comparing patients with N1 and N2 ($p = .063$) as well as N2 and N3 nodal disease ($p = .12$). There was a significant difference when comparing N1 and N3 nodal disease ($p = .047$).

There was no significant difference in DSS when stratifying by the current AJCC nodal classification system by the log-rank test ($p = .14$; Figure 3A). The 3-year DSS stratified by the current AJCC nodal classification system for N1, N2, and N3 nodal disease was 100%, 89%, and 74%, respectively. There were no significant differences in DSS when comparing patients with N1 and N2 ($p = .12$) as well as N2 and N3 nodal disease ($p = .30$). There was a significant difference when comparing N1 and N3 nodal disease ($p = .047$). Although the AJCC system demonstrates differences between patients with N1 and N3 disease, the DSS of all N classifications in this system is still above 60% at 5 years.

The 3-year DFS stratified by the current AJCC nodal classification system for N1, N2, and N3 nodal disease was 100%, 77%, and 53%, respectively. There were no significant differences in DFS when comparing patients with N1 and N2 ($p = .063$) or N2 and N3 nodal disease

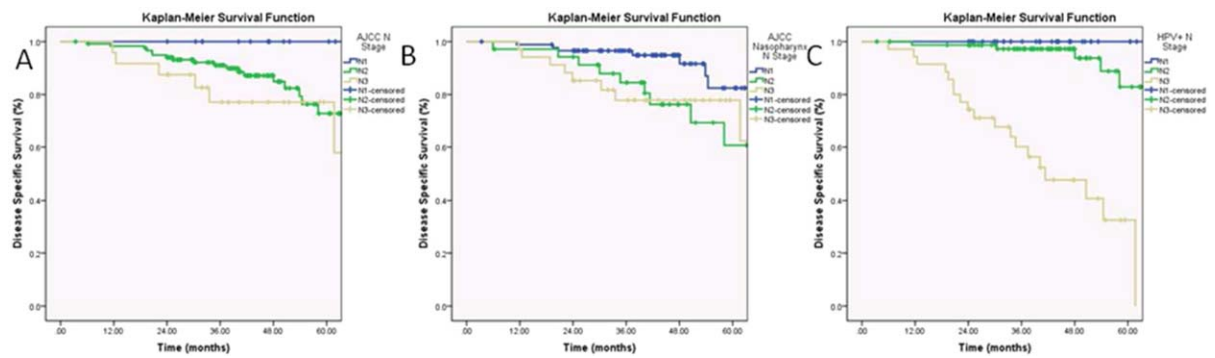


FIGURE 3. Disease-specific survival (DSS) curves of the entire cohort stratified by the American Joint Committee on Cancer (AJCC) oropharyngeal staging system, nasopharyngeal ($_{Naso}$N) staging system, and the human papillomavirus (HPV)-positive N ($_{HPV+}$N) staging system. (A) DSS of the entire cohort stratified by the staging AJCC system. There were no significant differences in DSS when comparing patients with N1 and N2 ($p = .12$) as well as N2 and N3 nodal disease ($p = .30$). (B) DSS of the entire cohort stratified by the $_{Naso}$N staging system. There was no significant difference in DSS when comparing $_{Naso}$N2 and $_{Naso}$N3 nodal disease ($p = .96$). (C) DSS of the entire cohort stratified by the $_{HPV+}$N staging system. There were significant differences in DSS when comparing patients with $_{HPV+}$N1 and $_{HPV+}$N2 ($p = .05$) as well as $_{HPV+}$N2 and $_{HPV+}$N3 nodal disease ($p = .0001$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

($p = .073$). There was a significant difference when comparing N1 and N3 nodal disease ($p = .011$).

N classification by current nasopharyngeal American Joint Committee on Cancer staging system

When stratifying by the $_{Naso}$N classification system, there was no significant difference in the OS by the log-rank test ($p = .12$; Figure 2B) The 3-year OS stratified by $_{Naso}$N1, $_{Naso}$N2, and $_{Naso}$N3 nodal stage disease was 92%, 80%, and 74%, respectively. There was a significant difference is OS when comparing patients with $_{Naso}$N1 and $_{Naso}$N2 ($p = .044$). There was no significant difference in OS when comparing $_{Naso}$N2 and $_{Naso}$N3 nodal disease ($p = .61$).

There was a significant difference in DSS when stratifying by the $_{Naso}$N classification system by the log-rank test ($p = .03$; Figure 3B). The 3-year DSS stratified by $_{Naso}$N1, $_{Naso}$N2, and $_{Naso}$N3 nodal stage disease was 95%, 83%, and 74%, respectively. There was a significant difference is DSS when comparing patients with $_{Naso}$N1 and $_{Naso}$N2 ($p = .015$). There was no significant difference in DSS when comparing $_{Naso}$N2 and $_{Naso}$N3 nodal disease ($p = .96$). The $_{Naso}$N staging system demonstrates a difference between patients with $_{Naso}$N1 and $_{Naso}$N2 disease, but the DSS of all N classifications in this system is still above 60% at 5 years.

The 3-year DFS stratified by $_{Naso}$N1, $_{Naso}$N2, and $_{Naso}$N3 nodal stage disease was 84%, 73%, and 59%, respectively. There were no significant differences in DFS when comparing patients with $_{Naso}$N1 and $_{Naso}$N2 ($p = .06$) or when comparing $_{Naso}$N2 and $_{Naso}$N3 nodal disease ($p = .41$). There was a significant difference is DFS when comparing patients with $_{Naso}$N1 and $_{Naso}$N3 ($p = .004$).

N classification by the new human papillomavirus–positive staging system

When stratifying by the $_{HPV+}$N staging system, there was a significant difference in the OS by the log-rank test ($p = .0001$; Figure 2C). The 3-year OS stratified by $_{HPV+}$N1, $_{HPV+}$N2, and $_{HPV+}$N3 nodal stage disease was 100%, 92%, and 55%, respectively. More importantly, there were significant differences in OS when comparing patients with $_{HPV+}$N1 and $_{HPV+}$N2 ($p = .03$) as well as $_{HPV+}$N2 and $_{HPV+}$N3 nodal disease ($p = .0001$).

There was a significant difference in DSS when stratifying by $_{HPV+}$N staging system ($p = .0001$; Figure 3C). The 3-year DSS stratified by $_{HPV+}$N1, $_{HPV+}$N2, and $_{HPV+}$N3 nodal stage disease was 100%, 96%, and 55%, respectively. More importantly, there were significant differences in DSS when comparing patients with $_{HPV+}$N1 and $_{HPV+}$N2 ($p = .05$) as well as $_{HPV+}$N2 and $_{HPV+}$N3 nodal disease ($p = .0001$). This new system demonstrates significant differences between each N classification and identifies a group of patients with extremely poor survival.

The 3-year DFS stratified by $_{HPV+}$N1, $_{HPV+}$N2, and $_{HPV+}$N3 nodal stage disease was 100%, 88%, and 30%, respectively. There were significant differences in DFS when comparing patients with $_{HPV+}$N1 and $_{HPV+}$N2 ($p = .013$) as well as $_{HPV+}$N2 and $_{HPV+}$N3 nodal disease ($p = .0001$). There was a significant difference in DFS when comparing patients with $_{HPV+}$N1 and $_{HPV+}$N3 ($p = .0001$) nodal disease.

The 3 different classification systems were also compared based on their performance in a Cox proportional hazards model using the AIC, in which smaller values are considered better. HPV-positive N classification had the best performance in models for DSS (AIC 171.4) compared to the current AJCC N classification (AIC 216.7) and nasopharyngeal AJCC N classification (211.8). There is no p value associated with type of measure, rather this is a "goodness of fit" model.

DISCUSSION

In this HPV-positive oropharyngeal cohort with N-positive disease, we were able to demonstrate improved risk stratification for the nodal classification system. This finding suggests that further examination of the nodal classification in the AJCC staging system with these criteria should be considered for patients with HPV-positive cancer.

In a recent prospective trial, Ang et al[1] examined "bulk of disease" in patients with oropharyngeal SCC. This was defined through the AJCC staging system as N2B, N2C, or N3 disease, and these patients were considered to be at higher risk for a disease-specific event. We recently have examined the prognostic implications of different patterns of nodal metastasis and have determined that patients with matted nodes, defined as 3 nodes abutting one another with loss of intervening fat plane that is replaced with radiologic evidence of ECS, have a poor prognosis independent of other known prognostic factors (T classification, epidermal growth factor receptor expression, and smoking status).[7] Therefore, this may by a more accurate way of determining bulk of disease and defines a high-risk group with a poor prognosis. Alternatively, the high incidence of other nodal metastatic patterns (AJCC N1, N2A, and N2C with a single node) may not portend as poor a prognosis in this patient population.

The current $_{Naso}$N classification system was first developed by Ho[8] in 1978 and later modified by the AJCC.[2] It has been externally validated to predict prognosis in nasopharyngeal SCC. When applying this system to our cohort of patients,[9] $_{Naso}$N did not predict prognosis. Although it was able to stratify patients with unilateral versus bilateral neck metastasis ($_{Naso}$N1 vs $_{Naso}$N 2), supraclavicular nodal metastasis and nodal metastasis >6 cm ($_{Naso}$N3) was not a poor prognostic factor. In addition, this system did not identify a patient group with a poor prognosis (5-year survival of all groups >60%).

Our new system takes into account both HPV status and pattern of nodal metastasis. HPV status has been identified as the single most important prognostic factor in oropharyngeal SCC (greater than smoking, and T and N classification),[1,7,10] and clinical trials are underway to de-escalate therapy in this cohort of patients. It is important during the de-escalation efforts that risk stratification is properly applied to identify patients at risk for treatment failure that could be placed at increased risk of partial response or recurrence by introducing less aggressive treatment regimens. Patients in the $_{HPV+}$N3 group had a

3-year DSS of 55%, and might be considered for exclusion or stratification in such de-escalation trials.

The limitations of this study include a small sample size treated under a single protocol (other protocols may yield different outcomes). Further expansion and validation of these data is necessary to support a broad change in N classification criteria.

In conclusion, a nodal classification system based on reclassification of size, bilaterality, and matted nodes more accurately reflects survival differences in this cohort of patients with oropharyngeal SCC. A larger review of the nodal classification in the AJCC staging system with these criteria should be considered for patients with HPV-positive oropharyngeal SCC.

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