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Radiographic nodal prognostic factors in stage I HPV-related oropharyngeal squamous cell carcinoma

Onita Bhattasali MD, MPH[1] | Lester D. R. Thompson MD[2] | Andrew J. Schumacher MD[1] | Shawn Iganej MD[1]

[1]Department of Radiation Oncology, Southern California Permanente Medical Group, Los Angeles, California

[2]Department of Pathology, Southern California Permanente Medical Group, Los Angeles, California

Correspondence
Shawn Iganej, MD, Southern California Permanente Medical Group, 4950 Sunset Boulevard, Department of Radiation Oncology, Los Angeles, CA 90027.
Email: shawn.x.iganej@kp.org

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Abstract

Background: The updated AJCC Cancer Staging Manual groups all p16-positive oropharyngeal squamous cell carcinoma (OPSCC) with unilateral nodal involvement within 6 cm into the new clinical N1 classification, consolidating a heterogeneous group of disease with varying radiographic findings.

Methods: A central radiological review was conducted identifying 233 patients with stage I node-positive (cT1-2N1) disease who underwent definitive concurrent chemoradiation. Factors evaluated included lymph node size, low-neck lymphadenopathy, retropharyngeal lymphadenopathy, overt radiographic extracapsular extension, and matted lymphadenopathy.

Results: On multivariate analysis adjusted for age, smoking history, and chemotherapy regimen, low-neck lymphadenopathy (hazard ratio (HR) = 6.55; $P < .001$) and retropharyngeal lymphadenopathy (HR = 3.36; $P = .009$) predicted for inferior progression-free survival (PFS). low-neck lymphadenopathy (HR = 6.38; $P = .001$) and retropharyngeal lymphadenopathy (HR = 3.32; $P = .02$) also predicted for inferior overall survival (OS). All other radiographic characteristics showed no prognostic impact for PFS or OS.

Conclusions: This analysis suggests that caution should be advised against de-intensification efforts among patients with stage I node-positive p16-positive OPSCC with low-neck lymphadenopathy or retropharyngeal lymphadenopathy.

KEYWORDS

HPV-associated, low-neck lymphadenopathy, oropharyngeal cancer, p16-positive, retropharyngeal lymphadenopathy

1 | INTRODUCTION

In recent decades, there has been an increase in the incidence of oropharyngeal squamous cell carcinoma (OPSCC) in the United States.[1,2] This phenomenon is attributed to the rise in human papillomavirus (HPV)-associated or p16-positive OPSCC which is a disease distinct from other head and neck malignancies which are more commonly associated with a history of heavy smoking or alcohol use.[3] Compared to p16-negative disease, p16-positive OPSCC demonstrates increased sensitivity to chemotherapy and radiation and is associated with more favorable survival outcomes.[4]

The previously established staging system for OPSCC does not accurately prognosticate outcomes for patients with HPV-associated disease.[5] Because of this, the new AJCC 8th Edition cancer staging manual now distinguishes p16-positive OPSCC as an entity separate from its p16-negative counterpart.[6] In the updated edition, all patients with p16-positive OPSCC with unilateral lymph node involvement no larger than 6 cm in size are

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consolidated under a new clinical N1 classification. As a result, this classification comprises a heterogeneous group of disease with considerable patient-to-patient variation of radiographic findings, some of which may portend a poorer prognosis.

In previous studies of patients with OPSCC, radiographic characteristics such as low-neck lymphadenopathy, retropharyngeal lymphadenopathy, overt radiographic extracapsular extension, and matted lymphadenopathy have been identified as predictors of inferior patient outcomes.[7–12] However, for early-stage HPV-associated OPSCC which is generally associated with excellent outcomes, it is not well understood if these radiographic characteristics have any prognostic impact. However, it is conceivable that within this seemingly favorable cohort, there may be pockets of patients who are poor performers due to various disease features that are not captured within the current staging system. To further investigate this hypothesis, we conducted a centralized radiology review of patients with early-stage node-positive p16-positive OPSCC to identify any radiographic characteristics which may be prognostic for inferior patient outcomes.

2 | PATIENTS AND METHODS

From May 2006 through September 2015, we conducted a centralized radiology review of the staging imaging studies of patients with AJCC 8th Edition TNM stage I node-positive (cT1-2N1) patients who underwent definitive concurrent chemoradiation for histologically confirmed p16-positive OPSCC. Institutional review board approval was obtained. All patients underwent initial evaluation in a multidisciplinary head and neck clinic. Patients who underwent oncologic surgery of any kind or received induction chemotherapy prior to definitive management were excluded from analysis, as were patients with prior head and neck radiotherapy or other known malignancies (excluding non-melanoma skin cancer) within the previous 5 years. Centralized pathology review was performed on all specimens, with p16 immunohistochemical staining obtained for all cases, with positive cases interpreted to be strong and diffuse, >70% nuclear and cytoplasmic immunoreactivity.[13]

Patients received intensity-modulated radiation therapy (IMRT) to a planned dose of 66-70 Gy with simultaneous-integrated boost technique. All patients were simulated with CT scan and immobilized with a thermoplastic mask. Concurrent systemic therapy was administered to all patients; 19 (8%) patients received cetuximab, 92 (39%) patients received triweekly carboplatin, 105 (45%) patients received triweekly cisplatin, 1 (0%) patient received weekly carboplatin, and 16 (7%) patients received weekly cisplatin. Evaluation with clinical examination and nasopharyngoscopy was performed 1 month following completion of treatment. Subsequent follow-up was scheduled initially every 2-3 months and gradually transitioned to every 6 months until 5 years at which point patients had the option of annual surveillance in head and neck clinic or routine care with their primary care provider. Post-treatment imaging studies were obtained periodically at the discretion of the treating physician.

All images underwent centralized review by a head and neck radiation oncologist. A total of 238 patients were identified with AJCC 8th Edition TNM stage I node-positive (cT1-2N1) disease and were included in our final analysis. All patients had at least an MRI or CT scan for evaluation; 110 (47%) patients also had a baseline PET/CT for review. The size of the largest lymph node was recorded for each patient. Imaging studies were also evaluated for the following findings: low-neck lymphadenopathy, retropharyngeal lymphadenopathy, overt radiographic extracapsular extension, and matted lymphadenopathy. Low-neck lymphadenopathy was defined as involvement of level IV and/or Vb in the neck. Overt radiographic extracapsular extension was defined as clear loss of the integrity of the nodal capsule with infiltration of disease into the adjacent fat planes or musculature. Matted lymphadenopathy was defined as multiple nodes abutting one another with loss of the intervening fat planes. Examples of radiographic factors evaluated are found in Figure 1.

A minimum of 1 year of follow-up was required for all surviving patients. Patient and disease characteristics were reported with descriptive statistics, and comparative statistics were performed using Fisher's exact test. Outcomes were measuring using the length of time from the day of treatment completion to the last day of follow-up. All surviving patients underwent a minimum follow-up of 1 year. Endpoints analyzed included progression-free survival (PFS)

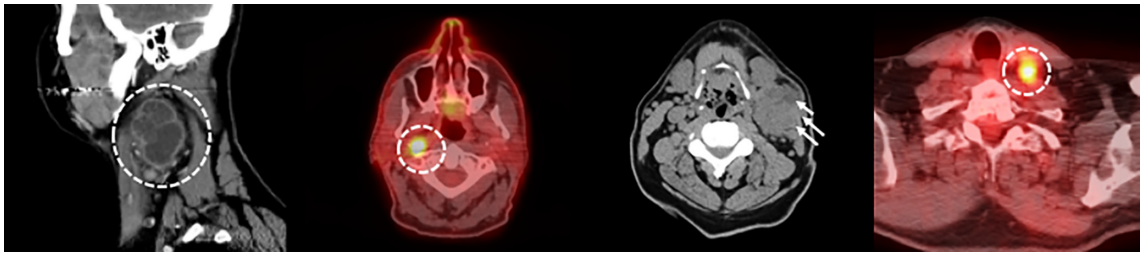

FIGURE 1 Examples of radiographic characteristics evaluated. From left to right: matted lymphadenopathy, retropharyngeal lymphadenopathy, overt radiographic extracapsular extension, and low-neck lymphadenopathy [Color figure can be viewed at wileyonlinelibrary.com]

and overall survival (OS). Survival outcomes were estimated by the Kaplan–Meier method. Univariate analysis using a Cox proportional hazards model was performed to identify which factors were prognostic for inferior PFS and OS. The statistical significance level was set at 0.05. Those factors that were significant on univariate analysis for either PFS or OS were subsequently included in a multivariate model adjusted for age, smoking history greater than 10 pack-years, and concurrent chemotherapy agent (triweekly cisplatin vs other).

3 | RESULTS

Median follow-up of surviving patients was 49 months (range: 16-121). Detailed patient characteristics are listed in Table 1. Median patient age was 61 years (range: 35-81). Patients were predominantly male (88%) with tumors of the tonsil (61%) and base of tongue (38%). At least a 10 pack-year smoking history was reported for 42% of patients. The 3-year PFS and OS rates for all-comers were 86% and 90%, respectively.

The frequency of the various radiographic characteristics evaluated in the cohort is listed in Table 2. The median largest lymph node size was 3.0 cm (range: 0.6-5.6). Size was evaluated as a continuous variable as well as at a threshold of 3 cm. On univariate analysis, size as a continuous variable (hazard ratio (HR) = 1.37 [0.95-1.99]; $P = .10$) did not demonstrate prognostic impact for PFS (HR = 1.37 [0.95-1.99]; $P = .10$) or OS (HR = 1.27 [0.83-1.95]; $P = .28$). Size of lymph node 3 cm or larger also did not demonstrate prognostic impact for PFS (HR = 1.96 [0.98-3.91]; $P = .06$) or OS (HR = 1.97 [0.89-4.34]; $P = .09$) (Table 3).

Additional radiographic characteristics in this cohort are as follows: Matted lymphadenopathy (27%), overt radiographic extracapsular extension (29%), low-neck lymphadenopathy (4%), and retropharyngeal lymphadenopathy (8%). On univariate analysis, matted lymphadenopathy was not prognostic for PFS (HR = 1.63 [0.81-3.30]; $P = .17$) or OS (1.32 [0.57-3.04]; $P = .52$). Overt radiographic extracapsular extension also did not demonstrate prognostic impact for PFS (HR = 1.43 [0.71-2.89]; $P = .32$) or OS (1.15 [0.50-2.65]; $P = .74$). Low-neck lymphadenopathy was an adverse prognostic factor for both PFS (HR = 7.07 [2.91-17.18]; $P < .001$) and OS (HR = 7.15 [2.68-19.10]; $P < .001$). The 3-year PFS with and without low-neck lymphadenopathy was 40% vs 89%, respectively; the 3-year OS with and without low-neck lymphadenopathy was 50% vs 92%. Retropharyngeal lymphadenopathy was also an adverse prognostic factor for PFS (HR = 3.85 [1.67-8.87]; $P = .002$) and OS (HR = 4.25 [1.69-10.65]; $P = .002$). The 3-year PFS with and without retropharyngeal lymphadenopathy was 60% vs 89%; the 3-year OS with and without retropharyngeal lymphadenopathy was 65% vs 92%.

The factors which were significant for either PFS or OS on univariate analysis were included in a multivariate Cox proportional hazards model which was adjusted for patient age, smoking history greater than 10 pack-years, and concurrent systemic therapy agent (triweekly cisplatin vs other). On multivariate analysis, low-neck lymphadenopathy (HR = 6.55 [2.48-17.27], $P < .001$) and retropharyngeal lymphadenopathy (HR = 3.36 [1.34-8.38], $P = .009$) remained independent negative prognostic factors for PFS; low-neck lymphadenopathy (HR = 6.38 (2.06-19.73], $P = .001$) and retropharyngeal lymphadenopathy (HR = 3.32 [1.19-9.27], $P = .02$) were also found to be independently prognostic for inferior OS. The results of multivariate analysis are outlined in Table 4.

TABLE 1 Patient characteristics

Characteristic	Value
Median follow-up of surviving patients (months)	49 (16–121)
Median age (years)	61 (35–81)
Sex	
Male	206 (88%)
Female	27 (12%)
Subsite	
Tonsil	142 (61%)
Base of tongue	88 (38%)
Soft palate	2 (1%)
Pharyngeal wall	1 (0%)
10 pack-year smoking history	98 (42%)

TABLE 2 Disease characteristics

Characteristic	Value
Median lymph node size (cm)	3.0 (0.6–5.6)
Matted lymphadenopathy	62 (27%)
Overt radiographic extracapsular extension	67 (29%)
Low-neck lymphadenopathy	10 (4%)
Retropharyngeal lymphadenopathy	18 (8%)

4 | DISCUSSION

The decision to consolidate all unilateral nodal disease within 6 cm in size into a singular clinical nodal classification within the AJCC 8th Edition staging manual followed a study conducted by the International Collaboration for Oropharyngeal Cancer Network for Staging (ICON-S) which concluded that the 7th Edition classification system did not adequately prognosticate outcomes for patients with HPV-associated OPSCC.[5] The ICON-S study found that the AJCC 7th Edition nodal groups N1-N2b all demonstrated similar survival outcomes in HPV-associated OPSCC, and it was concluded that within this group the size and number of lymph nodes was not prognostic. In our study, we also observed that lymph node size did not predict for inferior

TABLE 3 Univariate analysis of the prognostic impact of radiographic characteristics

	Progression-free survival		Overall survival	
Size continuous	HR = 1.37 [0.95–1.99]	$P = .10$	HR = 1.27 [0.83–1.95]	$P = .28$
Size 3.0 cm+	HR = 1.96 [0.98–3.91	$P = .06$	HR = 1.97 [0.89–4.34	$P = .09$
Matted lymphadenopathy	HR = 1.63 [0.81–3.30]	$P = .17$	HR = 1.32 [0.57–3.04]	$P = .52$
Overt radiographic extracapsular extension	HR = 1.43 [0.71–2.89]	$P = .32$	HR = 1.15 [0.50–2.65]	$P = .74$
Low-neck lymphadenopathy	HR = 7.07 [2.91–17.18]	$P < .001$	HR = 7.15 [2.68–19.10]	$P < .001$
Retropharyngeal lymphadenopathy	HR = 3.85 [1.67–8.87]	$P = .002$	HR = 4.25 [1.69–10.65]	$P = .002$

patient outcomes. One possible explanation for why size may not be prognostic for p16-positive disease is the prevalence of cystic lymphadenopathy in this cohort. Cystic lymph nodes are unlikely to harbor the same disease burden as their solid counterparts and may be easier to eradicate with treatment.

HPV-associated OPSCC has excellent locoregional control compared to HPV-negative OPSCC, although distant failure accounts for a higher proportion of relapses in this population.[14] As such, there is an interest in identifying the factors that increase the risk for distant failure and tailoring management to mitigate that risk. Riaz et al. previously identified low-neck lymphadenopathy as an independent predictor for distant failure, although their analysis included all OPSCC regardless of p16 status.[7] Nevertheless, in our study of early stage node-positive p16-positive OPSCC, we observed that low-neck lymphadenopathy was an independent predictor for inferior PFS and OS. The ICON-S study also identified low-neck lymphadenopathy as an independent predictor for inferior relapse-free survival and inferior OS; however, the impact of low-neck lymphadenopathy was mainly noted in patients more locally advanced disease.[5] Our study population differs slightly from the ICON-S study in that we excluded patients who underwent either definitive surgical management or induction chemotherapy from this analysis in order to have a homogeneous study population. At our institution, patient with low-neck lymphadenopathy often receive induction chemotherapy at the discretion of the treating physician with the intention of reducing the risk for distant failure. Previously, we reported superior outcomes with induction chemotherapy over concurrent chemotherapy alone for patients with p16-positive OPSCC with low-neck lymphadenopathy or N3 disease.[15] It is possible that the exclusion of patients who underwent treatment intensification with induction chemotherapy in our series unmasked the prognostic impact of low-neck lymphadenopathy in earlier stage patients. Our finding of the adverse prognostic impact of low-neck lymphadenopathy supports the decision to exclude patients with low-neck disease from HN002, the recently closed de-intensification trial for low-risk p16-positive OPSCC.[16]

Retropharyngeal lymphadenopathy was also found to be an independent prognostic factor for inferior PFS and OS. The presence of retropharyngeal lymphadenopathy may be a surrogate for late presentation of disease and, therefore, carry a higher likelihood for metastatic spread. Gunn et al. previously reported retropharyngeal lymphadenopathy as an independent predictor for inferior distant control and OS among patients with OPSCC, although analysis by p16 status was not performed.[13] A subsequent report by Samuels et al. showed that the impact of retropharyngeal lymphadenopathy on distant control and OS held true in the subset of patients with HPV-associated OPSCC.[10] Our study finds that the prognostic impact of retropharyngeal lymphadenopathy is maintained even in patients with stage I node-positive p16-positive OPSCC.

Pathologic extracapsular extension has long been identified as an adverse prognostic factor[16]; however, recent surgical series of p16-positive OPSCC have been unable to demonstrate the prognostic significance of this finding.[17,18] In the nonsurgical setting, overt radiographic extracapsular extension has been investigated more recently to evaluate for clinical significance. Among all-comer OPSCC, Kann et al. reported that overt radiographic extracapsular extension predicted for inferior distant control, PFS, and OS.[12] Liu et al. observed, however, that among patients specifically with HPV-associated disease, overt radiographic extracapsular extension had no impact on OS.[11] Our study corroborates the findings from the Liu study as well as the surgical reports. In addition, although previous studies have identified matted lymphadenopathy as prognostic for inferior distant control and survival in HPV-associated OPSCC, these studies have not focused on the subgroup of patient with early-stage disease.[8,9] For instance, within the report by Vainshtein et al., all risk groups assessed included N2 or higher disease, which was an exclusion criteria for our analysis. Within our population, we did not find matted lymphadenopathy to be predictive for patient outcomes, suggesting

TABLE 4 Multivariate analysis of the prognostic impact of radiographic characteristics

	Progression-free survival		Overall survival	
Low-neck lymphadenopathy	HR = 6.55 [2.48–17.27]	$P < .001$	HR = 6.38 [2.06–19.73]	$P = .001$
Retropharyngeal lymphadenopathy	HR = 3.36 [1.34–8.38]	$P = .009$	HR = 3.32 [1.19–9.27]	$P = .02$

that matted lymphadenopathy may be prognostic only among patients with more advanced stage disease.

Although long-term survival in p16-negative OPSCC is modest at best, patients with p16-positive OPSCC generally have favorable outcomes and are more likely to experience the long-term morbidity associated with definitive chemoradiation. At present, de-intensification efforts are aggressively being investigated to minimize toxicity associated with treatment. As these investigations are underway, it is important to identify which patients are truly appropriate candidates for de-intensification and which patients may still be at high risk for failure. In this radiographic study of patients with p16-positive OPSCC with early-stage node-positive disease, low-neck lymphadenopathy and retropharyngeal lymphadenopathy were features independently prognostic for inferior outcomes. Patients whose radiographic studies exhibit these characteristics may not be appropriate candidates for treatment de-intensification. Perhaps future staging systems will incorporate these characteristics within the nodal classifications in order to further risk stratify patients and tailor care.

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