Matted nodes: High distant-metastasis risk and a potential indication for intensification of systemic therapy in human papillomavirus–related oropharyngeal cancer

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ABSTRACT: *Background.* The purpose of this study was to determine whether matted nodes uniquely identify patients with human papillomavirus (HPV)-positive oropharyngeal cancer at disproportionately high distant failure risk who may benefit from intensified systemic therapy.

Methods. One hundred seventy-eight patients with stage III/IV HPV-positive oropharyngeal cancer who completed definitive chemoradiotherapy were stratified by risk group (low-risk = T1–3/N0–2c/<10 pack-years; intermediate-risk = T1–3/N0–2c/≥10 pack-years; and high-risk = T4 or N3). Prognostic impact of matted nodes was assessed.

Results. At the 52-month median follow-up, event rates with and without matted nodes were: locoregional failure: 23.3% versus 12.8% ($p = .16$), distant failure: 50.0% versus 1.4% ($p < .01$), any failure: 73.3% versus 14.2% ($p < .01$); cause-specific mortality: 56.7% versus 5.4% ($p < .01$), and death: 56.7% versus 13.5% ($p < .01$). In multivariate analyses, including risk group and individual risk factors, matted nodes were the strongest predictor for all endpoints except locoregional failure. Among patients without matted nodes, risk-group discriminated locoregional failure (at 3 years: low-risk = 2.0%; intermediate-risk = 14.4%; and high-risk = 24.2%; $p < .01$), but not distant failure (low-risk = 0.0%; intermediate-risk = 2.1%; and high-risk = 3.8%; $p = .53$).

Conclusion. Matted nodes portended dramatically increased distant failure and death risks in HPV-positive oropharyngeal cancer, identifying a candidate population for consideration of chemo-intensification. © 2015 Wiley Periodicals, Inc. *Head Neck* **38**: E805–E814, 2016

KEY WORDS: matted nodes, human papillomavirus, oropharyngeal cancer, distant metastases

INTRODUCTION

The rising incidence of oropharyngeal cancer in the United States, in contrast to the decreasing incidence of other head and neck squamous cell carcinomas (HNSCCs), has attracted increased attention to current management paradigms for oropharyngeal cancer.[1] The recognition of the favorable prognosis of oropharyngeal cancer related to human papillomavirus (HPV), which represents a growing majority of oropharyngeal cancer diagnoses, combined with the morbidity of current curative multimodality approaches for locally advanced disease has prompted clinical trials of deintensification trials for patients with HPV-related oropharyngeal cancer.[2–4] Although consideration of treatment deintensification based on the expectation of high rates of cure may be appropriate for certain subgroups of patients with locally advanced HPV-related oropharyngeal cancer, populations with a substantial risk of treatment failure after standard intensity chemoradiotherapy (CRT) are inappropriate candidates for reduced intensity therapy. Specifically, patients with T4 primary tumors, N3 nodal classification, and significant smoking histories have been identified as being at significantly increased risk of both locoregional failure[5] and distant failure.[6] Although such higher risk patients have been included in ongoing prospective studies of treatment deescalation for HPV-positive oropharyngeal cancer, intensification of therapy may, in fact, be the more appropriate modification of standard therapy for those at highest risk of failure. However, accurate identification of patients with a sufficiently poor prognosis after standard intensity therapy is necessary in order to consider treatment intensification within the HPV-positive population.

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Radiographically matted lymph nodes, defined as 2 nodes abutting one another with radiographic extracapsular spread (rECS) replacing the intervening fat planes, have been identified as a poor prognostic factor in HPV-positive oropharyngeal cancer, independent of T classification, N classification, and smoking status.[7,8] In particular, the presence of matted nodes seems to identify patients with an especially high risk of distant failure.[8] Whether matted nodes can improve risk stratification for treatment failure, pattern of failure, and death, compared with previously proposed HPV-related oropharyngeal cancer risk groups,[5] however, has not been assessed. We therefore sought to determine whether matted nodes could identify patients at highest risk of distant failure, independent of potential surrogates for high risk of distant failure, such as HPV-positive risk group and rECS,[9] and thereby serve as a robust selection criterion for evaluation of intensification of systemic therapy in future randomized studies.

MATERIALS AND METHODS

Patients

Under an institutional review board-approved protocol, the records of 233 consecutive patients with previously untreated, histologically confirmed, American Joint Committee on Cancer/Union for International Cancer Control stage III or IV oropharyngeal squamous cell carcinoma who completed definitive CRT at our institution between July 2003 and December 2010 were retrospectively reviewed. HPV detection for all patients was performed on prospectively collected primary tumor tissue using either multiplex polymerase chain reaction MassArray after DNA extraction from a core tissue sample or in situ hybridization for high-risk HPV genotypes 16, 18, 33, 35, 39, 45, 51, 52, 56, and 66 on paraffin-embedded tissue, as previously described.[10] Patients eligible for the present analysis included those with histologically confirmed HPV-related oropharyngeal cancers who had pretreatment CT imaging available for review. After exclusion of patients with HPV-negative oropharyngeal cancer or indeterminate HPV status and those who underwent surgical neck treatment before initiation of CRT, 178 patients meeting eligibility criteria were included in the present analysis.

Treatment

After staging, consisting of clinical examination, direct laryngoscopy, dedicated head and neck protocol CT or fused positron emission tomography (PET)/CT with contrast enhancement, and chest imaging, patients underwent CT simulation in a 5-point mask followed by intensity-modulated radiation therapy (IMRT) with concurrent chemotherapy, as previously described.[10–12] IMRT prescription doses were 70 Gy to the primary and nodal gross tumor volumes and 56 to 64 Gy to the at-risk clinical target volumes. Gross tumor volumes and clinical target volumes were uniformly expanded 3 to 5 mm to create planning target volumes. IMRT was delivered in 35 daily fractions to 178 patients (99%) and in twice-daily fractionation to 2 patients (1%). Concurrent chemotherapy consisted of weekly carboplatin (area under the curve 1) and paclitaxel (30 mg/m^2) in 175 patients (98%) and cisplatin-based regimens in 3 patients (2%).

Posttreatment surveillance and surgical management

All patients were routinely seen in follow-up in the departments of radiation oncology, otolaryngology, and hematology/oncology, with clinical examination performed every 6 to 12 weeks and posttreatment CT or PET/CT imaging at 3 months. In the earlier years of the study period, patients with advanced nodal disease often underwent planned neck dissection, whereas, in later years, patients were clinically and radiographically observed, with neck dissection reserved for clinical or PET-based suspicion of residual disease after CRT. Forty patients (22%) underwent adjuvant neck dissection as part of their initial course of therapy (ie, within 6 months within completion of CRT) as either planned therapy ($n = 23$) or because of clinical, radiographic, or scintigraphic suspicion for residual disease ($n = 17$).

Radiographic assessment of matted nodes and extracapsular spread

Pretreatment CT or CT/PET scans within 4 weeks of initiation of CRT for all patients were reviewed by either a neuroradiologist or in conjunction by a head and neck surgeon and radiation oncologist; reviewers were blinded to the clinical outcome of each patient. Matted nodes were defined as 3 nodes abutting one another with rECS replacing the intervening fat planes, as previously detailed (Figure 1).[7,8] The rECS was defined by CT evidence of loss of the sharp plane between the lymph node capsule and the surrounding fat.

Statistical analysis

The outcomes of interest in the present analysis were locoregional failure, distant failure, any failure, cause-specific mortality, and overall survival (OS). Because of the evolving neck dissection practices over the time period of the study, gross or microscopic residual disease present in the adjuvant neck dissection specimen was counted as a locoregional failure event in order to provide the most conservative estimate of treatment failure, as detailed previously.[5] For the endpoints, locoregional failure, distant failure, and any failure, patients were censored at the date of their last follow-up, treatment failure at another site, second primary tumor, or death, whereas for cause-specific mortality only nonoropharyngeal cancer-related deaths were censored as a competing event. Patients with synchronous locoregional failure and distant failure were counted as experiencing each endpoint.

Patients were stratified into previously proposed HPV-positive risk-groups.[5] Low risk was classified as those with American Joint Committee on Cancer stage T1 to 3 N0 to 2c disease and a smoking history of <10 pack-years; intermediate risk as T1 to 3 N0 to 2c stages and ≥ 10 pack-years; and high risk as T4 or N3 classifications, irrespective of smoking history. The rate of each endpoint was estimated using Kaplan–Meier methods with log-rank test used for comparison of survival trends across groups,[13,14] before and after adjustment for the presence of matted nodes. Univariable associations between risk

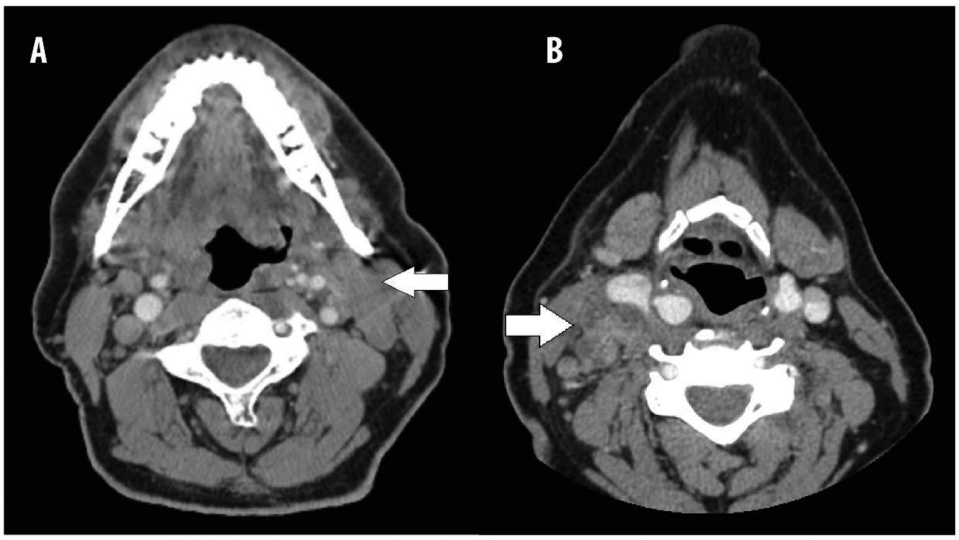

FIGURE 1. Matted nodes in human papillomavirus (HPV)-positive oropharyngeal cancer. (A) A 57-year-old male never smoker with HPV-positive cT2N2cM0 squamous cell carcinoma of the left tonsil with matted nodes in the left level II. (B) A 60-year-old female never smoker with HPV-positive cT2N2bM0 of the right tonsil with matted nodes in the right levels II and III.

group and each endpoint were tested using the log-rank test, with hazard ratios (HRs) for pairwise comparisons between risk groups calculated using the methods of Klein and Moeschberger.[15] Cox proportional hazards regression models were used to assess the impact of the HPV-positive risk group, matted nodes, and rECS on each endpoint. Proportional hazard assumptions for covariates in Cox models were tested using the non-zero slope method in a generalized linear regression of the scaled Schoenfeld residuals on functions of time,[16] and were met for all Cox models ($p > .05$). Baseline characteristics of patients with and without matted nodes were compared using either independent samples t test or chi-square test. A 2-sided p value $\leq .05$ was used to denote statistical significance for all analyses. Statistical analyses were performed using predominantly MedCalc (v 12.2.1.0; MedCalc Software, Mariakerke, Belgium), with RStudio (v 0.98.507; RStudio, Boston, MA) used for proportional hazard assumption testing.

RESULTS

Baseline characteristics for the study population, including when stratified by the presence of matted lymph nodes, are shown in Table 1. Matted nodes were present in 30 patients (16%; Figure 1). Consistent with the definition of matted nodes (at least 3 lymph nodes with confluent rECS), advanced nodal classification (ie, N2b–N3; $p < .001$) and rECS (100% vs 57%; $p < .001$) were more commonly present in patients with matted nodes, as was T4 classification ($p = .047$). However, only a minority of patients with advanced nodal classification (7 of 74 patients with N2b; 12 of 42 patients with N2c; and 11 of 25 patients with N3) or rECS (30 of 115 patients) had matted nodes present. Patients with matted nodes present were more likely than those without matted nodes to be classified as high risk by HPV-positive risk classification (70% vs 31.1%, respectively; $p < .001$), though two-thirds of high-risk patients did not have matted nodes present. Other characteristics, including age, smoking history, and use of adjuvant neck dissection, did not differ significantly between patients with and without matted nodes.

Median follow-up from the start of radiotherapy for the study population is 51.7 months (interquartile range, 35.4–67.6 months). Crude incidence for each endpoint for patients with and without matted nodes present was as follows: locoregional failure 23.3% versus 12.8% (chi-square $p = .16$); distant failure 50.0% versus 1.4% ($p < .001$); any failure 73.3% versus 14.2% ($p < .001$); cause-specific mortality 56.7% versus 5.4% ($p < .001$); and death from any cause 56.7% versus 13.5% ($p < .001$), respectively. Among 74 patients with N2b nodal classification, distant failure occurred in 1 of 67 patients without matted nodes versus 3 of 7 patients with matted nodes ($p = .002$). Among 42 patients with N2c disease, distant failure occurred in 0 of 30 patients without matted nodes versus 6 of 12 patients with matted nodes ($p < .001$), whereas among 25 patients with N3 disease, distant failure occurred in 0 of 14 patients without versus 6 of 11 patients with matted nodes ($p = .003$). The presence of matted nodes was significantly associated with all endpoints on univariable Cox regression, including locoregional failure (HR = 2.7; $p = .024$), distant failure (HR = 66.3; $p < .001$), any failure (HR = 8.3; $p < .001$), cause-specific mortality (HR = 15.1; $p < .001$), and OS (HR = 6.8; $p < .001$). The presence of rECS on univariable analysis was significantly associated with distant failure (HR = 10.7; $p = .021$), any failure (HR = 2.9; $p = .007$), and OS (HR = 2.2; $p = .045$), with a borderline trend for cause-specific mortality (HR = 2.4; $p = .075$) and a weak trend for locoregional failure (HR = 1.74; $p = .21$). The magnitude of the univariable association between ECS and each endpoint, however, was notably much weaker than the comparable endpoint's HR for matted nodes. Among 148 patients without matted nodes, the presence of rECS was not associated with any endpoint (3-year Kaplan–Meier estimates: locoregional control 85.7% vs 88.7% [log-rank $p = .50$]; distant control 98.7% vs 100% [$p = .90$]; freedom from treatment failure

TABLE 1. Baseline characteristics.

Characteristics	All HPV+ patients (*N* = 178)		No matted nodes (*N* = 148)		Matted nodes (*N* = 30)		*p* value*
	Median	Range	Median	Range	Median	Range	
Age, y	55.2	34.1–78.1	56.3	34.1–78.1	53.9	42.0–75.1	.24
Smoking pk-yrs	6	0–140	10	0–140	1.5	0–100	.20
	No. of patients	%	No. of patients	%	No. of patients	%	
Men	160	89.9	131	88.5	29	96.7	.26
Smoking history							
<10 pk-yrs	92	51.7	75	50.7	19	63.3	.31
≥10 pk-yrs	86	48.3	73	49.3	11	36.7	
Never	66	37.1	52	35.1	14	46.7	.27#
Former	61	34.3	52	35.1	9	30.0	
Current	51	28.7	44	29.7	7	23.3	
T classification							
T1	27	15.2	21	14.2	6	20.0	.37†
T2	69	38.8	60	40.5	9	30.0	.047‡
T3	34	19.1	32	21.6	2	6.7	
T4	48	27.0	35	23.6	13	43.3	
N classification							
N0	10	5.6	10	6.8	0	0.0	<.001†
N1	13	7.3	13	8.8	0	0.0	
N2a	14	7.9	14	9.5	0	0.0	
N2b	74	41.6	67	45.3	7	23.3	
N2c	42	23.6	30	20.3	12	40.0	
N3	25	14.0	14	9.5	11	36.7	
rECS	115	64.6	85	57.4	30	100.0	<.001
Consolidative neck dissection	40	22.5	30	20.3	10	33.3	.19
HPV+ risk group							
Low risk (T1–3, N0–2c, <10 pk-yrs)	57	32.0	52	35.1	5	16.7	<.001†
Intermediate risk (T1–3, N0–2c, ≥10 pk-yrs)	54	30.3	50	33.8	4	13.3	
High risk (T4 or N3)	67	37.6	46	31.1	21	70.0	

Abbreviations: HPV+, human papillomavirus-positive; rECS, radiographic extracapsular spread; pk-yrs, pack-years.
* Independent samples *t* test or chi-square test for comparison between patients with and without matted lymph nodes.
† Chi-square for trend.
‡ Comparison of T4 vs T1–3 classifications.

84.6% vs 88.8% [$p = .54$]; cause-specific survival 98.8% vs 96.7% [$p = .25$]; and OS 90.5% vs 96.7% [$p = .83$] for patients with and without rECS present, respectively). Stratification of rECS by the presence of matted nodes in a Cox regression model further demonstrates the lack of prognostic impact of rECS without matted nodes on locoregional failure, distant failure, any failure, cause-specific mortality, and OS ($p > .25$), in contrast to the statistically significant association between matted nodes and each of these endpoints (Table 2).

As shown in Figures 2A to 2C and 3A and 3B, stratification of the study population by the previously defined HPV-positive oropharyngeal cancer risk groups effectively discriminated the risk of locoregional failure, distant failure, any failure, cause-specific mortality, and OS (log-rank $p \leq .002$ for all comparisons; Table 3). After adjustment for risk group using Cox regression, the presence of matted nodes remained a significant predictor of distant failure (HR = 52.2; $p < .001$), any failure (HR = 6.2; $p < .001$), cause-specific mortality (HR = 12.5; $p < .001$), and OS (HR = 5.1; $p < .001$), and trended toward significance for locoregional failure (HR = 2.0; $p = .15$; Table 4). Adjustment by Cox regression for previously identified individual risk factors[5,6] in HPV-associated oropharyngeal cancer (T4 classification, N3 classification, and ≥10 smoking pack-years) yielded similar results, with matted nodes remaining the strongest prognostic factor for all endpoints (HR = 152.4 for distant failure, HR = 7.2 for any failure, HR = 14.1 for cause-specific mortality, and HR = 6.4 for OS; all $p < .001$) except for locoregional failure (HR = 1.9; $p = .2$; Table 5). Varying the stratification of nodal classification by other cutoff points (ie, N0–N2a vs N2b–N3, N0–N2b vs N2c–N3) did not change the prognostic value of matted results for each endpoint (data not shown). Categorizing patients with matted nodes into a separate fourth risk group (Table 3; Figures 2D and 2E and 3C–D) highlights the dramatic increase in risk of treatment failure and death among patients with matted nodes compared with patients without matted nodes, even among those with T4 or N3 disease classifications. Compared to high-risk patients without matted nodes, patients with matted nodes (irrespective of T classification, N classification, and smoking status) experienced a substantially increased risk of both distant failure (63.9% vs 3.8% at 5 years; HR = 34.5; 95% confidence interval [CI] = 6.2–190.6) and any failure (74.1% vs 24.2% at 5 years; HR = 4.1; 95% CI = 1.4–11.7) with correspondingly higher rates of cause-

TABLE 2. Cox regression model of radiographic extracapsular spread when stratified by presence of matted nodes.

	Locoregional failure			Distant failure			Any failure			Cause-specific mortality			All-cause mortality		
Covariates	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
rECS (−)	Ref	–	–	Ref	–	–	Ref	–	–	Ref	–	–	Ref	–	–
rECS (+); matted nodes (−)	1.4	0.5–3.5	.51	0.83	0.1–13.1	.90	1.3	0.5–3.2	.54	0.5	0.1–1.9	.28	1.1	0.5–2.7	.81
rECS (+); matted nodes (+)	3.3	1.2–9.5	.026	60.2	8.0–455.3	< .001	9.8	4.4–22.1	< .001	10.4	3.9–28.2	< .001	7.2	3.1–16.9	< .001

Abbreviations: HR, hazard ratio; CI, confidence interval; rECS, radiographic extracapsular spread; Ref, reference.

specific mortality (5-year cause-specific mortality: 71.0% vs 9.8%; HR = 12.6; 95% CI = 3.4–47.4) and OS (5-year OS: 71.0% vs 21.0%; HR = 3.9; 95% CI = 1.3–11.9), whereas the increase in locoregional failure risk was marginal and nonsignificant (5-year locoregional failure: 28.2% vs 24.2%; HR = 1.4; 95% CI = 0.4–5.3). Among patients without matted nodes (n = 148), the HPV-positive risk group remained prognostic for risk of locoregional failure (5-year locoregional failure: 2.0% vs 14.4% vs 24.2%, respectively; p = .005), but did not discriminate for risk of distant failure, which was minimal in all risk groups (5-year distant failure: 0.0% vs 2.1% vs 3.8% for low-risk, intermediate-risk, and high-risk patients without matted nodes, respectively; p = .53).

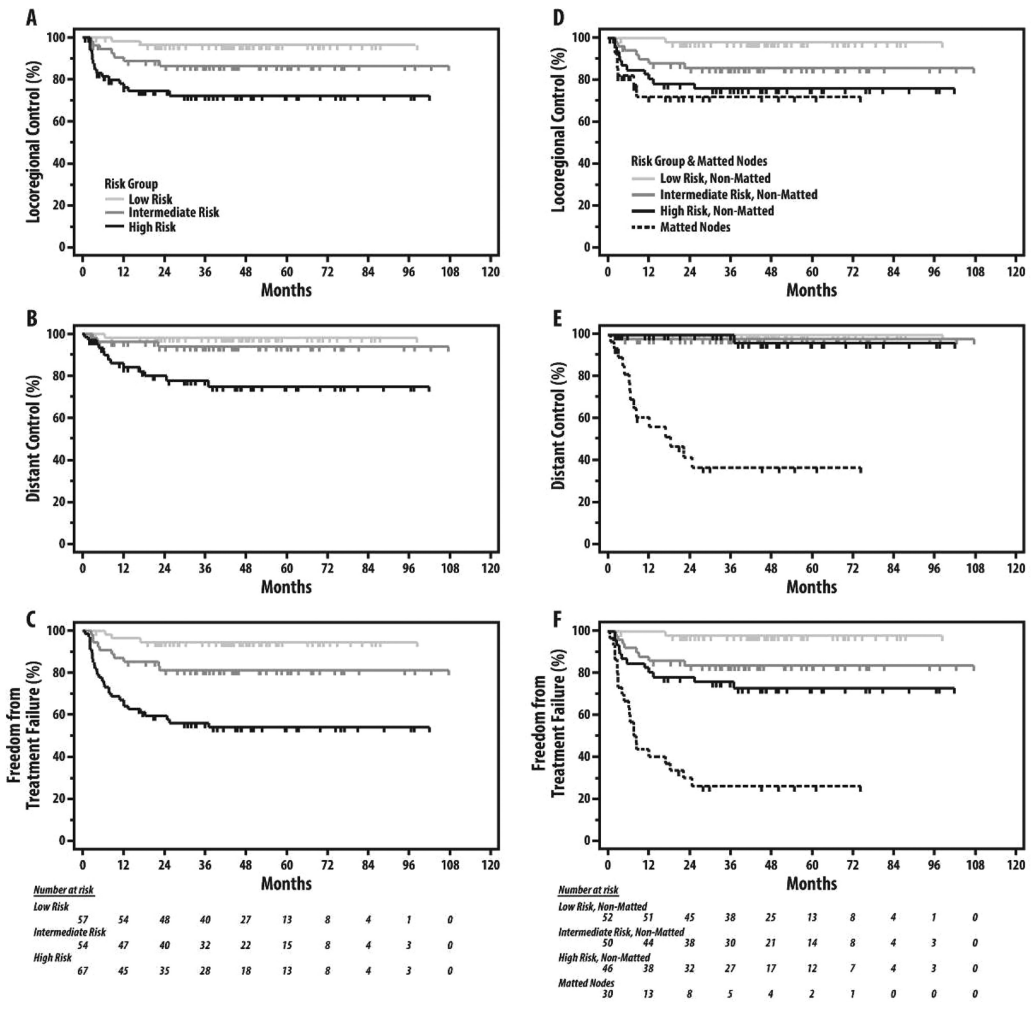

FIGURE 2. Risk of locoregional failure (A, D), distant failure (B, E), and any failure (C, F) by human papillomavirus (HPV)-positive risk group, without and with adjustment for matted nodes, respectively. Kaplan–Meier estimates and *p* values for all comparisons are shown in Table 2.

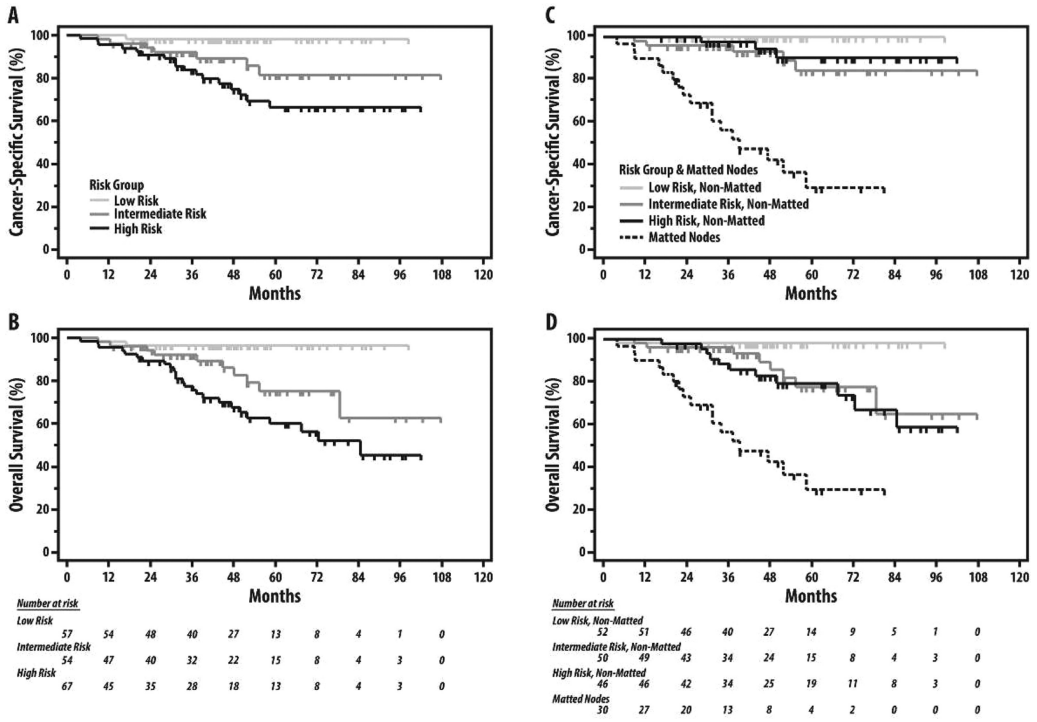

FIGURE 3. Cause-specific survival (A, C) and overall survival (B, D) by human papillomavirus (HPV)-positive risk group, without and with adjustment for matted nodes, respectively. Kaplan–Meier estimates and *p* values for all comparisons are shown in Table 2.

DISCUSSION

The primary finding of the present study was that the presence of matted lymph nodes in patients with HPV-related oropharyngeal cancer identified those patients with a greater than 60% risk of distant failure, whereas the absence of matted nodes was associated with a minimal distant failure risk. The prognostic impact of matted nodes on distant failure remained statistically and clinically significantly even after adjustment for the HPV-positive risk group and for previously identified risk factors in HPV-positive oropharyngeal cancer,[2,5,6] among which matted nodes were the strongest predictor for distant failure, any failure, cause-specific mortality, and OS. In contrast, the association between matted nodes and locoregional failure was only marginal and nonsignificant after separate adjustment for both risk group and individual risk factors. Finally, among patients without matted nodes, risk group was of minimal utility for stratifying risk of distant failure (<4% irrespective of risk group), although it remained highly prognostic for locoregional failure.

These present findings are highly pertinent to ongoing efforts to refine patient selection for treatment modification in HPV-related oropharyngeal cancer. Although the prognosis for this overall patient population is generally favorable, 15% to 25% of patients with HPV-related oropharyngeal cancer nonetheless experience disease recurrence despite treatment with full-intensity CRT.[2,5,17,18] Distant failure accounts for approximately 50% of treatment failures in HPV-positive oropharyngeal cancer, compared to a substantially lower proportion in patients with traditional smoking-related HNSCC.[2,6] These shifting patterns of failure have placed heightened importance on distant control in this population. Although advanced T and N disease classifications are established risk factors for distant failure, the incidence of distant failure in patients with T4 or N3 disease nonetheless remains <30% at 3 years in both the present study and prior reports.[6] Therefore, the characterization of a population of patients with matted nodes whose risk of distant failure exceeds 60% despite treatment with full-intensity CRT, represents an advance in our ability to identify patients with exceptionally poor distant control rates for whom escalation of treatment directed at reducing distant failure may be warranted.

Efforts to intensify systemic therapy in locally advanced head and neck cancer, to date, have been largely hampered by lack of a survival benefit and increased toxicity[19,20] compared to the standard of concurrent CRT. A meta-analysis of randomized trials of chemotherapy in HSNCC demonstrated that although the addition of induction chemotherapy to locoregional therapy (without concomitant chemotherapy) reduced distant failure, no improvement in survival could be detected.[21] The DeCIDE study, which randomized 280 patients with N2/3 nodal classifications to definitive chemoradiation with or without induction docetaxel, cisplatin, and 5-fluorouracil, similarly demonstrated an absolute 9% reduction in distant failure at 3 years with induction chemotherapy, although without any OS benefit, possibly because of competing events and low total event rates.[22] In contrast, the PARADIGM study, which enrolled 145

TABLE 3. Kaplan–Meier estimates of locoregional failure, distant failure, any failure, and cause-specific mortality outcome by human papillomavirus-positive risk group, before and after accounting for presence of matted nodes.

		HPV+ risk stratification				HPV+ risk stratification, adjusted for presence of matted nodes				
	Endpoint	Low risk ($n = 57$) (T1–3, N0–2c, <10 pk-yrs)	Intermediate risk ($n = 54$) (T1–3, N0–2c, >10 pk-yrs)	High risk ($n = 67$) (T4 or N3)	Log-rank p value	Low risk, nonmatted nodes ($n = 52$)	Intermediate risk, nonmatted nodes ($n = 50$)	High risk, nonmatted nodes ($n = 46$)	Matted nodes ($n = 30$)	Log-rank p value
3-y estimate (± 95% CI)	Locoregional failure	3.6% (0.0% to 8.1%)	13.6% (4.2% to 23.0%)	27.6% (16.2% to 39.0%)	<.001	2.0% (0.0% to 5.7%)	14.4% (4.4% to 24.4%)	24.2% (11.7% to 36.7%)	28.2% (10.0% to 46.4%)	.001
	Distant failure	1.8% (0.0% to 5.3%)	6.1% (0.0% to 12.8%)	22.3% (10.9% to 33.7%)	<.001	0.0% (0.0% to 0.0%)	2.1% (0.0% to 6.2%)	0.0% (0.0% to 0.0%)	63.9% (43.7–84.1%)	<.001
	Any failure	5.4% (0.0% to 11.3%)	18.8% (8.2% to 29.4%)	43.8% (31.9% to 55.8%)	<.001	2.0% (0.0% to 5.7%)	16.2% (5.8% to 26.6%)	24.2% (11.7% to 36.7%)	74.1% (58.2% to 90.0%)	<.001
	Cause-specific mortality	1.8% (0.0% to 5.3%)	7.8% (0.4% to 15.2%)	16.3% (6.9% to 25.7%)	.002	0.0% (0.0% to 0.0%)	4.0% (0.0% to 9.5%)	2.4% (0.0% to 7.1%)	43.9% (24.9% to 62.9%)	<.001
	All-cause mortality	3.5% (0.0% to 8.2%)	7.8% (0.4% to 15.2%)	22.5% (12.1% to 32.9%)	<.001	1.9% (0.0% to 5.6%)	4.0% (0.0% to 9.5%)	11.9% (2.3% to 21.5%)	43.9% (24.9% to 62.9%)	<.001
5-y estimate (± 95% CI)	Locoregional failure	3.6% (0.0% to 8.1%)	13.6% (4.2% to 23.0%)	27.6% (16.2% to 39.0%)	<.001	2.0% (0.0% to 5.7%)	14.4% (4.4% to 24.4%)	24.2% (11.7% to 36.7%)	28.2% (10.0% to 46.4%)	.001
	Distant failure	1.8% (0.0% to 5.3%)	6.1% (0.0% to 12.8%)	25.2% (13.0% to 37.4%)	<.001	0.0% (0.0% to 0.0%)	2.1% (0.0% to 6.2%)	3.8% (0.0% to 11.2%)	63.9% (43.7% to 84.1%)	<.001
	Any failure	4.8% (0.0% to 10.1%)	18.8% (8.2% to 29.4%)	45.9% (33.6% to 58.2%)	<.001	2.0% (0.0% to 5.3%)	16.2% (5.8% to 26.6%)	27.1% (13.8% to 40.4%)	74.1% (58.2% to 90.0%)	<.001
	Cause-specific mortality	1.8% (0.0% to 5.3%)	18.6% (5.3% to 31.9%)	33.6% (19.9% to 47.3%)	.002	0.0% (0.0% to 0.0%)	15.7% (2.2% to 29.2%)	9.8% (0.0% to 20.6%)	71.0% (50.4% to 91.6%)	<.001
	All-cause mortality	3.5% (0.0% to 8.2%)	24.7% (9.8% to 39.6%)	40.0% (26.5% to 53.5%)	<.001	1.9% (0.0% to 5.6%)	22.5% (7.2% to 37.8%)	21.0% (7.9% to 34.1%)	71.0% (50.4% to 91.6%)	<.001

Abbreviations: HPV+, human papillomavirus-positive; pk-yrs, pack-years; CI, confidence interval.

TABLE 4. Cox regression model for recurrence and survival endpoints with adjustment for matted nodes and risk group in human papillomavirus-related oropharyngeal cancer.

	Locoregional failure			Distant failure			Any failure			Cause-specific mortality			All-cause mortality		
Covariate	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Low-risk group (T1–3, N0–2c, <10 pk-yrs)	Ref	–	–	Ref	–	–	Ref	–	–	Ref	–	–	Ref	–	–
Intermediate-risk group (T1–3, N0–2c, ≥10 pk-yrs)	5.0	0.8–18.9	.087	3.7	0.4–35.5	.25	3.9	1.1–14.1	.039	7.5	0.9–60.6	.059	5.5	1.2–24.8	.028
High-risk group (T4 or N3)	8.2	1.9–35.6	.005	7.5	1.0–57.9	.054	7.70	2.3–25.4	< .001	7.1	0.9–53.9	.060	7.1	1.7–30.4	.009
Matted nodes (yes vs no)	2.0	0.8–4.8	.15	52.2	11.6–234.8	< .001	6.15	3.3–11.6	< .001	12.5	5.1–30.4	< .001	5.1	2.5–10.2	< .001

Abbreviations: HR, hazard ratio; CI, confidence interval; pk-yrs, pack-years; Ref, Reference.

TABLE 5. Cox regression model for recurrence and survival endpoints with adjustment for matted nodes and individual risk factors in human papillomavirus-related oropharyngeal cancer.

	Locoregional failure			Distant failure			Any failure			Cause-specific mortality			All-cause mortality		
Covariate	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
T classification (T4 vs T1–3)	2.0	0.9–4.4	.091	14.3	3.6–56.5	< .001	3.0	1.6–5.7	< .001	2.6	1.1–6.1	.025	2.9	1.5–5.6	.002
N classification (N3 vs N0–2c)	3.2	1.3–7.8	.013	1.5	0.5–4.2	.49	2.2	1.1–4.3	.033	1.3	0.4–3.3	.65	1.4	0.6–3.1	.44
Smoking pk-yrs (>10 vs <10)	1.2	0.6–2.6	.66	5.6	1.7–18.8	.006	1.7	0.9–3.2	.090	1.5	0.7–3.4	.32	1.6	0.8–3.2	.15
Matted nodes (yes vs no)	1.9	0.7–4.8	.20	152.4	26.9–864.3	< .001	7.2	3.7–14.3	< .001	14.1	5.8–34.2	< .001	6.4	3.1–13.0	< .001

Abbreviations: HR, hazard ratio; CI, confidence interval; pk-yrs, pack-years.

patients with locally advanced head and neck cancer with all extents of nodal involvement, failed to show a significant improvement in any endpoint, including distant control, although the low distant failure rate in both the induction chemotherapy (7%) and control arms (11%) may have limited the power of the study to detect a difference.[23] Importantly, neither these studies nor the meta-analysis suggested any improvement in locoregional failure, confirming that the sole potential benefit of induction chemotherapy in locally advanced head and neck cancer is in improvement of distant control. Therefore, if any role for induction chemotherapy exists for patients with locally advanced head and neck cancer, it is most likely in those patients at highest risk of distant failure with comparatively low rates of competing locoregional failure events, for whom improved distant control will be most likely to translate into improved survival. Our data suggest that patients with HPV-related oropharyngeal cancer with matted nodes represent precisely such a population, and provide the rationale for future studies that evaluate the role of systemic therapy intensification in this especially high-risk group.

An additional important finding of the present study was that the exceedingly low rate of distant failure among patients without matted nodes underscores the lack of any role for induction chemotherapy or other intensification of systemic therapy in such patients. Patients with low-risk, intermediate-risk, and high-risk HPV-related oropharyngeal cancer without matted nodes had 5-year distant failure rates of 0%, 2%, and 4%, respectively. These distant control rates leaves little, if any, room for improvement, and therefore provide little rationale for the systemic therapy intensification in the absence of matted nodes. In contrast, 3-year locoregional failure (including residual cells at adjuvant neck dissection) in these HPV-positive risk groups among patients without matted nodes was 2.0%, 14.4%, and 24.2%, respectively. Therefore, patients in the intermediate and high risk groups, even in the absence of matted nodes, remain at significant risk of locoregional failure despite concurrent chemoradiation, and argue against the inclusion of such patients in studies of treatment deintensification for HPV-related oropharyngeal cancer.

The present study had several strengths, specifically the inclusion of an unselected and uniformly treated population of patients with HPV-positive oropharyngeal cancer, long-term follow-up period, and detailed information on pattern of failure, and is among the largest studies to date reporting outcomes of patients with HPV-positive oropharyngeal cancer treated with uniform chemoradiation. Furthermore, this study builds on our previously published work identifying the prognostic import of matted nodes in oropharyngeal cancer[7,8,24] within an expanded uniform cohort of patients with HPV-positive oropharyngeal cancer with longer term follow-up, stratified by previously proposed HPV-positive risk group,[5] and analyzed for pattern of first failure endpoints. The present study differs from this prior work by focusing only on those patients with HPV-positive oropharyngeal cancer after stratification by risk group based upon T/N classification and smoking history, an analysis not performed by Spector et al.[8] The previously unreported survival and pattern of failure data included herein should contribute to the design of future clinical trials focusing on modification of both locoregional and systemic therapy for patients with HPV-positive oropharyngeal cancer, as well as inform counseling of such patients, both issues of increasing importance given the ongoing growth of this patient population.[25] Future studies to expand on the current work should include independent validation of the prognostic value of both matted nodes and the presently proposed risk stratification in patients with HPV-positive oropharyngeal cancer. Validation of interobserver agreement in identifying radiographically matted nodes, presently ongoing in a multi-institutional collaboration, will additionally be required in order for the presence of matted nodes to guide future clinical management decisions. Analysis of patterns of failure among patients with matted nodes who are treated with induction chemotherapy may additionally shed further light on the potential of intensification of systemic therapy to improve these patients' outcomes. Finally, limitations applicable to all retrospective studies pertain to the present study, including insufficient power to detect differences between risk groups with limited number of events.

In summary, the present study demonstrates that patients with HPV-related oropharyngeal cancer with matted nodes experience exceedingly high rates of distant failure after concurrent chemoradiation, and therefore represent a novel candidate population for assessing the efficacy of systemic therapy intensification. By comparison, the virtual absence of distant metastases in patients without matted nodes highlights the lack of rationale for induction chemotherapy or other intensified systemic therapy is such patients, irrespective of T or N classification. Finally, matted nodes did not significantly impact the risk of locoregional failure, suggesting that decisions regarding the intensity of locoregional therapy can be made irrespective of the presence of matted nodes.

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