Oral Oncology 114 (2021) 105147

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Prognostic impact of retropharyngeal lymphadenopathy in early-stage HPV-associated oropharyngeal cancer: Implications for staging optimization

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A B S T R A C T

Objectives: We analyzed the prognostic impact of retropharyngeal lymphadenopathy (RPL) in stage I node-positive HPV-associated oropharyngeal squamous cell carcinoma (OPSCC).

Materials and Methods: We performed a centralized and blinded radiographic review of the pre-treatment images of 234 consecutive patients with AJCC 8th edition stage I cT1-2N1 HPV-associated OPSCC treated with definitive chemoradiation from 2006 to 2016. Five-year disease control and survival outcomes were reported. The prognostic significance of RPL was evaluated through multivariable analysis adjusting for age, smoking history (<10 vs. >10 pack-years), and systemic regimen received.

Results: Median follow-up for surviving patients was 49 months (range: 16–121). RPL was associated with increased locoregional recurrence (LRR) (17.0% v. 3.4%, $p = 0.01$) and distant metastasis (DM) (29.1% v. 5.9%, $p = 0.001$) and inferior progression-free survival (PFS) (55.6% v. 88.2%, $p < 0.001$) and overall survival (OS) (60.6% v. 91.2%, $p < 0.001$). In stage I patients who did not receive high-dose cisplatin (HDC), RPL was associated with worse LRR ($p = 0.04$), DM ($p = 0.03$), PFS ($p < 0.001$), and OS ($p < 0.001$), whereas in those who did receive HDC, RPL was only associated with increased DM ($p = 0.002$) and inferior PFS ($p = 0.04$).

Conclusion: This study suggests that RPL portends a poor prognosis in stage I node-positive HPV-associated OPSCC. The negative impact on LRR may have been mitigated by receipt of HDC. Outcomes of stage I disease with RPL were comparable to historical reports of patients with more advanced-stage disease. Incorporation of RPL into future disease staging should be considered in order to optimize risk-stratification and exclude unsuitable candidates from treatment de-intensification efforts.

Introduction

Human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC) is established as a disease with generally favorable outcomes, particularly when contrasted to other head and neck squamous cell carcinomas which are commonly associated with heavy alcohol and tobacco use [1,2]. Prior cancer staging systems did not accurately prognosticate outcomes for HPV-associated OPSCC. Consequently, the American Joint Committee on Cancer (AJCC) 8th edition staging system reclassified HPV-associated oropharyngeal squamous cell carcinoma (OPSCC) as its own entity and adapted the risk-stratification system proposed by the ICON-S group for this cohort of patients [3].

The revised clinical nodal classifications in the AJCC 8th edition categorizes nodal involvement into three groups: ipsilateral nodal disease up to 6 cm in size, bilateral or contralateral nodal disease up to 6 cm in size, or any nodal disease >6 cm in size. As a result, there is considerable intragroup heterogeneity which may carry underlying prognostic significance. In particular, the presence of retropharyngeal lymphadenopathy (RPL) is not considered in risk stratification. In the pre-HPV era, a retrospective study by Gunn et al. found RPL to be a negative prognostic factor for disease control and survival for OPSCC [4].

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https://doi.org/10.1016/j.oraloncology.2020.105147
Received 29 September 2020; Received in revised form 6 December 2020; Accepted 12 December 2020
Available online 16 January 2021

Subsequently, additional studies have evaluated the prognostic impact of RPL in specifically HPV-associated OPSCC with conflicting results [5–10]. Treatment de-intensification is an area of active investigation for favorable-risk HPV-associated OPSCC, and it is not clearly understood if RPL is an adverse risk factor that should preclude enrollment in such efforts. Thus, the objective of this study was to evaluate the prognostic impact of RPL in patients with stage I node-positive HPV-associated OPSCC treated with definitive chemoradiation.

Materials and methods

A retrospective review was conducted of 481 consecutive patients with AJCC 7th edition TNM stage III-IV locally advanced p16-positive OPSCC who underwent definitive concurrent chemoradiation from June 2006 to December 2016. For the purposes of this study, disease staging was updated to the AJCC 8th edition. Of the 481 patients, 234 were identified with AJCC 8th edition stage I cT1-2N1 disease and were included in this analysis. Patients who underwent oncologic surgery or received induction chemotherapy prior to definitive chemoradiation were excluded from the analysis, as were patients with prior head and neck radiotherapy or other known malignancies (excluding non-melanomatous skin cancer) within the previous five years. A minimum of one year of follow-up was required. Centralized pathology review was conducted with p16 immunohistochemical staining performed as a surrogate for HPV-positivity with positive cases interpreted as those with $\geq$ 70% nuclear and cytoplasmic immunoreactivity [11]. Institutional review board approval was obtained.

Patients received intensity modulated radiotherapy to a planned dose of 66–70 Gy with simultaneous integrated boost technique. Involved retropharyngeal lymph nodes were treated to a dose of 70 Gy. The uninvolved bilateral retropharyngeal lymphatic chain and neck nodal basins were treated to an elective dose in all cases with the exception of select well-lateralized tonsil primaries with ipsilateral lymph node involvement, in which case only the ipsilateral retropharyngeal lymphatic chain and neck was treated. All patients were simulated with CT scan and immobilized in a thermoplastic mask. Concurrent systemic therapy was administered to all patients: 106 (45.3%) patients with high-dose cisplatin (100 mg/m^2), 92 (39.3%) patients with triweekly carboplatin (AUC = 5), 19 (8.1%) patients with cetuximab (400 mg/m^2 loading dose followed by 250 mg/m^2 weekly), 16 (6.8%) patients with weekly cisplatin (40 mg/m^2), and 1 (0.4%) patient with weekly carboplatin (AUC = 2). The first post-treatment evaluation with clinical exam and nasopharyngoscopy was performed approximately one month after completion of chemoradiation. Subsequent follow-up was scheduled every two to three months for the first year, every three to four months for the second year, and every six months until five years, at which point patients had the option of annual surveillance in the head and neck clinic or return to routine care with their primary care physician. No planned neck dissections were performed. A PET/CT was commonly performed at three months following completion of chemoradiation. Additional imaging was obtained when clinically indicated based on patient-reported symptoms or abnormal findings on examination at the discretion of the treating physicians.

All patients included in this analysis had at minimum a diagnostic CT and/or MRI of the neck for review, and 228 (47.4%) patients additionally had a baseline PET/CT performed. Radiographic studies were centrally reviewed to evaluate the presence of RPL by a neuroradiologist and a head and neck radiation oncologist who were blinded to baseline patient characteristics and disease outcomes. The retropharyngeal lymph nodes are a group of lymph nodes extending from the skull base to approximately the level of the hyoid bone bordered anteriorly by the pharyngeal constrictor muscles, posteriorly by the prevertebral fascia, and laterally by the internal carotid artery. Numerous sets of criteria have been used to classify pathologic retropharyngeal lymph nodes in the literature. For the purposes of this analysis, retropharyngeal lymph node positivity was defined as a lymph node with minimal axial diameter > 5 mm, presence of central necrosis, 2 or more clustered lymph nodes, or FDG-avidity on PET/CT. A characteristic example of an involved hypermetabolic retropharyngeal lymph node is depicted in Figure 1.

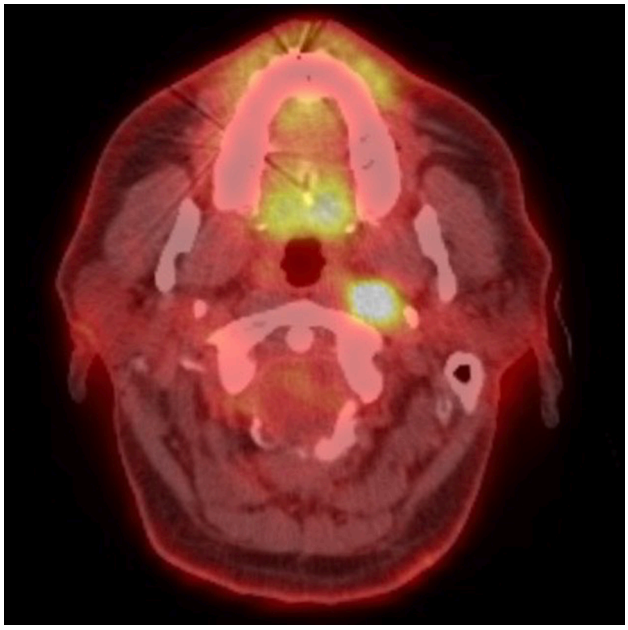

Fig. 1. Characteristic Example of an Involved Hypermetabolic Retropharyngeal Lymph Node on PET/CT Imaging.

Baseline patient characteristics were compared with independent *t*-test and Chi square test. Disease control and survival outcomes were estimated by the Kaplan-Meier method with five-year outcomes reported from the date of treatment completion. Endpoints analyzed included locoregional recurrence (LRR), distant metastasis (DM), progression-free survival (PFS), and overall survival (OS). Multivariable analysis for the entire cohort was performed using Cox proportional hazards models adjusted for patient age, smoking history ($\leq$10 vs. > 10 pack-years), and concurrent systemic agent received (high-dose cisplatin v. other). Two-sided statistical analysis was performed with the significance level set at 0.05.

Results

Patient and disease characteristics are listed in Table 1. Median follow-up for surviving patients was 49 months (range: 16–121). Median age was 61 years (range: 35–81). The majority of patients were male (88.5%) with tumors of the tonsil (59.8%) and base of tongue (38.0%). The incidence of RPL in stage I node-positive disease was 7.7%. The majority of patients with RPL had T2 disease (94.4%).

Disease control and survival outcomes are listed in Table 2. Five-year LRR for the entire cohort was 4.4%. On multivariable analysis, LRR was higher in patients with RPL compared to those without, 17.0% v. 3.4% (p = 0.01), respectively. Patients were further analyzed in two groups, those who received high-dose cisplatin and those who received an alternative regimen. In the high-dose cisplatin group, no difference was noted in LRR among those with RPL compared to those without. Among patients who received an alternative systemic agent, RPL was associated with higher rates of LRR (p = 0.04). Three patients with RPL experienced locoregional failures. Of these, one patient received high-dose cisplatin and two patients received an alternative systemic agent. The patient who received high-dose cisplatin had persistent disease in both the primary and neck after completion of chemoradiation. One patient who received cetuximab experienced a recurrence in the neck 17 months post-chemoradiation, and one patient who received triweekly

Table 1
Baseline Patient and Disease Characteristics.

	Total N = 234 (%)	RPL Absent N = 216 (%)	RPL Present N = 18 (%)	p-value
Median patient age (years)	61	57	61	0.48
Sex				0.99
Male	207 (88.5%)	191 (88.4%)	16 (88.9%)	
Female	27 (11.5%)	25 (11.6%)	2 (11.1%)	
Subsite				0.07
Tonsil	140 (59.8%)	127 (58.8%)	13 (72.2%)	
Base of tongue	89 (38.0%)	85 (39.4%)	4(22.2%)	
Soft palate	2 (0.9%)	1 (0.5%)	1 (5.6%)	
Pharyngeal wall	3 (1.3%)	3 (1.4%)	0 (0.0%)	
Clinical T stage				**0.008**
T1	80 (34.2%)	79 (36.6%)	1 (5.6%)	
T2	154 (65.8%)	137 (63.4%)	17 (94.4%)	
>10 pack-year smoking history				0.99
No	136 (58.1%)	125 (61.1%)	11 (57.9%)	
Yes	98 (41.9%)	91 (38.9%)	7 (42.1%)	
Concurrent systemic agent				0.33
High-dose cisplatin	106 (45.3%)	100 (46.3%)	6 (33.3%)	
Alternate regimen	128 (54.7%)	116 (53.7%)	12 (66.7)	

Table 2
Impact of Retropharyngeal Lymphadenopathy on Disease Control and Survival with Adjusted Hazard Ratios.

	5-year			
	RPL absent	RPL present	Adjusted HR (95% CI)	p-value
Locoregional recurrence	3.4%	17.0%	6.16 [1.54–24.62]	**0.01**
Distant metastasis	5.9%	29.1%	6.61 [2.29–19.06]	**<0.001**
Progression-free survival	88.2%	55.6%	5.85 [2.57–13.31]	**<0.001**
Overall survival	91.2%	60.6%	6.43 [2.63–15.71]	**<0.001**

carboplatin had persistent disease in the retropharyngeal lymph node after completion of treatment. Overall, five-year DM was 7.7%. On multivariable analysis, RPL was associated with higher rates of DM, 29.1% v. 5.9% ($p < 0.001$). Five patients with RPL experienced distant failures. Of these, two patients received high-dose cisplatin, two patients received cetuximab, and one patient received triweekly carboplatin. On subgroup analysis, RPL was associated with higher rates of DM in both patients who received high-dose cisplatin ($p = 0.002$) and patients who received an alternative systemic agent ($p = 0.03$).

Five-year PFS for the entire cohort was 85.6%. On multivariable analysis, inferior PFS was observed in patients with RPL compared to those without, 55.6% v. 88.2% ($p < 0.001$). On subgroup analysis, RPL was associated with inferior PFS in both patients who received high-dose cisplatin ($p = 0.04$) and patients who received an alternative systemic agent ($p < 0.001$). Overall, five-year OS was 88.6%. On multivariable analysis, OS was inferior in patients with RPL compared to those without, 60.6% v. 91.2% ($p < 0.001$). In patients who received high-dose cisplatin, no difference was noted in OS among those with RPL compared to those without. Among patients who received an alternative systemic agent, RPL was associated with inferior OS ($p < 0.001$).

Discussion

The new N1 classification for HPV-mediated OPSCC includes all nodal disease involving the ipsilateral neck<6 cm in size and consequently comprises a heterogeneous disease group. For instance, a patient with a single 1 cm lymph node in the ipsilateral level II cervical neck now has the same nodal classification as a patient with multiple bulky lymph nodes in the ipsilateral neck including the retropharyngeal chain and/or supraclavicular neck. It is conceivable that these two hypothetical patients may have different likelihood of disease control. This centralized radiographic study does indeed demonstrate that RPL is an independent negative prognostic factor for disease control in patients with stage I node-positive HPV-associated OPSCC treated with definitive chemoradiation. Patients without RPL had excellent rates of disease control with 5-year LRR and DM rates of 3.4% and 5.9%, respectively; however, their stage I counterparts with RPL had a 5-fold increase in LRR and DM, with rates of treatment failure more comparable to historical reports of patients with more advanced-stage disease [2]. These findings are pertinent as we pursue de-intensification strategies for early-stage HPV-associated OPSCC and highlight the need for caution before assuming that all patients with stage I disease within the current staging system are truly at low-risk.

We observed that the prognostic impact of RPL was less pronounced in patients who received chemoradiation with high-dose cisplatin which is the National Comprehensive Cancer Network guideline-concordant standard of care concurrent systemic agent. RPL was associated with increased risk of LRR and DM as well as inferior PFS and OS for patients who did not receive high-dose cisplatin, whereas those who received high-dose cisplatin were found only to have an increased risk of DM and inferior PFS without significant differences in other outcomes. This observation suggests that while RPL is an adverse prognostic factor, high-dose cisplatin may mitigate its negative impact to a certain extent. Patients in our study who did not receive high-dose cisplatin mainly received either triweekly carboplatin or cetuximab (86.7%). We previously published our institutional experience treating locally advanced HPV-associated OPSCC with definitive chemoradiation with triweekly carboplatin and high-dose cisplatin and found comparable disease control and survival outcomes in patients with stage I and stage II disease but superiority of high-dose cisplatin over triweekly carboplatin for patients with stage III disease [12]. Recently, two large randomized controlled trials, RTOG 1016 and De-ESCALaTE, found that cetuximab could not demonstrate non-inferiority when compared to high-dose cisplatin in the management of locally advanced HPV-associated OPSCC [13,14]. Although both studies failed to demonstrate non-inferiority, it is likely that the lack of refined prognostic factors led to poor patient selection for de-intensification. Indeed, the difference between high-dose cisplatin and cetuximab was most pronounced in patients with stage III disease, particularly in the De-ESCALaTE trial where a 2-year overall survival difference of nearly 26% was observed in contrast to a difference of only 5% in stage I and II disease. Collectively, the aforementioned studies demonstrate that cetuximab and triweekly carboplatin are inferior to high-dose cisplatin in treatment of stage III HPV-associated OPSCC. Our current study demonstrates that stage I disease with RPL has outcomes comparable to historical reports of stage III disease [2]. It is, therefore, reasonable to hypothesize that de-intensification of treatment through alternative systemic agents or the absence of concurrent systemic therapy altogether may magnify the negative impact of RPL and result in poor disease control.

We observed a higher incidence of RPL in tonsil primaries compared to base of tongue primaries which is not unexpected due to the proximity of the tonsil to the retropharyngeal lymphatic chain compared to the base of tongue. The retropharyngeal lymphatic chain is not characteristically considered the first echelon of lymphatic drainage for

oropharyngeal primaries. As such, RPL may be a marker of more advanced disease. In fact, we observed that the majority of patients with stage I disease with RPL had T2 disease with only one patient in this cohort having T1 disease. Among all-comers, RPL was associated with an increased rate of LRR. However, on subgroup analysis by systemic regimen received, the increased rate of LRR was only observed in patients with RPL who did not receive high-dose cisplatin. In contrast, we observed an increased rate of distant failure in patients with RPL compared to those without, even in the subgroup of patients who received high-dose cisplatin. Collectively, these findings suggest that the presence of RPL is mostly prognostic for the risk of distant relapse which is in concordance with other prior reports [5,9]. One study specifically evaluating outcomes of stage I node-positive HPV-associated OPSCC treated with definitive radiotherapy with or without concurrent systemic therapy found that RPL was associated with increased distant failure, although this did not translate into a PFS detriment [9]. In a separate cohort of HPV-associated OPSCC treated with chemoradiation with concurrent carboplatin and paclitaxel, Samuels et al. found that RPL was independently associated with inferior failure-free survival, freedom from distant failure, cancer-specific survival, and OS [5]. To our knowledge, this is the only other study to evaluate the impact of RPL in HPV-associated OPSCC exclusively in patients receiving concurrent chemoradiation; however, it is not known if weekly carboplatin and paclitaxel is as efficacious as high-dose cisplatin as there are no randomized or large retrospective studies comparing the two regimens. While it is reasonable to hypothesize that weekly carboplatin and paclitaxel provides adequate radiosensitization for locoregional control in HPV-associated OPSCC, the reduced intensity of this regimen is unlikely to have similar systemic coverage for micrometastatic disease compared to high-dose cisplatin. Given that the published data and our own results suggest that RPL is most strongly tied to the increased risk of distant failure, the use of a regimen with inadequate systemic coverage may have magnified this prognostic impact, leading to a survival detriment. In fact, in the De-ESCALaTE trial, high-dose cisplatin demonstrated significantly lower rates of DM when compared to cetuximab, suggesting that the choice of concurrent regimen can have an impact on distant control.

Other studies that did not demonstrate an independent prognostic impact of RPL included a variety of treatment regimens ranging from radiotherapy alone to the addition of induction chemotherapy [6,8]. Initial results from NRG HN002 demonstrated that radiotherapy alone did not meet the acceptability threshold for PFS to be considered a viable treatment regimen for locally advanced HPV-associated OPSCC [15]. Conversely, intensification of treatment with induction chemotherapy may have masked an elevated risk of distant failure associated with the presence of RPL. Additionally, while some of these studies attempted to adjust for confounding factors, including the receipt of systemic therapy, they did not account for the type of concurrent treatment administered. As previously discussed, we now know from RTOG 1016 and De-ESCALaTE that cetuximab is an inferior systemic agent compared to high-dose cisplatin. This finding suggests that a robust analysis should adjust for the specific concurrent agent received to minimize the risk of obscuring study results. In our study, to combat this issue, we performed a multivariable analysis adjusting for treatment with high-dose cisplatin versus an alternative regimen.

Certain limitations of our study should be considered. First, there is risk of underlying sparse data bias because of the overall low incidence of RPL and a limited number of events due to the generally favorable outcomes associated with early-stage HPV-associated OPSCC. Another limitation of our study is that we were unable to obtain pathologic confirmation of retropharyngeal lymph node involvement; however, these lymph nodes are challenging to biopsy and not routinely pathologically evaluated in clinical practice. To strengthen the validity of the study, we conducted a centralized radiographic review performed by two blinded physicians with second review of any discordant interpretations. Finally, the retrospective nature of the study lends itself to underlying bias. We attempted to minimize potential biases through multivariable analysis accounting for age, smoking history, and the concurrent systemic regimen received. We also excluded patients who received surgery, radiation alone, or induction chemotherapy prior to radiation in order to evaluate outcomes in a more homogeneous cohort of patients who were all treated with concurrent chemoradiation.

In conclusion, RPL independently predicted for inferior outcomes in stage I node-positive HPV-associated OPSCC treated with definitive chemoradiation. To our knowledge, this is the only study evaluating the prognostic impact of RPL in HPV-associated OPSCC exclusively treated with definitive chemoradiation that evaluated outcomes by the type of concurrent systemic therapy administered. Our findings suggest that the presence of RPL in stage I node-positive disease is associated with a prognosis akin to more advanced disease. On subgroup analysis, the negative prognostic impact of RPL was most evident among those who received a concurrent systemic regimen other than high-dose cisplatin. In patients who received high-dose cisplatin, the negative impact of RPL on LRR was no longer observed, though its association with inferior DM and PFS persisted. As clinicians aggressively pursue de-intensification strategies, disease factors must be considered which are not delineated in our current staging system. By incorporating these risk factors into a future staging system, we can feel more confident in de-intensifying treatment for those patients who have truly favorable-risk disease. The findings of this report suggest that RPL should be incorporated into the staging of HPV-associated OPSCC in order to improve disease risk-stratification and exclude unsuitable candidates from future de-intensification efforts.

Role of the funding source

This work was supported by a grant from the Regional Research Committee of Kaiser Permanente Southern California (KP-RRC-20160901). The committee was not involved in the preparation of this manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors wish to thank Hannah B. Herrera for her assistance with data collection.

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