Published in final edited form as:

Otolaryngol Head Neck Surg. 2018 January ; 158(1): 118–121. doi:10.1177/0194599817733677.

An algorithm to evaluate suspected lung metastases in patients with HPV-associated oropharyngeal cancer

Kyle K. VanKoeveering, M.D.^{1,*}, Emily Marchiano, M.D.^{1,*}, Heather M. Walline, PhD¹, Thomas E. Carey, PhD¹, Jonathan B. McHugh, M.D.², J. Chad Brenner, PhD¹, Christine M. Goudsmit¹, Emily Belille, MS³, Matthew E. Spector, M.D.¹, Andrew G. Shuman, M.D.¹, and the University of Michigan Head and Neck SPORE team

¹Department of Otolaryngology-Head and Neck Surgery, University of Michigan Health System, Ann Arbor, Michigan, USA

²Department of Pathology, University of Michigan Health System, Ann Arbor, Michigan, USA

³Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, Michigan, USA

Abstract

Distinguishing between distantly metastatic and metachronous lung primary carcinoma is challenging for patients with a history of head and neck cancer. There are implications for registry data, prognosis and related counseling, and management options including eligibility for precision oncology trials. Patients with human-papilloma virus (HPV) associated oropharyngeal squamous cell carcinoma (OPSCC) who were treated under a uniform clinical protocol and achieved a complete response were identified in a single-institution prospective head and neck cancer epidemiology database (n = 205). Fifteen patients presented with pulmonary nodule(s) after completion of therapy. We describe our algorithm for the evaluation of these patients including histopathology, p16 immunohistochemistry, and HPV in-situ hybridization (ISH).

Keywords

Oropharyngeal cancer; human papillomavirus; lung nodule; pulmonary metastases; head and neck cancer

INTRODUCTION

In patients with oropharyngeal squamous cell carcinoma (OPSCC), the lung is both the most common site of distant metastasis and the most likely site of a metachronous primary to arise outside of the head and neck region.^{1,2} In the human-papilloma virus (HPV) era,

Corresponding Author: Andrew G. Shuman, MD, Department of Otolaryngology – Head and Neck Surgery, University of Michigan Health System, 1500 East Medical Center Drive, Ann Arbor, MI 48109, Phone: (734) 232-0120, Fax: (734) 936 - 9625, shumana@med.umich.edu.

*Co-first Authors

Financial Disclosures: None

Conflicts of Interest: None

distant failure is unpredictable, occurring in atypical locations and at longer time intervals than HPV negative head and neck squamous cell carcinoma (HNSCC).³ The treatment algorithm for a pulmonary nodule(s) in this setting – including eligibility for clinical trials – varies widely and is influenced by its distinction as a metastasis rather than a second primary.⁴ As such, a reliable method for distinguishing between the two is critical. Although p16 overexpression is widely accepted as a surrogate marker for the presence of HPV in OPSCC, where the use of p16 immunohistochemistry and HPV in-situ hybridization in combination has a sensitivity of 90% and specificity of 88%.⁵ However, there is not a parallel paradigm in lung SCC. Ten to twenty percent of lung SCC stain positive for p16, but this does not signify the presence of HPV.^{4,6–8} Herein, we describe our approach and present a simple algorithm to evaluation of a lung nodule in patients with a history of OPSCC.

MATERIALS AND METHODS

Patients with HPV associated OPSCC treated under a uniform clinical protocol consisting of weekly carboplatin and paclitaxel with intensity modulated radiation therapy (IMRT) between 2003 and 2010 were identified in a single-institution prospective head and neck cancer epidemiology database (n = 205). Patients presenting with subsequent lung nodule(s) were identified. The study was approved by the University of Michigan Medical School Institutional Review Board (IRBMED).

Demographics, treatment modality, recurrence pattern, and outcomes were collected. p16 detection was performed on untreated primary tumor and on metastatic lesions as previously described, and on metastatic lesions using in-situ hybridization (ISH) for HPV DNA using a cocktail directed against a subset of high-risk HPV genotypes including 16,18, 33, 35, 39, 45, 51, 56 and 66 (INFORM HPV ISH assay, Ventana Medical Systems Inc., Tucson, AZ).⁹ In a subset of patients for which enough DNA could be isolated from the biopsies, MultiPlex HPV PCR-MassArray was performed. Descriptive statistics were tabulated using Excel 2013 (Microsoft Corporation).

RESULTS

Fifteen patients treated under this uniform clinical protocol developed pulmonary lesion(s). Fourteen patients were male with a mean age of 52 years. The primary tumor arose from either the tonsil (53%) or base of tongue (47%). All primary tumors were p16 positive. All patients had pulmonary lesions that were biopsied or resected. One-hundred percent of the lung lesions were p16 positive (positive defined as >20% staining). Thirteen of the 15 metastatic lesions were HPV positive by ISH and 2/15 were ISH negative (Table 1). The mean time from start of treatment to recurrence was 16 months (range 6 – 41). At last known follow-up, 73% (11/15) of patients died of disease, 13% (2/15) of patients were alive with no evidence of disease, and 13% (2/15) were lost to follow-up with unknown outcomes. Of those who were p16 and ISH positive, 10/13 (77%) died of disease, while 1/2 (50.0%) p16 positive and ISH negative patients died of disease at follow-up.

DISCUSSION

Distinguishing between distant relapse and metachronous lung primary in patients with a history of OPSCC has implications for maintaining accurate registry data, determining prognosis, and potentially altering management options including eligibility for oncology trials. Initial diagnostic assessment includes standard histologic evaluation. While OPSCC is classically characterized as “non-keratinizing” (Figure 1), this morphologic feature can overlap with poorly differentiated primary lung SCC and is not sufficient for clarification. If the lung lesion is suspected to be SCC among patients treated for p16 positive OPSCC, we suggest utilization of a simple algorithm for workup (Figure 2). Immunohistochemical staining for p16 should be performed. If negative, we identify the tumor as primary lung SCC, and management can be directed appropriately. However, if the lesion is positive for p16, HPV detection using ISH may distinguish whether the p16 overexpression is secondary to metastatic disease or from primary lung SCC.

In our cohort, we identified patients with a history of advanced stage OPSCC who subsequently presented with pulmonary nodule(s). Thirteen of these patients were correctly identified as having distant relapse using this diagnostic algorithm. Of the two discordant patients (p16 positive, ISH negative), one died of disease at follow-up. Our group has previously shown PCR to be more a sensitive test to determine HPV status in virally related OPSCC.¹⁰ In this study, we did attempt to perform PCR on the lung specimens, but only 8/15 patients had sufficient tissue available, highlighting a practical challenge of PCR testing with small biopsy samples. Of the 8 patients with PCR available, ISH and PCR concurred in 7/8 cases, confirming our previous findings. Due to practical challenges with PCR availability and implementation, we believe ISH should be used in the algorithm in the workup of these patients. In the future, the challenges associated with this multi-step process may be circumvented by next generation sequencing techniques.¹¹

These data are limited by the relatively low N and uniform treatment paradigm, thereby limiting generalizability. However, the use of a robust, “clean” prospectively maintained dataset with standardized treatment and surveillance is also a strength. The dearth of many p16 negative lung lesions reflects our patient population; cohorts with higher tobacco use histories may contain a higher percentage of second primary lung malignancies that can further “test” this algorithm.

We introduce a pragmatic system for categorizing lung lesions in patients with a history of OPSCC. A standardized methodology for evaluating these patients will ensure patients are directed to appropriate management, given accurate prognostic information, and stratified appropriately.

Acknowledgments

Funding Source: Supported by grant P50CA097248 from the National Institutes of Health–National Cancer Institute (NIH-NCI) Head and Neck SPORE (Specialized Programs of Research Excellence) and NIH Grant U01DE025184.

References

1. Huang SH, Perez-Ordóñez B, Weinreb I, et al. Natural course of distant metastases following radiotherapy or chemoradiotherapy in HPV-related oropharyngeal cancer. *Oral oncology*. 2013; 49(1):79–85. [PubMed: 22917550]
2. Jones AS, Morar P, Phillips DE, Field JK, Husband D, Helliwell TR. Second primary tumors in patients with head and neck squamous cell carcinoma. *Cancer*. 1995; 75(6):1343–1353. [PubMed: 7882285]
3. Huang SH, Perez-Ordóñez B, Liu FF, et al. Atypical clinical behavior of p16-confirmed HPV-related oropharyngeal squamous cell carcinoma treated with radical radiotherapy. *International journal of radiation oncology, biology, physics*. 2012; 82(1):276–283.
4. Bishop JA, Ogawa T, Chang X, et al. HPV analysis in distinguishing second primary tumors from lung metastases in patients with head and neck squamous cell carcinoma. *The American journal of surgical pathology*. 2012; 36(1):142–148. [PubMed: 22173119]
5. Schache AG, Liloglou T, Risk JM, et al. Evaluation of human papilloma virus diagnostic testing in oropharyngeal squamous cell carcinoma: sensitivity, specificity, and prognostic discrimination. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2011; 17(19):6262–6271. [PubMed: 21969383]
6. Gatta LB, Balzarini P, Tironi A, et al. Human papillomavirus DNA and p16 gene in squamous cell lung carcinoma. *Anticancer research*. 2012; 32(8):3085–3089. [PubMed: 22843877]
7. Yanagawa N, Wang A, Kohler D, et al. Human papilloma virus genome is rare in North American non-small cell lung carcinoma patients. *Lung cancer (Amsterdam, Netherlands)*. 2013; 79(3):215–220.
8. Jordan RC, Lingen MW, Perez-Ordóñez B, et al. Validation of methods for oropharyngeal cancer HPV status determination in US cooperative group trials. *The American journal of surgical pathology*. 2012; 36(7):945–954. [PubMed: 22743284]
9. Vainshtein JM, Spector ME, McHugh JB, et al. Refining risk stratification for locoregional failure after chemoradiotherapy in human papillomavirus-associated oropharyngeal cancer. *Oral oncology*. 2014; 50(5):513–519. [PubMed: 24565983]
10. Walline HM, Komarck C, McHugh JB, et al. High-risk human papillomavirus detection in oropharyngeal, nasopharyngeal, and oral cavity cancers: comparison of multiple methods. *JAMA otolaryngology-- head & neck surgery*. 2013; 139(12):1320–1327. [PubMed: 24177760]
11. Chandrani P, Kulkarni V, Iyer P, et al. NGS-based approach to determine the presence of HPV and their sites of integration in human cancer genome. *British journal of cancer*. 2015; 112(12):1958–1965. [PubMed: 25973533]

FIGURE 1.

A: H&E stain of primary tumor B: Positive p16 immunohistochemistry stain of primary tumor C: H&E stain of pulmonary metastasis D: Positive p16 immunohistochemistry stain of pulmonary metastasis E: Positive HPV ISH of pulmonary metastasis

Abbreviations: H&E = Hematoxylin and eosin; HPV = human-papilloma virus; ISH = in-situ hybridization

FIGURE 2.

Evaluation of lung nodule(s) in patients with a history of p16 positive oropharyngeal squamous cell carcinoma

Abbreviations: OPSCC = oropharynx squamous cell carcinoma; ISH = in-situ hybridization

Table 1

p16/HPV Status of Pulmonary Lesion(s) in Patients with Oropharyngeal Squamous Cell Carcinoma

Case	Metastasis	
	p16	HPV ISH
1	+	+
2	+	+
3	+	–
4	+	+
5	+	+
6	+	–
7	+	+
8	+	+
9	+	+
10	+	+
11	+	+
12	+	+
13	+	+
14	+	+
15	+	+

Abbreviations: ISH = in-situ hybridization; + = positive; – = negative

* Testing only performed on pulmonary metastasis