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## Combination of panendoscopy and PET/CT increases detection of unknown primary head and neck carcinoma

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### Abstract

**Objectives**—With PET/CT now commonplace as a diagnostic tool, new questions have arisen regarding the utility and cost-effectiveness of panendoscopy. In this retrospective review of a large cohort of head and neck squamous cell carcinoma of unknown primary (HNSCC-UP), we describe the enduring utility of panendoscopy in the detection of the primary site of mucosal disease even when PET CT is negative.

**Methods**—A retrospective analysis of patients presenting to the senior author (Y.D.) from July 1 1997 to July 1 2017 with FNA-proven metastatic squamous cell carcinoma to the neck. All patients underwent formal panendoscopy (direct laryngoscopy, bronchoscopy and rigid esophagoscopy). Presence of squamous cell carcinoma on final pathology was examined.

**Results**—A total of 190 patients had HNSCC-UP, with 87 positive and 103 negative on PET/CT. Of the PET/CT negative patients, 71 patients retained the HNSCC-UP designation after panendoscopy. 18 patients (56% of cases) were found to have primary tonsillar SCC. Eight of 32 primary sites were found in the base of tongue (25%), with HPV positivity in two of these patients. The sensitivity and negative predictive value of PET/CT in detecting the primary site in unknown primary head and neck squamous cell carcinoma in the total study population were 73.1% and 68.9% respectively.

**Conclusion**—Surgical panendoscopy has an important role in the work-up of patients with unknown primary head and neck squamous cell carcinoma. There is a high rate of cancer diagnosis, even in PET/CT negative patients.

### Keywords

Unknown primary; PET negative; panendoscopy

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## Introduction

Consensus on the ideal diagnostic workup of Head and Neck Squamous Cell Carcinoma of Unknown Primary (HNSCC-UP) remains elusive. In the United States, approximately 63000 new cases of head and neck squamous cell carcinoma are reported every year.<sup>1</sup> HNSCC-UP is a significant clinical entity and represents up to 7–10% of all head and neck cancers.<sup>2,3</sup> Identification of the primary site allows for more specific estimation of prognosis and targeted treatment planning and is associated with improved patient outcomes.<sup>4–6</sup>

Workup of HNSCC-UP typically includes further imaging (CT, MRI, or FDG-PET/CT) and frequently includes exam under anesthesia (EUA) of common mucosal primary sites.<sup>7</sup> EUA has traditionally taken the form of panendoscopy.<sup>8–11</sup> If EUA does not reveal a site suspicious for a mucosal primary, random biopsies of common sites may be obtained, and tonsillectomy may be performed.<sup>12,13</sup>

New questions regarding the utility and cost-effectiveness of panendoscopy in conjunction with PET/CT have arisen. Pattani et al analyzed a cohort of 23 HNSCC-UP patients and concluded that panendoscopy may not add significant value to PET/CT results.<sup>14</sup> However, Waltonen et al<sup>15</sup> and Rudmik et al<sup>16</sup> reported that detection of primary site in their cohort of HNSCC-UP was the greatest when PET/CT was combined with panendoscopy with directed biopsies.

In this retrospective review of a large cohort of HNSCC-UP patients with negative PET/CT findings, we describe the enduring utility of panendoscopy with site-directed biopsies in the detection of the primary site of mucosal disease.

## Materials and Methods

Approval was obtained from JPS Institutional Review Board. A retrospective analysis of patients presenting to the senior author (Y.D.) from July 1 1997 to July 1 2017 with FNA-proven metastatic squamous cell carcinoma to the neck without an identifiable site of primary disease following complete office examination with flexible fiberoptic endoscopy. These patients received PET/CT scans which were independently evaluated by a radiologist and the senior author. All patients underwent formal panendoscopy (direct laryngoscopy, bronchoscopy, nasopharyngoscopy and rigid esophagoscopy) to identify a primary site and verify PET/CT findings. Concerning lesions were biopsied as indicated, and directed biopsies of the base of tongue, pyriform sinuses, and nasopharynx at the fossae of Rosenmuller were performed in PET/CT negative patients. If no obvious concerning lesions were found in the tonsillar fossae, bilateral tonsillectomy was performed. Tonsillar biopsies were performed if specific lesions were found. Presence of squamous cell carcinoma on final pathology was examined. Sensitivity, specificity, positive predictive value, and negative predictive value of PET/CT with respect to the identification of the primary site were calculated.

## Results

Eighty seven patients were initially designated as ‘unknown primary’ head and neck cancer based on clinical examination, but were subsequently localized on PET/CT scan. The primary sites were ipsilateral tonsil in 43 patients (nineteen were HPV positive). 21 patients had base of tongue primaries, with HPV positivity in 11. Nine patients had pyriform sinus primaries, 2 patients had squamous cell carcinoma in the post cricoid space, and 2 patients were noted to have nasopharynx primaries. Other sites of positivity included paranasal sinus (3), cervical esophagus (2), trachea (2), posterior scalp (1), and soft palate (2).

A total of 103 patients had HNSCC-UP with negative PET/CT findings. After panendoscopy, 71 patients retained the HNSCC-UP designation. Primary sites were identified in 32 of 103 patients (31%) with negative PET/CT scans. 18 patients (56% of cases) were found to have primary tonsillar SCC. Of these, HPV positivity was noted in 10 of 18 patients (56%). Fifteen of the 18 tonsillar primary patients (83%) demonstrated primary lesions ipsilateral to the neck disease, while the three remaining patients demonstrated a tonsillar primary either contralateral or bilateral to the neck metastasis (2 contralateral, 1 bilateral). Eight of 32 primary sites were found in the base of tongue (25%), with HPV positivity in two of these patients. Two primary locations were found in the cervical esophagus, and one was identified in the pyriform sinus. One patient was noted to have a primary lesion of the epiglottis, one was noted to have a subglottic tracheal primary site, and one was noted to have a primary nasopharyngeal squamous cell carcinoma.

The sensitivity and negative predictive value of PET/CT in detecting the primary site in unknown primary head and neck squamous cell carcinoma in the total study population were 73.1% and 68.9% respectively. Specificity and positive predictive value of PET/CT detecting the primary site were both 100% in this study cohort. Normal physiologic uptake was excluded.

## Discussion

This is the largest reported cohort of PET/CT-negative HNSCC-UP patients to our knowledge. In our experience, panendoscopy with directed biopsies detected the primary site 31% (32/103) of our PET/CT negative HNSCC-UP patients. Furthermore, the sensitivity of PET/CT alone in detecting the primary site in HNSCC-UP is 73.1% (NPV 68.9%), which leaves a considerable portion of tumors with undetectable primary sites on PET/CT that were subsequently identified on panendoscopy. This rate of detection demonstrates the continued value of surgical panendoscopy in the evaluation of unknown primary head and neck squamous cell carcinoma in the setting of negative PET/CT evaluation.

There are several factors likely responsible for missed primary tumors on PET/CT. Lesions smaller than the resolution of the PET scanner (6–8mm) may not be detected unless there is a very intense FDG uptake by these lesions. This partial volume effect due to the limited resolution of the imaging system could also lead to decreased FDG uptake, and a false negative result.<sup>17</sup>

Identification of primary sites of head and neck squamous cell carcinoma is associated with better treatment planning and improved outcomes.<sup>4-6</sup> Detection of the primary site allows for the initiation of targeted therapy, and has the potential to reduce the degree of morbidity resulting from therapies directed at potentially uninvolved sites. Furthermore, deintensified treatment protocols for HPV-associated oropharyngeal cancers are under investigation.<sup>18</sup> In our cohort, 46% (12 of 26) of our detected oropharyngeal cases were positive for HPV.

In the management of HNSCC-UP, a recent shift toward performing bilateral tonsillectomy has occurred. Reasons for this include avoiding confusion in post treatment surveillance by creating a symmetric Waldeyer's ring,<sup>19</sup> and the grave consequences of failing to diagnose a contralateral tumor. Koch et. al reported rates of contralateral spread of metastatic cancer to be close to 10%.<sup>20</sup> In our study cohort, 17% of the detected tonsillar primary cases (3 of 18) were either contralateral or bilateral to the presenting neck disease.

In our series, subsites of the oropharynx are the most commonly identified mucosal primary sites in patients initially presenting with HNSCC-UP (81%, 26 of 32 detected primary cases). The nasopharynx and hypopharynx typically receive less attention in the workup of these tumors. We note a small but considerable rate of detection of nasopharyngeal and hypopharyngeal mucosal primaries by site-directed random biopsies: 3% nasopharynx and 3% hypopharynx. With newer reports identifying a subset of HPV-related squamous cell carcinoma in the nasopharynx,<sup>21</sup> identification of these primary sites potentially confer treatment and prognostic advantages.

## Conclusion

Surgical panendoscopy with directed biopsies remains an important role in the work-up of patients with PET/CT negative unknown primary head and neck squamous cell carcinoma. If panendoscopy does not reveal a site suspicious for a mucosal primary, site-directed biopsies of common sites should be obtained and bilateral tonsillectomies should be performed to optimize the chances of primary mucosal site detection.

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