Incidence and Significance of Hypermetabolic PET-CT Findings in Unilateral TVF Motion Impairment

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Abstract

Objective. To determine the incidence and significance of asymmetric hypermetabolic laryngeal findings on positron emission tomography–computed tomography (PET-CT) in patients with unilateral true vocal fold (TVF) motion abnormalities.

Study Design. Retrospective cohort.


Subjects and Methods. The medical records of patients with unilateral TVF motion abnormalities were reviewed. The incidence of normal and asymmetric hypermetabolic laryngeal findings was calculated in patients who underwent PET-CT and laryngeal examination, operative laryngoscopy with biopsy, or injection medialization laryngoplasty.

Results. A total of 135 patients with unilateral TVF motion abnormalities underwent PET-CT. After exclusion of patients who completed new or surveillance imaging for a laryngeal neoplasm (n = 27), asymmetric hypermetabolism in the larynx were noted in 21 (19%) cases: 13 (12%) on the contralateral side of the impaired TVF, 8 (7%) on the ipsilateral side. Two (25%) patients with ipsilateral hypermetabolism had concerning subsequent fiberoptic laryngeal examinations prompting operative biopsy. There was no evidence of inflammatory or neoplastic disease in all patients with contralateral hypermetabolic findings. Fifteen patients completed PET-CT scans after injection medialization procedures; 6 (40%) displayed avidity ipsilateral to the side of the injection. The median time from injection to scan was 27 days, as opposed to 193 days in the unremarkable scans (P = .011).

Conclusion. Contralateral hypermetabolism in patients with unilateral TVF motion abnormalities may represent a false-positive finding. Ipsilateral hypermetabolic uptake without recent fold instrumentation warrants prompt diagnostic evaluation.

Keywords

vocal fold paralysis, PET-CT, false positive, laryngeal cancer

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with known unilateral vocal fold dysfunction. This study aimed to define those frequencies with correlation to underlying pathologies and clinical outcomes in an effort to better understand the significance of this imaging result.

**Methods**

We retrospectively reviewed the electronic medical records of all adult patients diagnosed at our tertiary care institution with unilateral TVF paralysis, paresis, palsy, motion impairment, or dysfunction from September 2010 to December 2018. Approval from the Cooper Health System Institutional Review Board was obtained prior to the beginning of the study (18-129EX). The study cohort was identified with ICD-9 and ICD-10 codes (International Classification of Diseases) for each diagnosis. Physician in-hospital and outpatient clinic notes were reviewed. Patients were excluded upon chart review based on the absence of an endoscopic laryngeal examination, the presence of bilateral TVF motion impairment, or misdiagnosis/miscoding. The following information was extracted: reason for presentation to care, date of initial laryngeal diagnosis, laterality of the afflicted cord, the date and results of diagnostic flexible fiberoptic laryngoscopy, the date and results of subsequent laryngeal endoscopies, operative direct laryngoscopy with or without biopsy (when applicable), biopsy results (when applicable), history of cancer, history of head and neck cancer, and history and date of laryngeal instrumentation, including injection medialization or implantation procedures (when applicable).

The incidence of PET-CT imaging among the final cohort was calculated. All available imaging reports were analyzed, and mention of unilateral or asymmetric hypermetabolic activity in the larynx was recorded with the study date and the indication for each scan. When available, reported standardized uptake value (SUV) measurements were recorded. When unavailable, a board-certified radiologist retrospectively assigned SUVs for the noted FDG avidity.

For the purpose of this analysis, true-positive imaging results were defined as PET-CT findings (ie, FDG avidity) with corresponding findings on endoscopic laryngoscopy warranting an operative biopsy, such as mucosal change concerning for neoplasia. False-positive results were defined as remarkable PET-CT findings without any concerning findings on laryngoscopy. False-negative results were defined as unremarkable PET-CT findings in the context of a concerning laryngeal examination, while true-negative results were defined as unremarkable PET-CT findings without corresponding change on laryngoscopy.

Distributive statistics were performed with Poisson counts to determine the incidence of the end points of interest. When applicable, the time (days) from laryngeal injection procedures to imaging scans was calculated. Normally distributed variables were analyzed via mean and standard deviation and nonparametric variables via median and range. Statistical differences in the time from injection to PET-CT scan between select patient subgroups were calculated with the Mann-Whitney test and the Kruskal-Wallis test. Differences in SUVs among various subgroups were calculated with Mann-Whitney test. Chi-square was used to test the difference in incidence among the types of injectable materials. A 2-sided critical value of \( P < .05 \) was used to define significance. SPSS 23.0 software (IBM, Armonk, New York) was used to perform all analyses.

**Results**

The medical records of 758 patients diagnosed with unilateral TFV paralysis, paresis, palsy, motion impairment, or dysfunction were identified and reviewed. Of these patients, 135 underwent PET-CT scans. For the scope of this analysis, patients under surveillance for a history of subglottic, supraglottic, or glottic cancer and patients who underwent PET-CT for the initial staging of a newly diagnosed laryngeal malignancy were excluded (n = 27). The indications for PET-CT imaging are summarized in **Table 1**. Sixty-two (57%) patients had endoscopic confirmation of a unilateral TVF motion impairment before undergoing PET-CT imaging. The remaining 46 (43%) patients obtained imaging without a prior documented laryngeal examination. Seven of these patients were subsequently referred for formal evaluation based on their PET-CT results. All patients in the cohort had a laryngeal examination after PET-CT.

Overall, 81% of patients with unilateral TVF motion impairment demonstrated normal PET-CT findings in the larynx (n = 87). Asymmetric hypermetabolic findings in the larynx were noted in 21 (19%) cases. Specifically, hypermetabolic activity on the contralateral side of the known impaired TVF was noted in 13 (12%) patients. All 13 patients underwent subsequent flexible fiberoptic laryngeal examination, and no cases were found to have findings concerning for inflammatory or neoplastic disease.

Asymmetric uptake on the ipsilateral side of the impaired TVF was noted in 8 (7%) patients. Subsequent laryngeal visualization revealed irregularities prompting formal

**Table 1. Indications for PET-CT Imaging (N = 135).**

<table>
<thead>
<tr>
<th>Indication</th>
<th>n (%)</th>
</tr>
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<tbody>
<tr>
<td>Lung cancer</td>
<td>44 (33)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>16 (12)</td>
</tr>
<tr>
<td>New laryngeal cancer</td>
<td>15 (11)</td>
</tr>
<tr>
<td>New esophageal cancer</td>
<td>12 (9)</td>
</tr>
<tr>
<td>Unknown primary</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Mediastinal LAD</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Surveillance for previous head and neck cancer</td>
<td></td>
</tr>
<tr>
<td>Laryngeal</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Esophageal</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Oropharyngeal</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Hypopharyngeal</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Nasopharyngeal</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Abbreviations: LAD, lymphadenopathy; PET-CT, positron emission topography–computed topography.
Table 2. Incidence and Significance of PET-CT Findings (n = 108).

<table>
<thead>
<tr>
<th>Findings</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unremarkable laryngeal imaging findings</td>
<td>87</td>
<td>(81)</td>
</tr>
<tr>
<td>Asymmetric laryngeal hyperactivity</td>
<td>21</td>
<td>(19)</td>
</tr>
<tr>
<td>Contralateral hyperactivity</td>
<td>13</td>
<td>(12)</td>
</tr>
<tr>
<td>Benign laryngeal examination</td>
<td>13</td>
<td>(100)</td>
</tr>
<tr>
<td>Ipsilateral hyperactivity</td>
<td>8</td>
<td>(7)</td>
</tr>
<tr>
<td>Benign laryngeal examination</td>
<td>6</td>
<td>(75)</td>
</tr>
<tr>
<td>Laryngeal examination prompting biopsy</td>
<td>2</td>
<td>(25)</td>
</tr>
</tbody>
</table>

Abbreviation: PET-CT, positron emission topography–computed tomography.

Table 2. Figure 1 demonstrates examples of both ipsilateral and contralateral hypermetabolism observed.

Only 1 case was noted to have concerning vocal fold pathology seen on laryngopharyngoscopy following an unremarkable PET-CT scan that prompted an operative biopsy. Although the biopsy revealed a benign lesion, this case serves as the sole false negative in our analysis group.

The false-positive rate for the cohort was calculated to be 18%, while the false-negative rate was estimated at 33%. The specificity, or true-negative rate, was calculated to be 82%. The sensitivity, or true-positive rate, was estimated at 67%. A positive likelihood ratio of 3.2 and a negative likelihood ratio of 0.4 were calculated.

SUVs were reported or calculated in 18 of the 21 cases with asymmetric uptake. In the group with contralateral hyperactivity, the median SUV was 8.26 (n = 10; range, 4.3-16.4). In the cases with ipsilateral activity, the median SUV was 6.65 (n = 8; range, 4.3-13.24). No significant differences in SUVs were observed between the groups (P = .203).

Of the 135 patients, 43 had a history of vocal fold medialization injection procedures. Two patients underwent type 1 thyroplasty procedures with Silastic implants without arytenoid adduction. Fifteen patients completed subsequent PET-CT imaging after the injection procedures; 1 patient underwent PET-CT after the implant procedure. Hypermetabolic activity on the ipsilateral side of the injection was noted in 6 (40%) cases; however, the median time from injection to the scan was 27 days (range, 10-74 days). Four of these patients underwent additional follow-up PET-CT at a median 189 days (range, 186-247 days), all of whom demonstrated resolved FDG avidity. The remaining 9 cases showed unremarkable findings within the larynx. The median interval from injection to the unremarkable PET-CT scans was 193 days (n = 13; range, 46-882 days). A statistical difference was observed between the time interval of the 2 groups (P = .011). PET-CT findings were unremarkable 464 days after the Silastic implant procedure.

Injections were completed with aqueous/glycerin/carboxymethylcellulose gel implant (Prolaryn Gel, Radiesse Voice Gel) or synthetic calcium hydroxyapatite suspended in aqueous/glycerin/carboxymethylcellulose gel (Prolaryn PLUS, Radiesse Voice) based on the discretion of the operating surgeon. Both type 1 thyroplasty procedures were completed with the Montgomery Thyroplasty Implant System (Boston Medical Products Inc, Shrewsbury, Massachusetts). No statistical differences were observed between the incidence of hypermetabolism and the type of material injected or between SUV measurements and material injected.

Discussion

Our study aimed to determine the incidence of normal and abnormal laryngeal PET-CT findings in patients with unilateral TVF motion impairment. Eighty-one percent of scans in our study had unremarkable laryngeal findings. Of those who underwent PET-CT for reasons other than laryngeal cancer, 19% demonstrated incidental asymmetric hypermetabolic activity. Contralateral and ipsilateral FDG avidity was observed in 12% and 7% of cases, respectively. None of the patients with hypermetabolic activity on the contralateral side of the impaired TVF had laryngeal examination findings concerning for inflammatory or neoplastic disease. Thus, when encountered, this imaging finding may represent a false-positive result, secondary to physiologic compensation or normal activity of the contralateral functional TVF. Although recent vocal fold injection was associated with ipsilateral FDG avidity, one-quarter of the patients with TVF motion impairment who demonstrated this finding had endoscopic changes that warranted an operative biopsy. In the absence of recent instrumentation, ipsilateral hyperactivity should prompt immediate referral to an otolaryngologist for further evaluation.

When abnormal FDG avidity in the larynx is evaluated, the following should be considered: the laterality of the hypermetabolic activity, a history of head and neck cancer, previous radiation therapy, or recent chemotherapy treatment with vinca alkaloids. The 2 patients in our ipsilateral
This study first identified patients with TVF motion abnormalities and then analyzed PET-CT findings in the cohort. Previous reports in the literature have utilized an opposite approach: first identifying positive PET-CT scans, then analyzing vocal fold pathology in these groups. We believe that the former approach infers less bias and provides a more accurate incidence of the discussed findings. In an analysis exclusively composed of PET-CT scans with mention of laryngeal uptake from 23 patients, Seymour et al proposed that nearly 60% of laryngeal findings represent a true-positive result. However, the investigators defined true positivity by the presence of any vocal fold pathology, including malignancy or motion abnormality. Their analysis did not exclude patients who underwent PET-CT for primary laryngeal cancer, nor did it account for asymmetry or laterality. Lee et al found that 15 of 17 patients with unilateral laryngeal findings on PET imaging had underlying vocal fold paralysis. Twelve percent of all positive findings in their study represented an underlying head and neck malignancy. Note that all of the patients in this study had known lung cancer. An association between primary glottic tumors and chest malignancies is well described, including malignancy or motion abnormality. Their analysis was noted after a median interval of 193 days. Absence or resolution of the hypermetabolic activity in the remaining scans was noted after a median interval of 193 days. Furthermore, there were no statistical associations observed between the incidence of FDG avidity or SUV measurements and the type of material injected. Limited by the small sample size, a time interval for the expected resolution of the hypermetabolic activity cannot be concluded from this report, nor can associations with the injectable material. Previous reports hypothesized that materials with larger surface areas of breakdown cause significant metabolic activity over an increased time. However, we are unable to discern if the acute hypermetabolic activity observed in our study represents the local inflammatory response of laryngeal instrumentation and foreign material injection rather than the injectable material itself. By providing new insight into the local response to injection medialization procedures, this study may serve as a platform for future investigations.

Although we report estimations for sensitivity, specificity, false-positive and false-negative rates, and likelihood ratios, the limited sample size and temporal restrictions of this analysis secondary to its retrospective nature may influence the generalizability of these statistics. For example, some patients had undergone laryngeal endoscopy a year after the most recent PET-CT imaging was obtained. Any vocal fold pathology that may have developed in the interim would not have been captured by the imaging study, ultimately influencing the incidence of true and false negatives. Such statistical terminology should be reserved within reference to the gold standard of a diagnostic evaluation, of which PET-CT is not for vocal fold pathology. Furthermore, we presented likelihood ratio estimations instead of positive and negative predictive values, as predictive values are more dependent on the underlying prevalence of disease in the study cohort. Probably affected by the pretest, which is intrinsically low for patients similar to those included in this analysis, the positive predictive value holds little utility in guiding clinical decisions.

This analysis did not uncover any statistical associations among SUVs and the laterality of the FDG avidity. Komissarov et al found that SUV estimates for tumors and vocal cord paresis alone overlap, preventing the distinction between motion abnormalities and neoplasms. The data from our study are congruent with this conclusion. Due to the paucity of current data, SUV measurements should not be used to determine the underlying etiology for this incidental finding.

We acknowledge several limitations that may serve as additional areas of future investigation. Pilot data were not available to perform prospective power calculations, and our incidence data should serve only as an estimation. As this was a single-center retrospective review, a patient’s medical history and treatment records may not be fully captured. For example, a remote history of TVF injections at an outside institution may not be accurately reflected in our medical records, ultimately influencing the rates derived from our data. A similar analysis should be conducted at a multi-institution or population-based level to calculate true incidence rates. Finally, all PET-CT scans were not interpreted by the same radiologist. Only scanned reports from outside hospital systems were available for 3 cases, each demonstrating contralateral hyperactivity. This prevented our radiologist from retrospectively assigning SUVs to these cases. Additionally, the potential for interobserver bias exists in both image interpretation and verbiage used to portray the results. Our institutional protocol instructs patients to relax and not speak during imaging capture; however, a retrospective analysis cannot guarantee control for phonation and physiologic motion artifact.

The data presented in this study contribute to the growing knowledge regarding incidental imaging findings in the head and neck and their clinical significances. This evidence holds implications for not only practicing otolaryngologists but also medical and radiation oncologists, pulmonologists, and speech-language pathologists. This report will serve to guide physicians encountering this clinical scenario when caring for patients with TVF motion impairments.
Conclusions

Unilateral FDG avidity on PET-CT imaging has been reported as an incidental finding in patients with TVF motion abnormalities. Excluding those with primary laryngeal cancer, this report determined that 81% of these patients demonstrated no laryngeal findings on PET-CT. While 19% of the cohort showed asymmetric hyperactivity in the larynx, the false-positive rate was estimated at 18%. Contralateral asymmetric hypermetabolism in patients with unilateral TVF motion abnormalities may represent a false-positive finding. In contrast, ipsilateral hypermetabolic uptake without recent fold instrumentation should prompt laryngeal endoscopy. Recent vocal fold instrumentation and injection medialization are associated with ipsilaterial FDG avidity. The evidence presented in this analysis will help guide physicians encountering this imaging finding when caring for patients with TVF motion impairments and serve as a platform for future investigations.

Author Contributions
Luke Stanisce, conception and design, acquisition of data, analysis and interpretation, statistical analysis, drafting the article; critical revision of the article, final approval of the article; agreement to be accountable for all aspects of the work; Timothy Renzi, acquisition of data, critical revision of the article, final approval of the article; agreement to be accountable for all aspects of the work; Nikita Paripati, acquisition of data, critical revision of the article, final approval of the article; agreement to be accountable for all aspects of the work; Nadir Ahmad, analysis and interpretation, critical revision of the article, final approval of the article; agreement to be accountable for all aspects of the work; Thomas C. Spalla, analysis and interpretation, critical revision of the article, final approval of the article; agreement to be accountable for all aspects of the work; Howard L. Roth, acquisition of data, critical revision of the article, final approval of the article; agreement to be accountable for all aspects of the work; Yekaterina Koshkareva, conception and design, acquisition of data, analysis and interpretation, statistical analysis, drafting the article, critical revision of the article, final approval of the article; agreement to be accountable for all aspects of the work.

Disclosures
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References


