

# Normative Ranges for PET <sup>18</sup>F-FDG Activity in the Head and Neck of Pediatric Patients

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## Abstract

**Background:** Positron emission tomography (PET) with fluorine 18 fluorodeoxyglucose (<sup>18</sup>F-FDG) has been widely used for pediatric tumors. In order for <sup>18</sup>F-FDG to confer utility in its widespread use, normal ranges encompassing physiologic variation must be elucidated, such that abnormal variation can be identified. Normal physiologic activity may vary according to age group. Previous studies investigating physiologic uptake in the head and neck organs have not focused on a pediatric population.

**Objective:** The purpose of this study is to elucidate the normative values for <sup>18</sup>F-FDG uptake for head and neck structures in a pediatric population known to have no head or neck pathology.

**Materials and methods:** A total of 97 patients (43 females) ranging in age from 2.7 to 18 years old who had no history of head or neck malignancy/pathology (either at the time of study acquisition or on follow-up) were included in this retrospective study. PET/CT imaging was acquired approximately 60 minutes after injection of 5.18 MBq/kg (0.14 mCi/kg) <sup>18</sup>F-FDG. Twelve head and neck structures including 1. Lingual tonsils, 2. Adenoid tissues (pharyngeal tonsils), 3. Palatine tonsils, 4. Soft palate, 5. Tongue, 6. Sublingual glands, 7. Parotid glands, 8. Submandibular glands, 9. Spine at the level of C1, 10. Thyroid gland, 11. Inferior concha and 12. Vocal cords were evaluated in this study. The region of interest (ROI) was drawn over these structures in the axial view and the maximum and mean SUV normalized to body weight were recorded.

**Results:** Lingual tonsils, adenoid tissues, palatine tonsils and sublingual glands showed the highest uptake. The mean SUVmaxes ± SD were 2.67 ± 1.25 in lingual tonsils, 3.99 ± 1.56 in palatine tonsils, 3.04 ± 1.91 in adenoid tissues, and 3.00 ± 1.21 in the sublingual glands. Other head and neck organs showed a mild <sup>18</sup>F-FDG uptake; the mean SUVmax was 1.52 ± 0.43 for inferior concha, 1.51 ± 0.45 for soft palate, 1.33 ± 0.38 for tongue, 1.45 ± 0.52 for parotid glands, 1.97 ± 0.66 for submandibular glands, 1.68 ± 0.51 for the spine at the level of C1, 1.24 ± 0.40 for the thyroid gland, and 1.55 ± 0.87 for the vocal cords.

**Conclusion:** Adenoid tissues, lingual and palatine tonsils and sublingual glands show a moderate to high <sup>18</sup>F-FDG uptake (mean SUVmax>2.5), while other small head and neck organs show a mild <sup>18</sup>F-FDG activity.

**Keywords:** <sup>18</sup>F-FDG PET/CT; Children; Normal FDG uptake; PET; FDG

## Introduction

Positron emission tomography (PET) with fluorine 18 fluorodeoxyglucose (<sup>18</sup>F-FDG) is a widely used and well validated functional imaging modality that measures glucose metabolism in various tissues *in vivo* [1]. <sup>18</sup>F-FDG is primarily used in oncology for diagnosis, staging, re-staging, therapeutic planning, monitoring and prognostication [2-7]. However, the clinical applications of <sup>18</sup>F-FDG-PET are continually expanding beyond oncology, to other areas including cardiology, neurology, and inflammation/infection [8-11]. <sup>18</sup>F-FDG is given intravenously, and is then taken up by cells in a similar fashion to glucose. Many tumors exhibit increased expression of glucose transporters, and specific expression of glucose transporters with a higher affinity for glucose, and therefore for <sup>18</sup>F-FDG, compared to normal tissues [7]. Additionally, changes in cellular metabolism often precede changes in cellular morphology in neoplastic growths, further reinforcing the role of <sup>18</sup>F-FDG-PET in both neoplastic diagnosis and therapeutic response monitoring [7]. Further, increased uptake of <sup>18</sup>F-FDG has been demonstrated in tissues with higher concentrations of inflammatory cells, such as neutrophils and macrophages, which explain why increased uptake is seen in the setting of infection, inflammation, and tissues, that are healing [7]. <sup>18</sup>F-FDG-PET has been demonstrated to have a high degree of sensitivity, specificity and accuracy in detection of head and neck malignancies and is frequently used for this indication [5]. Wide physiologic variation in

the uptake of <sup>18</sup>F-FDG has been noted in a variety of tissues [1,3,7,12]. Specifically, areas in the head and neck that fit the profile of having a high concentration of lymphoid cells like Waldeyer's ring have been demonstrated to show increased <sup>18</sup>F-FDG uptake compared to other body tissues [1,3,7]. Therefore, in order for <sup>18</sup>F-FDG-PET to confer utility in its widespread use, we must be able to delineate pathology from normal physiologic variation. Moreover, normal physiologic activity may vary according to age group. For example, palatine tonsils are more active and pronounced in children and adolescents, and atrophy in adulthood. This corresponds to higher <sup>18</sup>F-FDG uptake for palatine tonsils in a younger age group [12].

Studies of physiologic uptake of <sup>18</sup>F-FDG in head and neck structures have published normal <sup>18</sup>F-FDG uptake values in structures

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such as inferior concha, cervical spinal cord, salivary glands, different tonsils, vocal cords and thyroid gland [1,3,12]. Specifically, these studies have illustrated intense uptake in the palatine tonsils, soft palate and lingual tonsils, minimal uptake in the thyroid gland, inferior concha and tongue, and varying levels of uptake in the salivary glands and spinal cord [3]. However, these studies have not investigated normal uptake values specifically in a pediatric population, in which these head and neck structures take on a different level of metabolic activity [12]. Therefore, there is ambiguity in distinguishing acceptable physiologic variation from pathology for parameters such as signal intensity and pattern of distribution in a pediatric population. This study aimed to elucidate the normative values for <sup>18</sup>F-FDG uptake for head and neck structures, specifically in a pediatric population known to have no head and neck pathology.

## Materials and Methods

This study has been approved by our institutional Research Ethics Board and the informed consent requirement was waived due to the relatively large number of subjects and retrospective review study design.

### Study population

A total of 97 patients (54 males, 43 females) under 18 years old with no history of head and neck malignancy or other pathology (either at the time of study acquisition or on follow up) were included in this retrospective study. Patients who had any symptoms in the head and neck region, a recent history of upper respiratory infection (based on the patient's chart), signs of infection on the correlative CT scan (e.g. sinusitis), a history of surgery in the head and neck region (e.g. tonsillectomy), or a technical artifact on imaging (e.g. motion artifact) were not included in the study.

### PET/CT scanning

All PET/CT examinations were acquired according to our standard clinical protocol of using a Philips PET/CT scanner (Gemini GXL; Philips Healthcare, Cleveland, OH, USA) [13]. All patients had blood glucose concentrations that were recorded and noted to be <11 mm before administration of the radiotracer. Approximately 60 minutes after injection of 5.18 MBq/kg (0.14 mCi/kg) <sup>18</sup>F-FDG (with a minimum dose of 37 MBq (1 mCi) to a maximum of 370 MBq (10 mCi)), imaging was acquired from the basal head to mid-thigh in most cases (e.g. lymphoma), and from the top of the head to toes in other cases (e.g. sarcoma). Images were acquired with a three minutes imaging time per bed position. Correlative CT scan (either low-dose or diagnostic) was used for the attenuation correction. Patients who had a previous diagnostic CT scan were imaged using a low-dose CT scan (5 mm/slice, 90 kV; 20 and 30 mA for patients weighing <30 and ≥ 30 kg, respectively) and, when clinically indicated, (usually in those patients without a recent diagnostic CT scan) diagnostic CT scan (5 mm/slice, 120 kV, and a weight-based range for the mA, with a maximum of 200 mA with dose modulation). The PET images were reconstructed using the iterative method of line-of-response (line of response row action maximum-likelihood algorithm or 3D row action maximum-likelihood algorithm). The system had a spatial resolution of 5.1 mm transversely and 6.0 mm axially [14].

### Image analysis

Two nuclear medicine physicians (A.S. with 10 years of experience and R.V with 4 years of experience post-pediatric nuclear medicine and PET/CT fellowship) evaluated 12 head and neck structures, including:

1. Inferior concha, 2. Adenoid tissues (pharyngeal tonsils), 3. Palatine tonsils, 4. Soft palate, 5. Tongue, 6. Sublingual glands, 7. Parotid glands, 8. Submandibular glands, 9. Spine at the level of C1, 10. Thyroid gland and 12. Vocal cords. The region of interest (ROI) was drawn over these structures in the axial view and the maximum SUV (SUVmax) and mean SUV (SUVmean) normalized to body weight were recorded using the standard software supplied by the vendor. All evaluations were based on consensus agreement between the two physicians. The SUV is used as a surrogate for a distribution volume of tracer.

It was calculated based on the formula:

$$SUV = r (a'/w)$$

Where r refers to the concentration of the radioactivity [kBq/ml] measured by the PET scanner within a ROI,

a' refers to the decay-corrected amount of injected radiolabeled FDG [kBq], and w is the weight of the patient [g] [1,15].

Similarly, the background activity was also measured by drawing ROIs over the right lobe of the liver and descending aorta (mediastinal activity) in the axial views, as suggested by Wahl et al. [3] in the PET response criteria in solid tumors (PERCIST) 1.0 criteria [16]. The right and left sides were assessed separately for each of the paired tissues (i.e. palatine tonsils, adenoids, sublingual gland, parotid gland, submandibular gland, inferior conchae, and thyroid). The final result for the quantitative assessment of the paired tissues was calculated as the average of the SUVmax or SUVmean measured on both sides.

Visual analysis was also performed and a four-grade categorization was employed, similar to what was previously described by Nakamoto et al. [3] in which grade 0 indicated no or faint activity; grade 1 indicated activity comparable to the blood pool; grade 2 indicated moderate activity (greater than that in the blood pool); and grade 3 indicated intense activity. We also calculated the rate percentage (RP) of group 0 and 1, indicative of no or mild uptake, and group 2 and 3, indicative of moderate to severe uptake, by measuring the quotient of the number of cases with no or mild uptake (visual grade 0 or 1) and also moderate to severe activity (visual grade 2 or 3) divided by the total number of cases, multiplied by 100 [3].

### Statistical analysis

Categorical variables were expressed as integers and percentages. Distributions of continuous variables were assessed using Shapiro Wilk test. Continuous variables were described using median and interquartile range or mean and standard deviation as appropriate. The maximum difference between tracer uptake in males and females was compared using an independent t-test or Mann Whitney U test for each organ, as appropriate. Maximum SUV of each organ was normalized to Mediastinum and their correlations with patient demographics (sex and age) were evaluated using Spearman or Pearson Correlation coefficient, where appropriate. Correlation between Maximum SUVs among the major salivary glands were assessed using the Spearman correlation coefficient. A two-tailed p<0.05 was considered statistically significant. Analyses were performed with SPSS (IBM SPSS Statistics for Windows, Version 24.0, 2016. IBM Corp. Armonk, NY).

## Results

A total of 97 patients (F/M=43/54) were included in this study. The age range was 2.7 to 18 years with a mean age of 12.7 years (153.22 ± 48 months). The mean age was 12 years (144.00 ± 51 months) in girls and 13.3 years (160.56 ± 45) in boys. No significant difference was seen

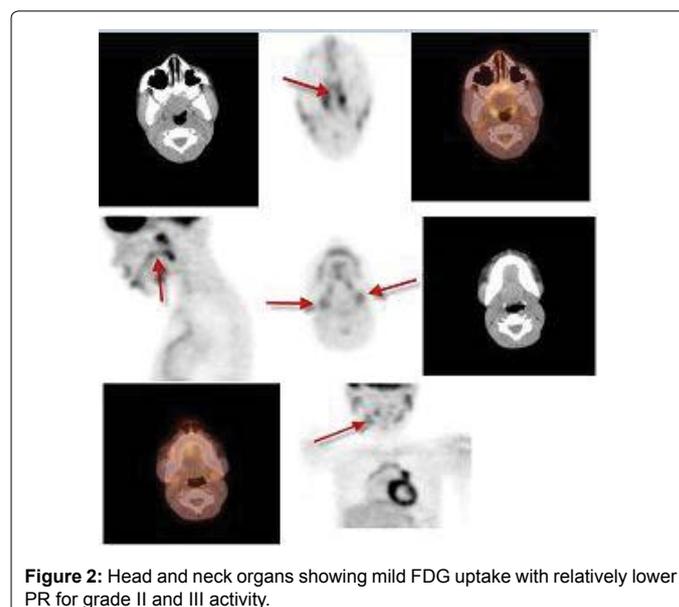
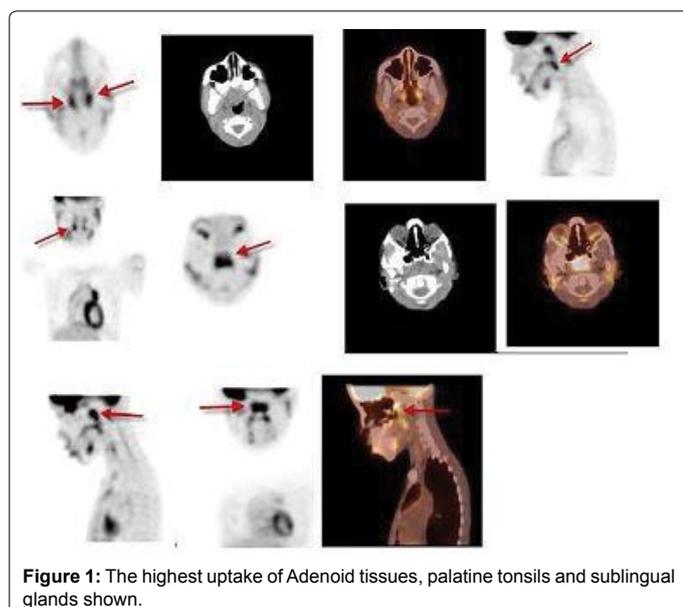
between the mean ages of male and female groups (Mann Whitney U test  $p > 0.05$ ). Visual and quantitative analysis results of <sup>18</sup>F-FDG uptake in the 12 head and neck organs are summarized in Table 1. The results show that in most cases, there is mild to moderate activity in head and neck organs. Adenoid tissues, palatine tonsils and sublingual glands showed the highest uptake (Figure 1). In many cases palatine tonsils were more active than other head and neck organs with a mean SUVmax of  $3.99 \pm 1.56$  and a PR of 99% for grade II and III activity. Palatine tonsils are round to oval shaped lumps of lymphoid tissue located behind the buccal cavity at the lateral wall of the pharynx. Adenoids, which are lymphoid soft tissues in the back of the nasal cavity, also showed a high activity with a mean SUVmax of  $3.04 \pm 1.91$  and a PR of 91.8% for grade II and III activity. The mean SUVmax was  $3.00 \pm 1.21$  in the sublingual glands with PR of 96.9% for grade II and III activity. Other head and neck organs showed a mild FDG uptake with relatively lower PR for grade II and III activity (Figure 2). The mean SUVmax was  $1.52 \pm 0.43$  for inferior concha (PR of 55.7%),  $1.51 \pm 0.45$  for soft palate (PR of 67%),  $1.33 \pm 0.38$  for tongue (PR of 43%),  $1.45 \pm 0.52$  for parotid glands (PR of 57.7%),  $1.97 \pm 0.66$  for submandibular glands

(PR of 80.4%),  $1.68 \pm 0.51$  for the spine at the level of C1 (PR of 87.6%),  $1.24 \pm 0.40$  for the thyroid (PR of 23.7%), and  $1.55 \pm 0.87$  for the vocal cords (PR of 52.6%). No significant difference was noted for the head and neck <sup>18</sup>F-FDG uptake between the male and female patients (Table 2). No significant correlation was found between the patient's age and mean SUVmax in the sublingual, parotid, and submandibular glands, C1 spine, thyroid glands, adenoid tissues, soft palate, tongue or vocal cords (Table 3). There was a weak negative correlation between patient age and mean SUVmax in palatine tonsils and inferior concha (Figure 3). We found a moderate to strong correlation between the major salivary glands' uptake. A strong correlation was seen between the <sup>18</sup>F-FDG uptake of the parotid and the submandibular glands ( $r = 0.61$ ,  $p < 0.001$ ) and a moderate correlation was seen between the uptake of parotid and the sublingual glands ( $r = 0.54$ ,  $p < 0.001$ ) and between the uptake of the submandibular glands and the sublingual glands ( $r = 0.55$ ,  $p < 0.001$ ). There was also a moderate correlation between the <sup>18</sup>F-FDG uptake of adenoid tissues and the palatine tonsils ( $r = 0.54$ ,  $p < 0.001$ ) (Table 4).

S. No	Organ	Mean SUVmax	95% CI	Visual grade 0-1	RP (%)	Visual grade 2-3	RP (%)
1	Inferior concha	$1.52 \pm 0.43$	1.43-1.61	43	44.4	54	55.6
2	Adenoid tissues	$3.04 \pm 1.91$	2.66-3.43	8	8.2	89	91.8
3	Palatine tonsils	$3.99 \pm 1.56$	3.67-4.30	1	1	96	99
4	Lingual tonsils	$2.67 \pm 1.25$	2.41-2.92	4	4.1	93	95.9
5	Soft palate	$1.51 \pm 0.45$	1.42-1.60	32	33	65	67
6	Tongue	$1.33 \pm 0.38$	1.25-1.41	55	56.7	42	43.3
7	Sublingual glands	$3.00 \pm 1.21$	2.75-3.23	3	3.1	94	96.9
8	Parotid glands	$1.45 \pm 0.52$	1.35-1.56	41	42.3	56	57.7
9	Submandibular glands	$1.97 \pm 0.66$	1.84-2.11	19	19.6	78	80.4
10	C1 spine	$1.68 \pm 0.51$	1.58-1.79	12	12.4	85	87.6
11	Thyroid	$1.24 \pm 0.40$	1.16-1.32	74	76.3	23	23.7
12	Vocal cord	$1.55 \pm 0.87$	1.37-1.72	46	47.4	51	52.6

\* Data are mean values  $\pm$  standard deviations.

Table 1: <sup>18</sup>F-FDG activity in head and neck: Quantitative (mean SUVmax) and Qualitative Results.



S. No	Organ	Male (n=54) <sup>*</sup>	Female (n=43) <sup>*</sup>	p Value <sup>†</sup>
1	Inferior concha	1.48 ± 0.12	1.58 ± 0.51	0.43 <sup>**</sup>
2	Adenoid tissues	2.69 ± 1.27	3.49 ± 2.43	0.21 <sup>**</sup>
3	Palatine tonsils	3.74 ± 1.28	4.30 ± 1.82	0.21 <sup>**</sup>
4	Lingual tonsils	2.47 ± 0.88	2.91 ± 1.57	0.43 <sup>**</sup>
5	Soft palate	1.47 ± 0.43	1.55 ± 0.48	0.10 <sup>***</sup>
6	Tongue	1.27 ± 0.34	1.40 ± 0.41	0.10 <sup>**</sup>
7	Sublingual glands	3.00 ± 1.23	2.98 ± 1.20	0.94 <sup>**</sup>
8	Parotid glands	1.50 ± 0.48	1.40 ± 0.57	0.84 <sup>**</sup>
9	Submandibular glands	1.98 ± 0.67	1.96 ± 0.65	0.87 <sup>***</sup>
10	C1 spine	1.66 ± 0.41	1.70 ± 0.62	0.86 <sup>**</sup>
11	Thyroid	1.18 ± 0.32	1.33 ± 0.48	0.25 <sup>**</sup>
12	Vocal cords	1.46 ± 0.91	1.66 ± 0.81	0.14 <sup>**</sup>
13	SR muscle	2.47 ± 0.88	2.91 ± 1.57	0.43 <sup>**</sup>
14	Mediastina	1.22 ± 0.31	1.27 ± 0.46	0.56 <sup>***</sup>
15	Liver	1.69 ± 0.39	1.64 ± 0.52	0.61 <sup>***</sup>

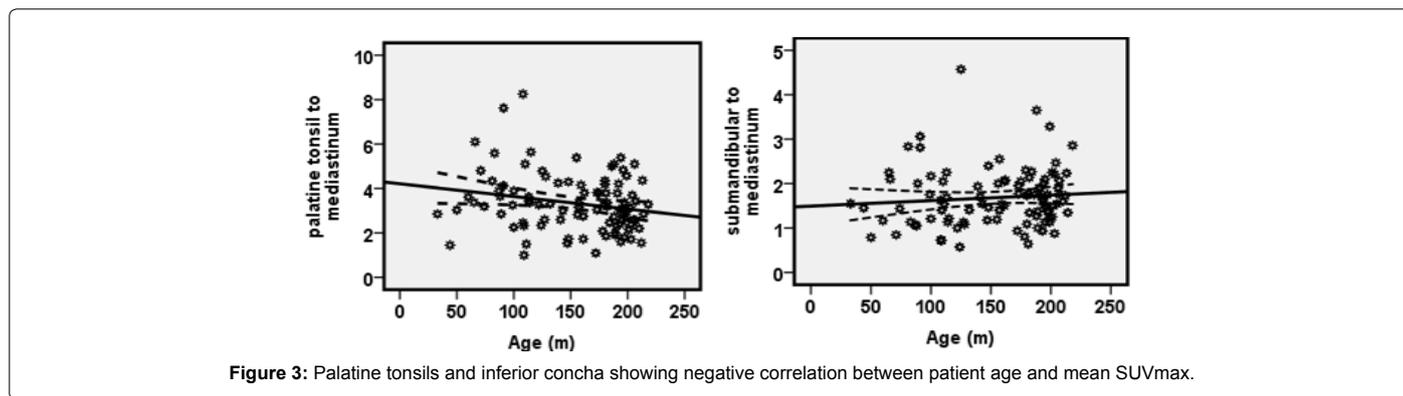
<sup>\*</sup> Data are mean SUVs ± standard deviations; <sup>\*\*</sup> Mann Whitney U test; <sup>\*\*\*</sup> Independent t-test; <sup>†</sup> Statistically significant difference in values between male and female patients.

**Table 2:** Differences in mean SUVmax of different head and neck organs according to sex.

S. No	Organ	Correlation	p Value <sup>*</sup>
1	Adenoid tissue	-0.09	0.38
2	Palatine	-0.2	0.05
3	Soft palate	-0.15	0.15
4	Tongue	-0.16	0.12
5	Sublingual glands	0.16	0.12
6	Parotid glands	0.09	0.37
7	Submandibular glands	0.15	0.15
8	C1 spine	0.09	0.38
9	Thyroid gland	-0.02	0.84
10	Vocal cords	-0.17	0.1
11	Inferior concha	-0.29	0.004

<sup>\*</sup> Spearman correlation

**Table 3:** Correlation between mean SUVmax of each organ/mediastinum SUV and age.



**Figure 3:** Palatine tonsils and inferior concha showing negative correlation between patient age and mean SUVmax.

S. No	Organ	Correlation	P Value <sup>*</sup>
1	Between parotid and submandibular	0.61	<0.001
2	Between parotid and sublingual	0.54	<0.001
3	Between sublingual and submandibular	0.55	<0.001
4	Between palatine and adenoid	0.54	<0.001

<sup>\*</sup> Spearman Correlation

**Table 4:** Correlation between mean SUVmax among the major salivary gland and between palatine tonsils and adenoids.

## Discussion

Differentiation of physiologic uptake of small organs in the head and neck from pathologic uptake is of pivotal importance for interpretation of <sup>18</sup>F-FDG PET/CT scans, in order to minimize false positive and false negative results. The distribution and intensity of physiologic <sup>18</sup>F-FDG uptake in the head and neck organs may be different in children compared with the adult population. Tonsils, for example, reach their largest size near puberty and undergo atrophy gradually thereafter. Additionally, brown fat activity, which may act to elevate uptake intensity, is more common in children than adults. Children may also have increased muscle and vocal cord <sup>18</sup>F-FDG uptake compared to adults due to motion, speaking or crying during the uptake phase. The tongue and oral muscles of children may also have increased uptake due to sucking. It is therefore crucial to not only elucidate normative head and neck values for <sup>18</sup>F-FDG PET scanning in general, but also to establish a distinct set of values for a pediatric population. In this retrospective study we evaluated the physiologic activity of 12 head and neck organs in a pediatric population. In our study, adenoid tissues, palatine tonsils and sublingual glands showed the highest uptake while inferior concha, soft palate, tongue, parotid glands, submandibular glands, spine at the level of C1, thyroid gland, and vocal cords showed mild <sup>18</sup>F-FDG activity.

Waldeyer's ring, which includes the lymphoid tissues of the nasopharynx, tonsils, and base of the tongue, plays a significant role in the initiation of an immune response following exposure to various antigens [17]. Waldeyer's ring is also a common site for bacterial and viral infections, as well as extra-nodal non-Hodgkin's lymphomas (NHL). Palatine tonsils are the most frequent site of extra-nodal NHL involvement [18]. Both malignant and infectious processes may increase the uptake of <sup>18</sup>F-FDG. Therefore, it is important to know the degree of physiologic <sup>18</sup>F-FDG uptake in the Waldeyer's ring. In our study adenoid tissues, and palatine tonsils showed a moderate to high uptake with a mean SUVmax of  $3.99 \pm 1.56$  (PR of 99%) for palatine tonsils and a mean SUVmax of  $3.04 \pm 1.91$  (PR of 91.8%) for adenoid tissues. Our findings were inconsistent with the results found by Nakamoto et al. [3] in their patient's population (which consisted of primarily adults). However, we didn't find any significant correlation between degree of uptake and patient age within this study's pediatric population. Notably, there was a nearly significant association between palatine uptake and patient age. In other words, Waldeyer's ring is relatively and consistently active throughout the early and late childhood periods (including teenage years).

Although diseases of the salivary glands are relatively rare in children, they do occur. Both inflammatory process such as acute and chronic sialadenitis, and tumoral involvement may be seen in salivary glands. Therefore, it is important to know the degree of <sup>18</sup>F-FDG uptake in a normal population. In our study, the three major paired salivary glands (parotid, submandibular and sublingual glands) showed variable uptake. The mean SUVmax was relatively high in the sublingual glands ( $3.00 \pm 1.21$ ; PR of 96.9%) and much lower for the parotid ( $1.45 \pm 0.52$ ; PR of 57.7%) and submandibular glands ( $1.97 \pm 0.66$ ; PR of 80.4%). Despite the salivary glands gradually increasing in size after birth until adulthood [19], we didn't find a correlation between the uptake of <sup>18</sup>F-FDG in the salivary glands and patient age.

Other head and neck organs evaluated in this study (inferior concha, tongue, soft palate, spine at the level of C1, thyroid gland, and vocal cords) showed a mild <sup>18</sup>F-FDG uptake with relatively lower PR. Therefore any significant focal or diffuse increased uptake in these organs may suggest pathology. Increased <sup>18</sup>F-FDG activity in the

thyroid gland, for example, may suggest an inflammatory process (e.g. thyroiditis) or tumoral involvement (e.g. adenoma or malignancy). Although focal or unilateral increased <sup>18</sup>F-FDG uptake in the vocal cord may suggest pathology, asymmetric super-physiologic <sup>18</sup>F-FDG uptake can be seen in a normal vocal cord contralateral to a paralyzed vocal cord [20]. Nakamoto et al. [3] also found mild uptake in these organs (inferior concha, tongue, spine at the level of C1, thyroid gland, and vocal cords). However, they reported a relatively high <sup>18</sup>F-FDG uptake in the soft palate. This may be due to differences in the region of interest selected in different studies. Applying the ROI more postero/superiorly or inferiorly may include some activity from the adenoid tissues, and palatine tonsils, respectively. Conversely, applying the ROI more anteriorly includes a part of hard palate and may underestimate the <sup>18</sup>F-FDG uptake.

## Limitations and Conclusion

One of the limitations of this study relates to the retrospective nature of the investigation. Although we only included patients with no history of head and neck pathology or upper respiratory tract infection, patients may have had a subclinical infection or simply forgot to mention the recent history of infection. Further prospective studies would be useful to further validate the normative values published here. The other limitation is the referral bias in this study. Our patient's population is not recruited from the normal population outside the hospital. Patients who were referred for <sup>18</sup>F-FDG PET/CT scan were all evaluated for a disease condition which may influence the <sup>18</sup>F-FDG uptake of the head and neck organs. However, we believe that this is more representative of the patients who are routinely referred for clinical PET/CT scanning. It also may not be ethical to study children with no underlying pathology for this specific purpose, which made retrospective review more appropriate. This study demonstrates ranges of head and neck <sup>18</sup>F-FDG uptake values for head and neck structures in a pediatric patient population with no head or neck pathology. It specifically finds a near-significant association between age and palatine tonsillar uptake, as well as moderate to high uptake in adenoid tissues, lingual and palatine tonsils and sublingual glands in children. These normative values may be utilized to help better delineate abnormal uptake in head and neck pathology on <sup>18</sup>F-FDG PET/CT scanning in a pediatric population.

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