***Original Article / Çalışma - Araştırma***

# Positron emission tomography evaluation of sinonasal inverted papilloma and related conditions: a prospective clinical study

## Sinonazal inverted papillom ve ilişkili durumların pozitron emisyon tomografi ile değerlendirilmesi: Bir prospektif klinik çalışma

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***ABSTRACT***

**Objectives:** This study aims to determine whether there is a difference between inverted papilloma (IP) and nasal polyp, and squamous cell carcinoma (SCC) with regard to fluorodeoxyglucose uptake.

**Patients and Methods:** Between September 2007 and May 2014, positron emission tomography computed tomography (PET/CT) images of 27 patients (20 males, 7 females; mean age 53.4 years; range 18 to 74 years), with unilateral polyposis diagnosed on examination and tomographic scans of paranasal sinus were obtained. Nasal polyps in eight of the patients (group 1), IP in 10 patients (group 2), and SCC in nine patients (group 3) were found. The data were compared with Kruskal-Wallis and Mann-Whitney U tests.

**Results:** The mean maximum standardized uptake ($SUV_{max}$) values were found to be 2.9 in the group 1; 7.8 in the group 2, and 17.8 in the group 3. There was significant difference in the $SUV_{max}$ values between the group 1 and the group 2 (p=0.016), the group 1 and the group 3 (p=0.001), and the group 2 and the group 3 (p=0.01).

**Conclusion:** According to the results of this study, PET/CT scan in the patients with unilateral polyposis is invaluable to distinguish nasal polyp from IP and SCC. It is also useful to recognize the distinctions between IP and SCC. In our study of 27 patients, a $SUV_{max}$ of 6 or higher ruled out the presence of nasal polyp [95% CI (5.93 to 13.39), specificity 100%] might also be clinically useful.

***Keywords:*** Computed tomography; fluorodeoxyglucose; inverted papilloma; maximum standardized uptake; nasal polyp; positron emission tomography; squamous cell carcinoma.

***ÖZ***

**Amaç:** Bu çalışmada inverted papillom (İP) ile nazal polip ve yassı hücreli karsinom (YHK) arasında florodeoksiglukoz tutulumu açısından fark olup olmadığı belirlendi.

**Hastalar ve Yöntemler:** Eylül 2007 ile Mayıs 2014 yılları arasında, muayene ve paranazal sinüs tomografi taramalarında tek taraflı polipozis tespit edilen 27 hastanın (20 erkek, 7 kadın; ort. yaş 53.4 yıl; dağılım 18-74 yıl) pozitron emisyon tomografi bilgisayarlı tomografi (PET/BT) görüntüleri elde edildi. Hastaların sekizinde nazal polip (grup 1), 10'unda İP (grup 2) ve dokuzunda YHK (grup 3) saptandı. Veriler Kruskal-Wallis ve Mann-Whitney U testleri ile karşılaştırıldı.

**Bulgular:** Ortalama standardize edilmiş maksimum tutulum ($SUV_{maks}$) değerleri, grup 1'de 2.9; grup 2'de 7.8; grup 3'te 17.8 olarak bulundu. Grup 1 ve 2 (p=0.016), grup 1 ve 3 (p=0.001) ve grup 2 ile 3 arasında (p=0.01) $SUV_{maks}$ değerleri arasında anlamlı bir fark bulundu.

**Sonuç:** Bu çalışmanın sonuçlarına göre tek taraflı polipozis hastalarında PET/BT taraması nazal polibi İP ve YHK'den ayırt etmede değerlidir. Bununla birlikte, İP ve YHK ayrımının yapılmasında da yararlıdır. Yirmi yedi hastalık çalışmamıza göre, 6 ya da üzerinde $SUV_{max}$ değeri nazal polip varlığının dışlanmasında da klinik olarak kullanılabilir [95% CI (5.93 to 13.39), özgünlük %100].

***Anahtar Sözcükler:*** Bilgisayarlı tomografi; florodeoksiglukoz; inverted papillom; maksimum standart alım; nazal polip; positron emisyon tomografi; yassı hücreli karsinom.

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Sinonasal inverted papillomata (IP) are usually encountered as unilateral polypoid nasal masses and are classified among the 'intermediate neoplasms' of the nose. Histologically, they contain squamous, transitional or respiratory type epithelium folded inwards. The rate of transformation into malignancy is assumed to be nearly 10%.[1] The incidence of coexistence with squamous cell carcinoma (SCC) is reported to be 5.5% to 27%.[2]

Fluorine-18-fluorodeoxyglucose [(18F-FDG); half-life, 110 minutes] positron emission tomography/computed tomography (PET/CT) is used for staging and follow-up of SCCs of the head and neck. It has been shown that there is a strong correlation between increased tumoral uptake of FDG and the number of live tumor cells.[3] Although there are studies indicating increased uptake of FDG in the coexistence of IP and SCC,[2] limited data are available about FDG uptake in patients with sole IP.[3,4]

The primary aim of this study is to determine whether there is a difference in terms of FDG uptake between IP and SCC, which require therapeutic approaches different from each other. Although a unilateral sinonasal polypoid mass may evoke IP, histopathologic examination may reveal nasal polyposis. Another purpose of the study is to disclose the distinctions relating to uptake that may exist between nasal polyposis, IP, and SCC.

## PATIENTS AND METHODS

The study was done at the Adana Seyhan Hospital, Research and Application Center of the Başkent University School of Medicine between September 2007 and May 2014. The approvals of the Başkent University Research Committee and Local Ethics Committee were received (KA07-139). All patients included in the study were asked to sign the informed consent form. Positron emission tomography/computed tomography images of 30 patients diagnosed with unilateral polyposis on examination and paranasal sinus tomographic views were obtained after probable sinonasal infection was treated. Punch biopsy and adequate surgical treatment were then performed. The definitive histopathologic results were compared with PET/CT findings. The evaluators of PET/CT and histopathology were blinded. Patients with bilateral allergic nasal polyposis and unilateral fungus ball were not included in the study.

Of the 30 patients, three were excluded from the study because histopathologic results revealed melanoma. Among the remaining 27 patients (20 males, 7 females; mean age 53.4 years; range 18 to 74 years), eight patients had nasal polyp (group 1), 10 patients had IP (group 2), and nine patients were diagnosed with SCC (group 3). None of the patients in the group 2 had signs of malignant transformation. One patient from group 2 had associated oncocytic Schneiderian component.

### PET/CT imaging and maximum standardized uptake ($SUV_{max}$) analysis

Positron emission tomography/computed tomography (Discovery-STE 8, General Electric System, Milwaukee, WI, USA) imaging studies were carried out in the Department of Nuclear Medicine. The patients were injected with 370-555 MBq (10-15 mCi) of F-18-FDG during rest after six-hour fast period. The blood glucose levels of the patients measured prior to the injection were below 150 mmol/L. Positron emission tomography images were obtained 60 min after the injection. Computed tomography images were taken just before PET imaging to adjust attenuation in low dose. The images were reconstructed using iterative reconstruction algorithm (section thickness was 3.4 mm; magnification of pixel was 4.37 mm).

In all patients, $SUV_{max}$ values were automatically calculated semi-quantitatively by the device, drawing volumetric interest areas from the lesion areas.

### Histopathologic examination

The specimens were fixed in 10% formalin solution and were embedded in paraffin blocks after routine preparation procedure. The 5-micron thickness slices cut from the paraffin blocks were placed on glass slides coated with pol-L-lysin, then the slides were stained with hematoxylin-eosin and examined microscopically. In nasal polyp specimens, the intensity of inflammation and the presence of squamous metaplasia were assessed. For the evaluation of density and distribution of inflammatory cells, the average of 5 high-power fields in 20 high-power fields was counted. In the patients with inverted papilloma, the type

of laying epithelium (squamous, transitional, oncocytic) and endophytic and exophytic patterns of growth were assessed.

### Statistical assessment

Statistical assessments were performed using Kruskal-Wallis and Mann-Whitney U tests. A $p$ value <0.05 was set to be statistically significant. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of the cutoff value for study were calculated using *Win Episcope 2.0 software (*developed by University of Zaragoza, Spain, and University of Wageningen, Netherlands).

## RESULTS

The data about the patients is summarized in the Table 1. The average $SUV_{max}$ values were 2.9 in group 1, 7.8 in group 2, and 17.8 in group 3. The groups were compared using Kruskal-Wallis test in terms of $SUV_{max}$ values. The results of the analysis indicated that there was a significant difference in the medians, $\chi^2(2, n=27)=15.96$, $p=0.000$. Because the overall test was significant, pairwise comparisons among the three groups were completed using the Mann-Whitney U test. The a priori alpha level was divided by the number of comparisons

**Table 1.** The characteristics of the patients

| Group | Age | Sex | Side | SUVmax* | Additional pathologic features |
|---|---|---|---|---|---|
| 1 | 28 | Female | Left | 2.7 | – |
| 1 | 36 | Male | Left | 5.3 | Inflammation |
| 1 | 74 | Female | Left | 3 | Squamous metaplasia |
| 1 | 45 | Male | Right | 2.6 | – |
| 1 | 66 | Male | Right | 2.5 | – |
| 1 | 37 | Male | Left | 1.8 | – |
| 1 | 58 | Male | Left | 2.9 | – |
| 1 | 18 | Male | Right | 2.6 | – |
| 2 | 31 | Female | Left | 2.7 | Inflammation, epithelial islets |
| 2 | 65 | Male | Right | 31 | Associated oncocytic Schneiderian component |
| 2 | 57 | Male | Right | 2.5 | – |
| 2 | 58 | Male | Left | 5.6 | Increased intensity of the epithelial islets |
| 2 | 62 | Male | Right | 9.1 | Increased intensity of the epithelial islets, increased cell layering of superficial epithelium |
| 2 | 45 | Male | Left | 4.4 | Epithelial islets in polypoid stroma |
| 2 | 64 | Male | Left | 6.2 | Epithelial islets in edematous stroma that has intact basal membrane |
| 2 | 40 | Male | Left | 4.3 | Epithelial islets growth into stroma |
| 2 | 56 | Female | Left | 5.1 | Epithelial islets growth into stroma |
| 2 | 57 | Male | Right | 6.7 | Epithelial islets growth into stroma, epithelial inflammatory cells |
| 3 | 62 | Male | Left | 6.1 | Poorly differentiated |
| 3 | 54 | Female | Left | 13 | Poorly differentiated |
| 3 | 64 | Male | Left | 11 | Poorly differentiated |
| 3 | 52 | Male | Right | 37.8 | Moderately differentiated |
| 3 | 68 | Male | Left | 21.4 | Moderately differentiated |
| 3 | 60 | Male | Left | 6.2 | Poorly differentiated |
| 3 | 43 | Female | Left | 13.6 | Poorly differentiated |
| 3 | 70 | Male | Left | 27.6 | Poorly differentiated |
| 3 | 73 | Female | Left | 23.3 | Well differentiated |

* $SUV_{max}$: Maximum standardized uptake value.

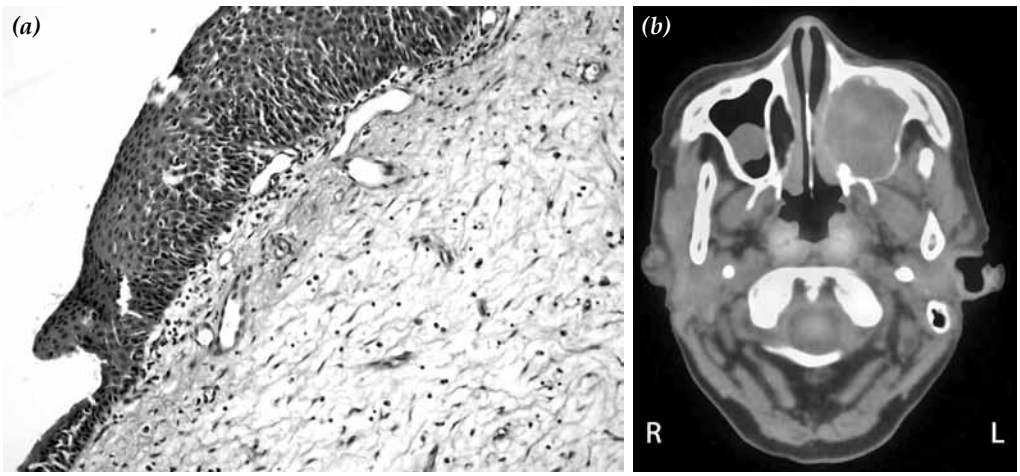


***Figure 1.*** *In polyp,* ***(a)*** *inflammation extending to surface epithelium, rich in eosinophils (H-E x 400).* ***(b)*** *Positron emission tomography/computed tomography image of the same patient.*

due to Bonferroni adjustment ($\alpha$=0.05/3=0.017). In between-group comparisons of $SUV_{max}$ values revealed a significant difference between group 1 and group 2 (p=0.016), between group 1 and group 3 (p=0.001), and between group 2 and group 3 (p=0.01).

In group 1, among the patients showing slight FDG uptake, one patient had inflammation and another had squamous metaplasia (Figures 1a and b). In group 2, one patient with associated oncocytic Schneiderian component (Figure 2a) had an $SUV_{max}$ value of 31 (Figure 2b), and therefore the mean value of group 2 increased. On histopathologic examination of group 2, particularly in the patient with an $SUV_{max}$ value of 9.1, increased cell layering of superficial epithelium in the endophytic growth pattern and increased intensity of the epithelial islets invading the stroma were observed (Figures 3a and b).

The mean ages increased from group 1 to group 3 (the mean age was 45.3 years in group 1; it was 53.5 years in group 2; and 60.7 years in group 3). As to gender, there was a non-balanced distribution in the groups; male/female ratio was 3:1 in group 1, 4:1 in group 2, and 3:1 in group 3. As to location of the mass, there was a non-balanced distribution in the groups; the lesions were located dominantly in the left side in patients in groups 1 (5:3), 2 (3:2) and 3 (8:1). Eight IP cases originated from the lateral wall while two cases originated from the maxillary sinus.

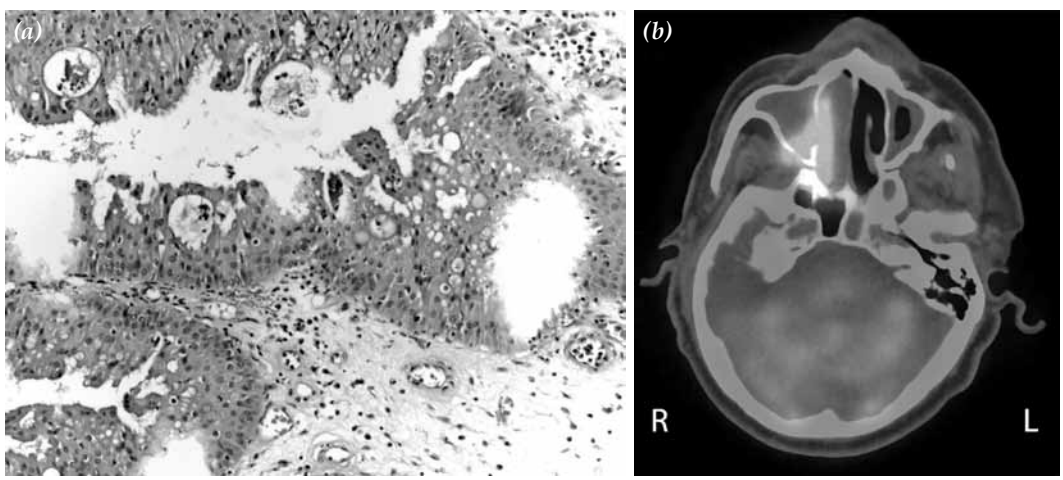


***Figure 2.*** *In inverted papilloma,* ***(a)*** *areas including oncocytic epithelium (H-E x 200).* ***(b)*** *Positron emission tomography/computed tomography image of the same patient.*

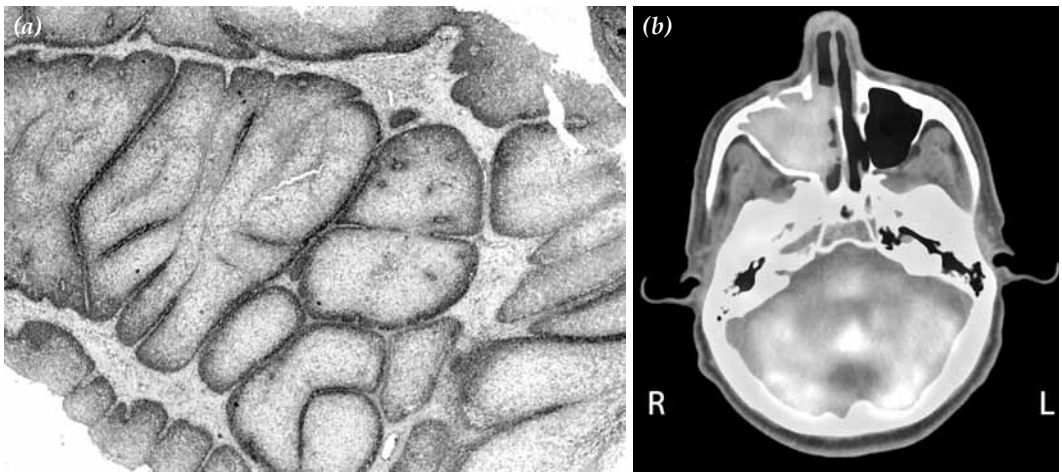


***Figure 3.*** *In inverted papilloma,* ***(a)*** *hyperplasic epithelial islets (H-E x 200).* ***(b)*** *Positron emission tomography/computed tomography image of the same patient.*

In addition, for all 27 patients, the average $SUV_{max}$ values were found to be 9.7±9.9 with 95% confidence interval (5.9 to 13.4). According to this data, when the cutoff value of the study was assigned to six, sensitivity, specificity, positive predictive value, negative predictive value and accuracy were 40%, 100%, 0%, 43% and 55.6%, respectively.

## DISCUSSION

In IP, the inversion of the epithelium into underlying stroma instead of proliferating outwards is the characteristic histological feature.[1,4] It is known as a histologically benign tumor, but it has certain malignant features including high tendency to recur, local aggressiveness and multifocal character.[5] Co-existence with SCC was reported at a rate ranging from 5.5% to 27%[2] while transformation into SCC was reported at a rate varying from 2% to 53%.[4] Although many studies about the mechanisms of growth and malignant transformation of IP have been carried out, these issues have not yet been clarified. Bacterial and viral infections, chronic inflammatory situations, allergy, tobacco use, and several occupational exposures are presented as potential etiologic factors.[6]

Sinonasal papillomata represent 0.4% to 4.7% of all sinonasal tumors. Sinonasal papillomata are benign tumors classified in three subgroups-inverted, oncocytic and exophytic. Inverted papillomata is the most common among these tumors occurring at a rate of 62%.[7] They often originate from the lateral nasal wall, less commonly from a paranasal sinus (most often maxillary). Men are affected 3 to 5 times more frequently. The age of occurrence is usually between 40-70 years.[2] Our study results, locations of IP (eight originated from the lateral

**Tablo 2.** Positron emission tomography/computed tomography studies with patients with inverted papillom without any malignant transformation

| Study | Upper and lower values of $SUV_{max}$‡ | Mean $SUV_{max}$‡ value | Number of patients (n) |
|---|---|---|---|
| Ninomiya et al.[10] | 1.98-4.65 | 3.49 | 5 |
| Shojaku et al.[2] | 4.9-7.3 | 5.8 | 3 |
| Lee et al.[9] | 9 | 9 | 1 |
| Cohen et al.[3]* | 3.5-9 | 6.4 | 4 |
| Jeon et al.[4] | 7.8-8.2 | 8 | 2 |
| *Present study** | 2.5-9.1 | 5.2 | 9 |

‡ $SUV_{max}$: Maximum standardized uptake value; * Those having oncocytic component were not included in order to be compatible with other studies containing only inverted component, because the oncocytic component has high $SUV_{max}$ values and it also increases mean values.

nasal wall and two arose from the maxillary sinus) the mean age (53.5 years) and male/female ratio of 4:1, are consistent with the literature.

Among the situations that may result in false positive PET/CT scans are inflammatory disorders such as infection and granulomatous diseases, asymmetric muscle activity, physiologic uptake, the presence of inflammation and granulation in surgical wounds.[8] In our study, of two patients showing slight FDG uptake in group 1 consisting of patients with fully benign nasal polyps, one patient had inflammation, and the other had squamous metaplasia (Figure 1). Therefore, it is proposed to include squamous metaplasia among the situations leading to a false positive PET/CT scan. Furthermore in the present study, Table 1 indicated that any lesion with $SUV_{max}$ over six is likely to be an IP or SCC and unlikely to be an inflammatory nasal polyp.

In a study conducted by Katori et al.,[6] it has been shown that an increase in proliferation of epithelial cells, which is shown by high Ki-67 scores, is a crucial factor in the development of IP. Taking this information one step forward, in our study it was found that an increase in the cell layering on the surface epithelium and the density of the epithelial islets invading the stroma affected the $SUV_{max}$ values in IP patients, and it is thought that $SUV_{max}$ values will increase as these properties enhance.

Table 2 shows published PET/CT studies on patients with IP without any malignant transformation when this study was carried out.[2-4,9,10] Given these data, it is seen that the average $SUV_{max}$ values ranged from 3.49 to 9. The $SUV_{max}$ value was nine in a patient with IP reported by Lee et al.[9] and the authors opined that such a high uptake could not be distinguished from maxillary sinus cancer and was likely due to inflammation in the lesion. In our study, the patients treated for probable infection before obtaining PET/CT images were also examined histopathologically for inflammation. Given these data, inflammation was found in only one IP patient ($SUV_{max}$: 2.7); it was suggested that the increase in $SUV_{max}$ values might be due to increased epithelial cell arrangement and presence of intense epithelial islets rather than inflammation.

Oncocytic Schneiderian papillomas are least frequently encountered among the sinonasal papillomata. They are benign tumors with a tendency to local recurrence of 33-40% and a risk of malignant transformation of 4-17%. Their FDG-PET uptake may be high even if they do not have typical radiologic signs. The $SUV_{max}$ value of the patient presented by Lin et al.[11] was reported to be 28. It was suggested that increased glucose metabolism was non-specific, which tumor cells as well as non-neoplastic cells such as fibroblast and neutrophils might account for.[11] According to Tallini,[12] increased FDG uptake seen in Warthin's tumor, oncocytoma and oncocytic papilloma in spite of their benign nature is due to the high number of mitochondria in tumor cells. In our study, an oncocytic component was found in one IP patient; and it was thought that intensity of oncocytic cells played a role in the $SUV_{max}$ value of 31 seen in that patient.

Although the number of our patients was small to draw a general meaningful conclusion, all other previous studies were smaller than our present study. Other limitations of this study may be the cost or exposure of the patient to radioactive material and radiation. The decision should be made according to profit and loss account in comparing coexistence with SCC and cost or exposure.

**Conclusion**

In our study, it was found that inflammation and squamous metaplasia affected FDG uptake in nasal polyps. In IP, it was observed that increased cell layering of superficial epithelium and the intensity of the epithelial islets invading the stroma affected the $SUV_{max}$ values, and it was thought that $SUV_{max}$ values would increase as these properties enhance. Therefore, according to the results of this study, it is concluded that PET/CT scan in patients with unilateral sinonasal polyposis is valuable to distinguish nasal polyp from IP and SCC. Moreover, it is also useful to recognize the distinctions between IP and SCC in contrast to some other previous studies.[2,3,9] In our study of 27 patients, an $SUV_{max}$ of 6 or higher ruled out the presence of simple benign nasal polyp [95% CI (5.9 to 13.4), specificity 100%] and might be clinically useful.

**Declaration of conflicting interests**

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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