Significance of Incidental Nasopharyngeal Uptake on ^{18}F -FDG PET/CT: Patterns of Benign/Physiologic Uptake and Differentiation from Malignancy

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Abstract

Purpose The purpose of this study was to assess the significance of incidental nasopharyngeal uptake on ^{18}F -FDG PET/CT and to identify image patterns useful in the differentiation between benign or physiologic activity and nasopharyngeal carcinoma.

Methods We retrospectively reviewed medical records of patients with nasopharyngeal uptakes on ^{18}F -FDG PET/CT scans taken between January 2010 and July 2011. Patients with head and neck cancer, other metastatic head and neck lesions, or lymphoma were excluded. Total 177 patients were enrolled (Group A). PET images were reviewed for patterns of nasopharyngeal FDG uptake, presence/absence of cervical lymph node uptake and pattern of cervical node uptake. Diagnostic confirmation was made by pathology or clinical and radiological follow-up for 1 year or longer. Furthermore, initial PET/CT images of 48 patients with nasopharyngeal carcinoma (Group B) were reviewed for comparison with PET/CT images of Group A patients.

Results All nasopharyngeal uptakes in Group A were confirmed to be benign. Group B showed significantly more intense FDG uptake (SUVmax of Group A 3.9 ± 1.4 vs. Group B 10.4 ± 4.6 , $p < 0.001$), and asymmetric nasopharyngeal uptake (asymmetric uptake of Group A 67.8% vs. Group B 89.6%). When SUVmax of 6.0 was used as cut off for

detection of malignant nasopharyngeal uptake, the area under the ROC curve was 0.93 (95% confidence interval, 0.88–0.98), with a sensitivity of 88.1% and a specificity of 91.7%. Metastatic nodes in Group B showed higher SUVmax (Group A 2.3 ± 0.6 vs. Group B 7.1 ± 4.0 , $p < 0.001$) and larger size (short axis of Group A 5.3 ± 2.0 mm vs. Group B 13.1 ± 4.7 mm, $p < 0.001$) than benign nodes of Group A. The majority of Group B cases demonstrated retropharyngeal lymph node uptake (70.8%), compared to only 2 cases in Group A.

Conclusions In patients without a history of underlying malignancy involving head and neck, incidental nasopharyngeal uptake on PET/CT does not indicate malignancy. However, if the nasopharyngeal uptake is intense (SUVmax ≥ 6.0) or concomitant retropharyngeal lymph node uptake is present, the possibility of a malignant condition should be considered.

Keywords Nasopharynx · FDG · PET/CT · Nasopharyngeal carcinoma · Physiologic activity

Introduction

^{18}F -FDG PET/CT has been successfully applied in detecting and staging various malignancies [1–3]. Tumor imaging with ^{18}F -FDG PET/CT is based on the increased glucose metabolism of malignant tumors. Increased FDG uptake is suspicious for malignancy if not explained by other benign or physiologic conditions [4]. However, ^{18}F -FDG accumulation is not specific for malignant lesions. Increased FDG accumulation can be seen in cases of infectious or inflammatory processes and other benign conditions [2, 4–8]. Also, physiological ^{18}F -FDG uptake in normal structures of the head and neck, such as the muscles, mucosa, lymphoid tissue and tonsils, can produce false-positive results. It is reported that in oncological patients with primary tumors that are not head and neck cancer, PET/CT often depicts physiologic uptake of ^{18}F -FDG in the head

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and neck region, with several foci showing moderate to intense tracer uptake [8]. The nasopharynx is one of the common head and neck sites showing such increased uptake on PET using ^{18}F -FDG [6], and the uptake can present as diverse patterns.

Nasopharyngeal carcinoma (NPC) is an aggressive head and neck cancer and is one of the most common malignant tumors occurring in Southern China and Southeast Asia [5, 7, 9, 10]. As with most other tumors, the extent of an NPC is the most important prognostic factor [11, 12]. However, prompt diagnosis of small tumors in the nasopharynx is difficult [6]. Because symptoms related to NPC in the early stage are usually nonspecific, most NPC patients are diagnosed in the advanced stage [13]. Since ^{18}F -FDG PET/CT can provide metabolic information, it is expected to help with early detection of malignancy compared to conventional anatomical imaging alone [14].

However, the variability in the image patterns of physiologic or benign nasopharyngeal uptake may make it difficult to differentiate these from malignant ones. Nevertheless, a few studies have reported the differentiation points. The aim of this retrospective study was to assess the significance of incidental nasopharyngeal uptake on ^{18}F -FDG PET/CT and to identify image patterns valuable in the differentiation between benign/physiologic and malignant uptake.

Materials and Methods

Patient Population

From January 2010 to July 2011, a total of 12,405 consecutive subjects performed 16,191 ^{18}F -FDG PET/CT scans in our institution for cancer management ($n=11,831$) and preventive health checkups ($n=574$). From this population, 641 patients showed increased nasopharyngeal uptake defined as intensity distinctly greater than the background physiologic activity. Among them, 29 patients had PET/CT scans for preventive health checkups and 612 patients for cancer management. The exclusion criteria for the study were: (1) pathologically proven head and neck cancer, thyroid malignancy, or head and neck metastases; (2) pathologically proven lymphoma; (3) history of prior surgery or radiation therapy in the head and neck region; (4) cancer of unknown primary; (5) accompanying morphological abnormality highly suspicious for the malignancies mentioned above; (6) a less than 1-year follow-up period without pathologic confirmation of the nasopharyngeal uptake. As a result, 177 patients were enrolled, and they were categorized as group A (70 males and 107 females; age: 53.8 ± 12.1 years). The reasons for the ^{18}F -FDG PET/CT imaging were staging for gastrointestinal cancer ($n=69$), breast cancer ($n=36$), gynecologic cancer ($n=32$), lung cancer ($n=13$),

hepatobiliary cancer ($n=11$), genitourinary cancer ($n=4$), sarcoma ($n=1$) and preventive health checkups ($n=11$).

For comparison with the group A patients, we retrospectively recruited 48 patients with pathologically proven nasopharyngeal carcinoma (group B: 36 males and 12 females; age: 56.4 ± 15.3 years) and reviewed their initial pretherapeutic ^{18}F -FDG PET/CT taken between August 2004 and November 2013. The numbers of patients for each stage of the nasopharyngeal cancer in group B were as follows: I ($n=1$), II ($n=10$), III ($n=20$), IVA ($n=10$), IVB ($n=12$) and IVC ($n=5$).

^{18}F -FDG PET/CT Scan

All patients fasted for at least 6 h before the ^{18}F -FDG PET/CT study. ^{18}F -FDG was injected intravenously (370–555 MBq), and scanning began 60 min later. Combined inline PET/CT systems, either Biograph Duo or Biograph TruePoint (Siemens Medical Solutions, Knoxville, TN), were used. Torso images were acquired, and the acquisition time was 2–3 min per bed position (130 kVp, 80 mA and 5-mm slice thickness; 120 kVp, 50 mA and 5-mm slice thickness). PET image acquisition followed immediately over the same body region. The CT data were used for attenuation correction, and images were reconstructed using a standard ordered-subset expectation maximization (OSEM) algorithm. The axial spatial resolution was 6.5 or 4.5 mm at the center of the field of view.

Image Interpretation

All ^{18}F -FDG PET/CT images were both qualitatively and quantitatively investigated by two experienced nuclear medicine physicians, who were unaware of the subjects' clinical history, working to form a consensus. For qualitative evaluation, the location of nasopharyngeal uptake—the fossa of Rosenmüller (FOR), posterior wall (PW) or lateral wall (LW)—was visually assessed. Maximum standardized uptake values (SUVmax) were measured by drawing a manual volume of interest over the site of abnormal nasopharyngeal uptake. Asymmetry of the nasopharyngeal uptake was defined as unilateral FDG uptake or the difference in the SUVmax value greater than 1.0 between the two sides [6]. CT abnormalities such as the presence of a mass or wall thickening at the site of nasopharyngeal uptake were assessed in the corresponding CT portion of the ^{18}F -FDG PET/CT scans, and the findings were categorized as absent, equivocal or evident.

Cervical lymph node uptake was also evaluated. Lymph node uptake was defined as “present” if there was increased FDG accumulation discernible from the physiologic background activity. The directionality (unilateral/bilateral), SUVmax value and short axis diameter of cervical lymph

nodes were assessed. When there was uptake of more than one lymph node present in one nodal station, the most hypermetabolic and largest node was measured.

Standard of Reference

Pathologic results served as the standard of reference for nasopharyngeal and lymph node uptake. If there was no pathologic result available, clinical and radiological follow-up of at least 1 year was used to determine whether the uptake was benign or malignant.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences 19 for Windows (SPSS Inc., Chicago, IL). First, Student's *t*-test was used to test for statistically significant differences in the SUVmax values of nasopharyngeal uptake between group A and group B. Second, Fisher's exact test was used to evaluate differences in the symmetry of nasopharyngeal uptake between group A and B. For lymph node analysis, Student's *t*-test was used to test for statistically significant differences in SUVmax values and the size of cervical lymph node uptake between group A and group B. Receiver-operating characteristic (ROC) curve analysis was applied to evaluate the efficacy of the imaging methods. A *p* value less than 0.05 was considered to indicate a statistically significant difference.

Results

Incidence of Incidental Nasopharyngeal Uptake

Among 12,405 patients who underwent ^{18}F -FDG PET/CT scans at our institution from January 2010 to July 2011, 641 patients (5.2 %) showed increased nasopharyngeal uptake.

Incidental Nasopharyngeal Uptake Group (Group A)

All incidental nasopharyngeal uptake in group A (177 patients, SUVmax range 1.8–10.5, mean 3.9 ± 1.4) was confirmed to be benign by pathology (3 patients) or follow-up of 1 year or longer (174 patients).

Patterns of image findings of incidental benign nasopharyngeal uptake in group A are given in Table 1. An asymmetric pattern (67.8 %) was more common than a symmetric pattern (32.2 %). The most common pattern was asymmetrically increased uptake involving the fossae of Rosenmüller (50.8 %) (Fig. 1). The second most common pattern was symmetrically increased ^{18}F -FDG uptake involving the bilateral fossa of Rosenmüller (12.4 %). Most of the

Table 1 Image patterns of nasopharyngeal uptake in group A and B

Symmetry	Location	Group A (<i>n</i> =177)	Group B (<i>n</i> =48)
Symmetric	FOR ^a	22	0
	PW ^b	14	0
	FOR and PW	19	0
	LW ^c	1	0
	FOR and LW	0	0
	FOR, PW and LW	1	5
	Total	57 (32.2 %)	5 (10.4 %)
Asymmetric	FOR	90	8
	PW	1	3
	FOR and PW	21	12
	LW	2	0
	FOR and LW	5	4
	FOR, PW and LW	1	16
	Total	120 (67.8 %)	43 (89.6 %)

^a FOR: fossa of Rosenmüller

^b PW: posterior wall

^c LW: lateral wall

nasopharyngeal uptake involved the fossa of Rosenmüller (89.4 %), and only 11.6 % of patients showed nasopharyngeal uptake involving the posterior or lateral wall without involvement of the fossa of Rosenmüller. Nasopharyngeal wall thickening in the CT portion of the PET/CT was evident in 106 patients (59.9 %), and 21 patients (11.9 %) showed equivocal findings. The SUVmax value of nasopharyngeal uptake was not different between groups of patients with (4.0 ± 1.5) and without nasopharyngeal wall thickening (3.9 ± 1.4).

One hundred ten patients from group A (62.1 %) had accompanying cervical lymph node uptake in a total of 225 stations (SUVmax range 1.2–4.7, mean 2.3 ± 0.6 ; short axis diameter range: 0.7–14.7 mm, mean: 5.3 ± 2.0 mm). All of the uptake-positive cervical lymph nodes from group A were confirmed to be benign or physiologic by follow-up. Among them, 89 patients demonstrated bilateral cervical lymph node uptake, and 21 patients showed unilateral cervical lymph node uptake. The most common cervical lymph node uptake pattern from group A patients was bilateral (*n*=64) or unilateral (*n*=21) uptake in cervical level II lymph nodes. The number of patients showing positive FDG uptake in the cervical LNs is shown by the nodal station: I (*n*=15), II (*n*=107), III (*n*=6), IV (*n*=2), V (*n*=1) and the retropharyngeal area (*n*=2).

Nasopharyngeal Carcinoma Group (Group B)

Image findings of nasopharyngeal carcinoma uptake in group B (SUVmax range 3.0–22.0, mean 10.4 ± 4.6) are given in Table 1. The most common pattern was asymmetrically increased FDG uptake involving all three sites (fossa of Rosenmüller, lateral and posterior wall) of the nasopharynx

Fig. 1 A 58-year-old female with stomach cancer. a, b, c: Axial PET/CT images show asymmetrically increased nasopharyngeal uptake (SUVmax: 10.7, involving the right fossa of Rosenmüller without cervical lymph node uptake). d, e, f: Follow-up PET/CT images after 1 year show spontaneous regression of the nasopharyngeal uptake

(33.3 %) (Fig. 2). Most of the group B patients presented evident CT abnormalities such as a mass or nasopharyngeal wall thickening in the CT portion of the PET/CT ($n=46$, 95.8 %), and only two patients with stage T1 disease demonstrated equivocal findings.

Forty-four patients in group B had cervical lymph node uptake. Among them, metastatic cervical lymph node uptake in a total of 121 stations (SUVmax range 1.6–24.5, mean 7.1 ± 4.0 ; short axis diameter range: 3.3–25.6 mm, mean: 13.1 ± 4.7 mm) of 38 patients was confirmed by biopsy ($n=8$) or follow-up ($n=112$). Cervical lymph nodes from eight patients could not be confirmed because of insufficient follow-up data. Twenty-five of the 38 patients demonstrated bilateral metastatic cervical lymph node uptake, and the other 13 patients showed unilateral cervical lymph node uptake. The number of patients showing positive FDG uptake in the cervical LNs is shown according to the nodal station: I ($n=5$), II ($n=29$), III

($n=9$), IV ($n=4$), V ($n=11$) and the retropharyngeal area ($n=27$). Most of the group B patients demonstrated retropharyngeal lymph node uptake (70.8 %).

Comparison and Differences Between Group A and B

Nasopharyngeal carcinoma uptake in group B patients showed significantly higher SUVmax values compared with the incidental uptake in group A (group A 3.9 ± 1.4 vs. group B 10.4 ± 4.6 , $p < 0.001$). Most patients in group B showed asymmetric nasopharyngeal uptake, and the rate was statistically higher than in group A (group A: 68.2 % vs. group B: 85.7 %, $p = 0.02$ by Pearson's chi-square test). When the SUVmax value of nasopharyngeal uptake was used to differentiate benign from malignant nasopharyngeal uptake on ROC curve analysis (cutoff: 6.0), the area under the curve was 0.93 (95 % CI 0.88–0.98), with a sensitivity of 88.1 %

Fig. 2 A 62-year-old male with nasopharyngeal carcinoma. a, b, c, g: Axial PET/CT images show asymmetrically increased uptake involving the left lateral wall, posterior wall and fossa of Rosenmüller of the

nasopharynx (arrows, SUVmax 8.3). d, e, f, g: Bilateral enlarged retropharyngeal lymph nodes show increased FDG accumulation (arrowheads, SUVmax of right: 5.5; left: 6.6)

and specificity of 91.7 %. The fossa of Rosenmüller (FOR) was the most commonly involved site in both group A and B. However, nasopharyngeal carcinoma uptake in group B usually involved the FOR with involvement of additional sites, whereas incidental nasopharyngeal uptake in group A usually involved only the FOR. CT abnormalities were evident in most group B patients and in over half of the group A patients in the corresponding CT portion.

Both the benign cervical lymph nodes in group A and metastatic cervical lymph nodes in group B most often demonstrated a bilateral uptake pattern (group A: 80.9 %; group B: 65.8 %). Metastatic lymph nodes in group B showed higher SUVmax values (group A: 2.3 ± 0.6 vs. group B: 7.1 ± 4.0 , $p < 0.001$) and larger size (short axis

in group A: 5.3 ± 2.0 mm vs. group B: 13.1 ± 4.7 mm, $p < 0.001$) than benign lymph nodes in group A. When the SUVmax value of cervical lymph node uptake was used to differentiate benign from malignant lymph nodes on ROC curve analysis (cutoff: 3.0), the AUC was 0.94 (95 % CI 0.91–0.97), with a sensitivity of 88.4 % and specificity of 85.3 %. When the diameter of the cervical lymph node was used to differentiate benign from malignant lymph nodes on ROC curve analysis (cutoff: 7.0 mm), the AUC was 0.95 (95 % CI 0.92–0.98), with a sensitivity of 92.6 % and specificity of 86.7 %.

Retropharyngeal lymph node uptake was present in the majority of group B patients (70.8 %). On the contrary, only two patients in group A (1.1 %) showed increased

retropharyngeal lymph node uptake, and they spontaneously regressed on follow-up.

Discussion

In nasopharyngeal carcinoma, the bulk of the tumor is an important prognostic factor [11], and if nasopharyngeal carcinoma can be diagnosed at an early stage, it may improve the patient's prognosis. As biochemical changes in a tumor occur before morphologic changes, ^{18}F -FDG PET/CT has the potential to provide diagnostic information earlier than CT or MRI [14]. However, increased FDG accumulation can be seen in cases of a physiologic metabolic process and of infectious, inflammatory and other benign conditions; such accumulations are not uncommon in the nasopharynx [15, 8]. Thus, for the differential diagnosis of incidental nasopharyngeal uptake on ^{18}F -FDG PET/CT, we investigated how many of the incidental nasopharyngeal uptake cases were truly nasopharyngeal carcinoma; in addition, we evaluated patterns from the image findings to differentiate benign or physiologic nasopharyngeal uptake from nasopharyngeal carcinoma.

Yen-Kung Chen et al. [6] previously reported that the intensity and patterns of ^{18}F -FDG uptake in various regions of Waldeyer's ring, with the CT scan findings, provide a feasible method to differentiate benign from malignant nasopharyngeal lesions. They evaluated ^{18}F -FDG PET/CT images of 1,628 subjects from a cancer-screening program, and increased uptake in the FOR was observed in 80 subjects (4.9 %) presenting with benign lesions. They compared the 80 subjects as a control group with 21 patients with newly diagnosed nasopharyngeal carcinoma. The SUVmax values of the FOR uptake (7.03 ± 3.83 vs. 3.0 ± 1.16) and ratio of lateral pharyngeal recess uptake to palatine tonsil uptake (N:P ratio) (2.3 ± 1.62 vs. 0.81 ± 0.37) in malignant lesions were significantly higher than those in benign lesions. Also, higher incidences of asymmetric ^{18}F -FDG lateral pharyngeal recess uptake and cervical lymph node uptake were observed in patients with nasopharyngeal carcinoma.

Similar results were obtained in our retrospective study. Incidental nasopharyngeal uptake on ^{18}F -FDG PET/CT was seen in 5.2 % of subjects. The incidental nasopharynx uptake was seen at similar rates in the cancer management group (5.2 %) and preventive health checkup group (5.1 %). Among them, all the nasopharyngeal uptake of patients without a history of malignancy in the head and neck (group A) was confirmed to be benign. The mean SUVmax value of nasopharyngeal carcinoma uptake in group B was significantly higher than that in benign/physiologic nasopharyngeal uptake in group A, similar

to a previous report [6]. On ROC curve analysis, sensitivity was 88.1 % and specificity 91.7 % when a SUVmax value of 6.0 was used as cutoff. However, benign nasopharyngeal uptake in this study presented with an asymmetric pattern twice as often as with a symmetric pattern (asymmetric: 68.2 % vs. symmetric: 31.8 %), which is contrary to the previous report by Yen-Kung Chen et al. (asymmetric: 29 % vs. symmetric: 71 %), although the same standard for defining symmetric uptake was used. This discrepancy could possibly be related to the fact that we enrolled patients according to the subjective standard of nasopharyngeal uptake 'distinctly' greater than the background. Also, an associated ^{18}F -FDG uptake in the cervical lymph nodes was very common in the incidental benign nasopharyngeal uptake in group A in our study, but was very rare in a study by Chen et al., possibly due to differences in the number of subjects and ratio of patients with infectious or inflammatory conditions. Differences in the definition of positive uptake could also have influenced the results. Chen et al. did not specify the criteria used for cervical lymph node uptake, while we defined the presence of cervical lymph node uptake by a subjective standard, 'FDG uptake visually discernible from background physiologic activity.' The most common pattern of benign/physiologic nasopharyngeal uptake was asymmetrically increased uptake involving the FOR (90 of 177 patients), possibly related to the abundant lymphatic vessels in this region. This pattern of asymmetric FOR uptake was also noted in eight patients with nasopharyngeal carcinoma. However, there were some differential points. Seven of the 8 nasopharyngeal carcinoma patients demonstrated intense ($\text{SUVmax} > 6.0$) nasopharyngeal uptake, and all of them presented unilateral or bilateral metastatic retropharyngeal lymph nodes, while only 4 of the 90 patients in group A showed nasopharyngeal uptake with $\text{SUVmax} > 6.0$; only one showed retropharyngeal lymph node uptake. In nasopharyngeal carcinoma patients, although FOR was the most often involved site, and as in previous reports [9, 11], involvement of all three sites of the nasopharynx was the most common finding in our study. This may be due to the fact that detection of early nasopharyngeal carcinoma is difficult and most patients are diagnosed at a locally advanced stage. In the analysis of symmetry, the rate of asymmetric lesions in the nasopharyngeal carcinoma group was significantly higher than that in the benign/physiologic nasopharyngeal uptake group (group B 85.7 % vs. group A 68.7 %, $p < 0.001$). Both group A (71.8 %) and B patients (100 %) demonstrated equivocal or evident abnormalities in the CT portion of the PET/CT. In the cases in group A, the abnormality in the corresponding CT images could be related to the hypertrophy of lymphoid tissues due to infectious or inflammatory conditions.

In lymph node uptake analysis, metastatic lymph nodes in group B showed higher SUVmax values and larger size than the benign lymph nodes in group A. The most common cervical lymph node uptake pattern in group A subjects was bilateral ($n=64$) or unilateral ($n=21$) cervical level II lymph node uptake, while that in group B patients was bilateral or unilateral cervical level II with concomitant retropharyngeal metastatic lymph node uptake ($n=24$). Most of the group B patients demonstrated retropharyngeal lymph node metastasis (28 of 38 patients) as they are the first echelon nodes of nasopharyngeal carcinoma. This result is concordant with previous reports on the pattern of lymph node metastasis in nasopharyngeal carcinoma [9, 11, 16–18]. On the contrary, only two patients from group A demonstrated unilateral retropharyngeal lymph node uptake (SUVmax 4.0 and 2.8; short axis diameter 5.6 mm and 6.2 mm). These reactive nodes spontaneously resolved on follow-up images.

There are some limitations to this study. First, there was an insufficient number of stage I nasopharyngeal carcinoma patients ($n=1$) in group B. Therefore, it was difficult to compare the benign nasopharyngeal uptake from group A with that of early nasopharyngeal carcinoma to determine whether FDG PET/CT has the ability to differentiate incidental small malignancy from non-specific uptake. Second, we did not consider the patients' other underlying conditions such as infection, inflammation and smoking history, which could all affect ^{18}F -FDG uptake of nasopharynx. Another limitation is that we could not check by pathologic confirmation whether each of the individual lymph nodes with increased FDG uptake was really metastatic per node.

Nevertheless, this study is meaningful since, while incidental nasopharyngeal uptake is a relatively common finding, there have been only a few studies explaining its clinical significance. Despite the limitations mentioned above, we could conclude that incidental nasopharyngeal uptake on PET/CT is less likely to indicate malignancy when there is no history of underlying malignancy involving the head and neck, even when the FDG uptake pattern is asymmetric.

Conclusion

In patients without a history of underlying malignancy involving the head and neck, incidental nasopharyngeal uptake on PET/CT did not indicate malignancy, even when the FDG uptake pattern was asymmetric. For differentiating benign and malignant nasopharyngeal uptake, the history should be considered first. However, there were statistically significant differences in the

SUVmax values of the nasopharyngeal uptake and the frequency of the accompanying retropharyngeal lymph node between the benign and malignant groups. Thus, if the nasopharyngeal or cervical lymph node uptake is intense (SUVmax > 6.0) or concomitant retropharyngeal lymph node uptake is present, the possibility of a malignant condition should be considered.

Acknowledgment

Conflict of Interest Narae Lee, Je Ryung Yoo, Sonya Youngju Park, Hyukjin Yoon, Yeongjoo Lee and Jin Kyoung Oh declare that they have no conflict of interest.

Ethical Statement The institutional review board approval number of this study is KC14RISI0296. Informed consent was waived.

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