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HEAD & NECK

Performance of whole-body ^{18}F-FDG PET/CT as a posttreatment surveillance tool for sinonasal malignancies

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Abstract

Purpose To determine the diagnostic utility of posttreatment surveillance whole-body ^{18}F-FDG PET/CT in detecting local tumor recurrence (R), regional lymph-node metastasis (LM), and distant metastasis (DM) in asymptomatic sinonasal cancer patients.

Methods Eighty consecutive patients (53 men, 27 women; mean age, 60 years; range, 28–92 years) who had undergone 197 posttreatment whole-body ^{18}F-FDG PET/CT examinations for sinonasal malignancies between January 2009 and August 2017 were retrospectively reviewed. ^{18}F-FDG PET/CT findings were categorized as positive or negative for R, LM, and DM, separately. Outcomes of ^{18}F-FDG PET/CT scans were compared with the final diagnosis confirmed by histological analysis or follow-up period for a minimum 12 months. The diagnostic accuracy of scans was calculated for each site using contingency tables. Impact on the management of ^{18}F-FDG PET/CT examinations was additionally evaluated.

Results ^{18}F-FDG PET/CT scans identified 37/44 of local recurrences, 21/23 of LMs, and 30/37 of DMs. For local recurrence, sensitivity, specificity, positive predictive value, and negative predictive value were 84% (68–97%), 95% (80–100%), 84% (68–97%), and 95% (80–100%), respectively. For LM, the respective values were 91% (75–100%), 99% (83–100%), 91% (75–100%), and 99% (83–100%). For DM, the values were 81% (64–97%), 99% (85–100%), 97% (81–100%), and 96% (81–100%), respectively. ^{18}F-FDG PET/CT accounted for a change in management of 85% patients with recurrences.

Conclusions Whole-body ^{18}F-FDG PET/CT is a suitable surveillance tool for sinonasal malignancies in detecting locoregional and distant recurrences in asymptomatic patients without any evidence of recurrence on regular follow-up and endoscopy during the posttreatment period.

Keywords ^{18}F-FDG PET/CT · Sinonasal malignancies · Surveillance · Recurrence · Posttreatment

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Introduction

A broad range of malignancies includes those with mesenchymal, epithelial, or neuroectodermal differentiation might derive from the nasal cavity and paranasal sinuses [1, 2]. While the diverse tumor subtypes present at different stages, the initial management is usually similar: surgery is the primary treatment method, accompanied by adjuvant radiotherapy and chemotherapy [3]. Regardless of current developments in the management of sinonasal malignancies [4], a significant number of patients experience locoregional recurrence in the posttreatment setting, while distant metastasis (DM) is rather uncommon [5]. Even though the overall incidence of DM in sinonasal malignancies is not very high, the survival rate of patients with DM is disappointing [6]. Patients with recurrent disease limited to the sinonasal cavity may be candidates for salvage surgery and radiotherapy

[7]. However, palliative strategies may be favorable for those with DMs. Therefore, the ability to identify locoregional recurrences and exclude DM is essential to guide the ongoing management of patients [8].

In this background, whole-body ^{18}F-fluorodeoxyglucose positron emission computed tomography (^{18}F-FDG PET/CT) seems to be a promising tool. ^{18}F-FDG PET/CT has been utilized as a standard imaging modality for staging, restaging, detection of DM, and monitoring the therapy response in this diverse group of neoplasms [9–11]. ^{18}F-FDG PET/CT examination has some benefits over traditional imaging methods, as it allows quantification of the metabolic activity of tumor [12]. It is particularly useful in the postoperative setting, where altered anatomy could lead to a significantly less accurate clinical examination [13]. Nevertheless, ^{18}F-FDG PET/CT is expensive and has some inherent drawbacks [14]. False-positive findings as a result of posttreatment inflammation could lead to unnecessary invasive procedures [15]. Although ^{18}F-FDG PET/CT is regarded as a novel gold-standard imaging method in the initial staging of sinonasal malignancies [16], this imaging modality has not yet been integrated into routine therapy assessment and follow-up of sinonasal malignancies. Consequently, distinct guidelines of whole-body ^{18}F-FDG PET/CT for posttreatment imaging surveillance are needed.

In our study, the aim is to determine the diagnostic performance of surveillance whole-body ^{18}F-FDG PET/CT in asymptomatic patients with treated sinonasal malignancies in the detection of local recurrence, LM, and DM as well as to determine the clinical impact on management.

Materials and methods

Patient characteristics and study design

A retrospective chart review was conducted of patients who underwent whole-body ^{18}F-FDG PET/CT for malignancies of the nasal cavity and paranasal sinuses treated with definitive surgical resection and adjuvant radiotherapy (RT) with or without chemotherapy at the University of Minnesota Medical Center (M-Health). All patients had been recruited as part of a larger study assessing the utility of whole-body ^{18}F-FDG PET/CT in the sinonasal region for which local institutional review board approval had been provided. All the whole-body ^{18}F-FDG PET/CT images of enrolled patients were reviewed by a double-board certified radiologist and nuclear medicine physician (Z.C.) with ten years of expertise in interpretation of whole-body ^{18}F-FDG PET/CT examination. Electronic medical and imaging records of patients with sinonasal malignant lesions between January 2009 and August 2017 were reviewed, and 130 patients with malignant tumors in the sinonasal region who underwent whole-body ^{18}F-FDG PET/CT for posttreatment surveillance staging were determined before application of exclusion criteria. Each patient had at least 12 months clinical and imaging follow-up period following the conclusion of therapy. Patients who fulfilled the following criteria were included; (a) primary sinonasal malignancies with histopathological confirmation and (b) patients underwent primary surgery and combined adjuvant radiotherapy with or without concomitant chemotherapy and after that no residual tumor tissue was discovered in the early postoperative period by clinical examination, endoscopy, and/or conventional radiological methods (contrast-enhanced CT and MRI). Exclusion criteria were: (a) patients with the benign sinonasal lesions ($n=47$); (b) unsuccessful primary treatment ($n=9$); and (c) distant metastatic disease at pretreatment staging ($n=21$). Patients diagnosed with sinonasal lymphoma ($n=11$) were not included in the analysis because of the completely distinct treatment strategy. Only fused ^{18}F-FDG PET/CT images acquired at M-Health were assessed; those from outside institutions ($n=3$) were not included in the study. Considering the reference standard to get additional data analysis was the recognition of recurrences at surveillance ^{18}F-FDG PET/CT screening as well as within the follow-up period of 12 months, three patients were excluded from the analysis, because the deaths were not due to the sinonasal malignancy. Of the remaining study population, two patients were excluded, because they were lost to follow-up or did not have satisfactory reports ($n=1$). In the end, the study cohort comprised of 80 patients (53 men, 27 women; mean age, 60 years; range, 28–92 years) (Table 1).

Table 1 Patient characteristics

Characteristic	No. of patients or mean ± SD
Sex	
Male	53
Female	27
Age	60 (range 28–92)
Site of primary tumor	
Nasal cavity	36
Maxillary sinus	29
Sphenoid sinus	6
Ethmoid sinus	7
Frontal Sinus	2
T stage	
T1	9
T2	18
T3	21
T4	32

No Number

Interpretation of ^{18}F-FDG PET/CT images

Whole-body ^{18}F-FDG PET/CT images were evaluated visually by a radiologist, who was informed for all clinical data, such as physical examinations records and the results of conventional radiological examinations. The attenuation-corrected ^{18}F-FDG PET/CT images were utilized for evaluation for all patients. We applied a routine visual analysis to review every follow-up ^{18}F-FDG PET/CT findings, and no standardized uptake value (SUV) was utilized to determine positive findings. The lesions with suspicious findings for malignancy on ^{18}F-FDG PET/CT were verified using additional follow-up radiological examinations, endoscopic assessment, and histological analysis utilizing a logical approach.

Outcome determination and surveillance data

Clinical surveillance including endoscopic examination was accomplished every 8–10 weeks following the conclusive treatment. At our institution, there is an accepted standard protocol to get whole-body ^{18}F-FDG PET/CT studies. According to the determined protocol, patients are supposed to get the initial surveillance whole-body ^{18}F-FDG PET/CT scan at 3 months, then at 9 months and at 1 year following completion of curative treatment in asymptomatic patients without clinical suspicion of recurrence. However, it was not rare for a planned ^{18}F-FDG PET/CT to be acquired earlier or later than the planned time. The reason sometimes they do not follow the accepted protocol is when a patient has some compliant or insurance issues. Additionally, patients with suspicious clinical and/or physical findings for recurrence in between periods were promptly further examined with CT and MRI. To be involved in the final patient cohort, patients had to have as a minimum one surveillance whole-body ^{18}F-FDG PET/CT examination in the posttreatment period, while asymptomatic without any suspicious radiological or endoscopic examination findings.

^{18}F-FDG PET/CT images were correlated with histopathology for locoregional recurrences and with conventional images for distant metastases. If a patient had negative test results and no DMs were observed within 12 months (mean follow-up time, 16.8 months; range, 12–44 months), screening by ^{18}F-FDG PET/CT was considered true negative (TN). ^{18}F-FDG PET/CT findings were regarded true positive (TP) when they correlated with histopathological findings with follow-up imaging results positive for locoregional recurrence and distant metastasis. If a follow-up period of 12 months did not identify recurrences, such positive findings for recurrences on ^{18}F-FDG PET/CT were categorized as false positive (FP). If a patient had a negative ^{18}F-FDG PET/CT findings yet developed recurrences within the 12-month follow-up period, screening was regarded as false negative (FN), presuming that these lesions were present at the time of screening.

While the main purpose of screening is to identify DMs, detection of second primary tumors is a further, clinically important finding. Second primary tumors observed in the course of screening or follow-up period were studied separately.

Additional diagnostic examinations, procedures, and clinical examinations thought to be associated with ^{18}F-FDG PET/CT findings were recorded to help establish how whole-body ^{18}F-FDG PET/CT examinations influenced patient care in the study population.

^{18}F-FDG PET/CT acquisition

All patients were imaged using a regular clinical whole-body ^{18}F-FDG PET/CT protocol. A combined ^{18}F-FDG PET/CT in-line system (Biograph Sensation 16; Siemens Medical Solutions, Malvern, PA, USA) was conducted 1 h after intravenous injection of 3 MBq/kg of ^{18}F-FDG with a continuous spiral technique using an 16-slice helical CT along with a gantry rotation speed of 0.8 s. The patients fasted a minimum of six hours before imaging, and their blood glucose levels were less than 150 mg/dl during the ^{18}F-FDG injection. Fifty minutes after ^{18}F-FDG injection, whole-body ^{18}F-FDG PET/CT was obtained from the vertex to feet. In addition, dedicated head and neck ^{18}F-FDG PET/CT scans were additionally acquired with the arms down to reduce attenuation artifact. The 3-mm slice thickness triplanar reconstructions of contrast-enhanced diagnostic CT for attenuation correction were obtained. PET/CT images were displayed and interpreted with commercially available software—Syngo.Via® (Siemens Healthcare Forchheim, Germany).

Statistical methods

Continuous variables are presented as means with standard deviations for normally distributed variables or medians with ranges for skewed data. Categorical variables are presented as counts with corresponding percentages. Each ^{18}F-FDG PET/CT scans was examined for its capability to predict disease at the primary site, regional lymph nodes, and distant sites. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated utilizing the 2×2 contingency tables for each site. Statistical differences in demographics and tumor-specific factors between patients with and without metastases were assessed by applying the Mann–Whitney *U* test for continuous variables and Fisher's exact test or the x^2 test for categorical data. The Pearson Chi-square or Fisher's exact test was utilized to compare the diagnostic accuracy of ^{18}F-FDG PET/CT resulting from the time interval in between

the conclusion of treatment and surveillance ^{18}F-FDG PET/CT examinations. All tests were two-sided, and P values <0.05 were considered statistically significant. Statistical analyses were performed using Statistical Package for Social Science (SPSS) version 23 software. Records were inserted into Excel spreadsheets (Microsoft, Redmond, WA).

Results

Population

Total of eighty patients fulfilled the inclusion criteria and underwent 197 whole-body ^{18}F-FDG PET/CT examinations in the study period between January 2009 and August 2017 with a mean of 2.5 ^{18}F-FDG PET/CT scans for each patient. Thirty-two patients had one scan; 19 patients had two scans, ten patients had three scans, eight patients had four scans, six patients had five scans, and five patients had more than five scans. The average time to initial posttreatment ^{18}F-FDG PET/CT examination was 6.5 months. Squamous cell carcinoma was the most common tumor, followed by malignant melanoma and adenoid cystic carcinoma. Tumor subtypes are displayed in Table 2. Most primary tumors were found in the nasal cavity ($n=36$) and maxillary sinuses ($n=29$) with a smaller portion in the ethmoid sinuses ($n=7$), sphenoid sinuses ($n=6$), and frontal sinuses ($n=2$). The majority of patients had an advanced stage (66% with T3 and T4 stage) according to the American Joint Committee on Cancer (AJCC) criteria [17] and the University of California Los Angeles staging system [18] for olfactory neuroblastoma. Nonetheless, the incidence of locoregional and distant recurrences was not statistically different between various T stages ($p>0.05$). No significant differences were detected between the subtypes of sinonasal malignancies related to the occurrence of local recurrences, DMs and LMs ($p>0.05$).

No significant differences in the mean age or sex distribution were recognized regarding the presence or absence of recurrent disease ($p>0.05$). Thirty-eight patients received chemotherapy implementing within their primary treatment.

Table 2 Tumor histological subtypes

Tumor histology	
Squamous cell carcinoma (SCC)	30
Olfactory neuroblastoma	7
Adenocarcinoma	3
Sinonasal undifferentiated carcinoma (SNUC)	5
Small cell carcinoma	2
Malignant melanoma	8
Rhabdomyosarcoma	6
Poorly differentiated carcinoma	4
Adenoid cystic carcinoma	8
Osteosarcoma	2
Neuroendocrine carcinoma	2
Carcinosarcoma	2
Clear cell carcinoma	1
Total	80

Accuracy of whole-body posttreatment ^{18}F-FDG PET/CT

Of the patient population ($n=80$), 24 patients (30%) developed local recurrences, 13 patients (16%) developed regional LMs, and 18 patients (23%) developed DMs. In a total of 197 posttreatment surveillance ^{18}F-FDG PET/CT scans obtained from 80 patients, 37/44 of local recurrences, 21/23 of LMs, and 30/37 of DMs were diagnosed accurately.

Local recurrence (R)

In the detection of recurrences at the primary site, ^{18}F-FDG PET/CT scan demonstrated 146 TN, 7 FN, 37 TP and 7 FP results. Consequently, the sensitivity, specificity, PPV, and NPV of ^{18}F-FDG PET/CT studies for detecting local recurrences were 84% (95% CI 68–97%), 95% (95% CI 80–100%), 84% (95% CI 68–97%), and 95% (95% CI 80–100%), respectively (Table 3).

Of the seven false-negative studies, three patients exhibited no evidence of recurrence at the primary site regardless of the utilization of MRI and succeeding clinical course revealed tumor infiltration (two at the nasal cavity and one

Table 3 Statistics of surveillance whole-body ^{18}F-FDG PET/CT for local recurrence (R), regional nodal metastasis (LM), and distant metastasis (DM)

	Local recurrence (R)	Regional nodal metastasis (LM)	Distant metastasis (DM)
Sensitivity	84 (68–97)	91 (75–100)	81 (64–97)
Specificity	95 (80–100)	99 (83–100)	99 (85–100)
PPV	84 (68–97)	91 (75–100)	97 (81–100)
NPV	95 (80–100)	99 (83–100)	96 (81–100)

All values are expressed as percentage (%); 95% confidence intervals listed in parenthesis

PPV positive predictive value, *NPV* negative predictive value

at the sphenoid sinus). Another false negative was a local recurrent disease of sinonasal adenocarcinoma along the nasal septum, which was proven by histopathological analysis. A patient with a recurrence of squamous cell carcinoma in the maxillary sinus was identified by posttreatment ^{18}F-FDG PET/CT at 6 months; with a preceding false-negative ^{18}F-FDG PET/CT examination at 1 month following treatment. Another patient with a negative ^{18}F-FDG PET/CT findings at 4 and 10 months was found to have a local recurrence in the ethmoid sinus identified by posttreatment ^{18}F-FDG PET/CT at 13 months following definitive treatment. The remaining 146 studies with negative findings on ^{18}F-FDG PET/CT were true negatives. For the seven studies with false-positive ^{18}F-FDG PET/CT findings in whom relapse was not confirmed, 2 had biopsies that were negative, and five false-positive results had resolved on the subsequent whole-body ^{18}F-FDG PET/CT scans (Table 4).

Correspondingly, 31/37 (%84) patients with TP studies had an advanced stage at initial presentation, whereas only (4/7) of the patients with FP results presented at advanced stage (stage T3 and T4).

Of the 24 patients with local recurrences, 16 patients underwent surgery with curative intent. During follow-up, none of them developed metastases or second primary tumors. In the remaining eight patients, surgery was avoided due to concurrent distant metastases.

Regional nodal metastasis (LM)

Regional nodal FDG uptake was identified in 23 posttreatment ^{18}F-FDG PET/CT examinations, and 174 ^{18}F-FDG PET/CT studies revealed no nodal FDG uptake in the cervical region. Of the patients with positive uptake on ^{18}F-FDG PET/CT, 21 patients were TP, while two patients were FP. Of the 174 patients with negative findings on ^{18}F-FDG PET/CT, 172 patients were TN, while two patients were FN. Thus, the sensitivity, specificity, PPV, and NPV of ^{18}F-FDG PET/CT for detecting LM were 91% (95% CI 75–100%), 99% (95% CI 83–100%), 91% (95% CI 75–100%), and 99% (95% CI 83–100%), respectively (Table 3).

In one patient with an FP result, the cervical nodal uptake had resolved on the subsequent ^{18}F-FDG PET/CT examinations. Another patient with FP result underwent a fine needle aspiration (FNA), but FNA did not demonstrate any evidence of tumor.

Two patients with FN scans, isolated recurrences were identified in the cervical lymph nodes by ^{18}F-FDG PET/CT examinations at 9 and 17 months, respectively (Table 5).

Of the 21 TP studies and two FN studies for LM among 13 different patients, each one of them led to an upstaging of patients by the recognition of regional nodal metastases, which were not determined in primary neck dissection. Of the 13 patients, six of them underwent surgery with cervical lymph-node dissection. The remaining seven patients were referred to medical and radiation oncologists for nonsurgical treatment because of concomitant distant metastases.

Distant metastasis (DM)

In the detection of DMs, whole-body ^{18}F-FDG PET/CT scans showed 159 TN, 7 FN, 29 TP, and 1 FP results. According to these numbers, the sensitivity of ^{18}F-FDG

Table 4 Surveillance ^{18}F-FDG PET/CT examinations with false-negative (FN) and false-positive (FN) results for local recurrences (R)

Pt	Sex	Age	Tumor type	Site	T stage	Outcomes	Time of false PET/CT (mo)	Diagnostic method
1	M	55	ACC	Ethmoid sinus	T4	FN	4, 10[a]	PET/CT at 13 months
2	M	58	ACC	Sphenoid sinus	T3	FN	1	Clinical follow-up
3	M	47	Adenocarcinoma	Nasal cavity	T2	FN	5	Endoscopy
4	M	68	Poorly D. C	Nasal cavity	T3	FN	10	Clinical follow-up
5	M	62	Rhabdomyosarcoma	Nasal cavity	T3	FN	17	Clinical follow-up
6	F	61	SCC	Maxillary sinus	T4	FN	1	PET/CT at 6 mo
7	M	81	ACC	Maxillary sinus	T3	FP	8	PET/CT at 12 mo
8	M	46	ONB	Nasal cavity	T1	FP	8	Clinical follow-up
9	M	58	ONB	Nasal cavity	T2	FP	20	Endoscopy
10	M	60	SCC	Sphenoid sinus	T2	FP	6	PET/CT at 8 mo
11	F	64	SCC	Maxillary sinus	T3	FP	7, 13[b]	PET/CT at 17 mo
12	M	45	SCC	Nasal cavity	T3	FP	7	PET/CT at 11 mo

Pt Patient, *m* male, *f* female, *mo* month, *FP* false positive, *FN* false negative, *Poorly D. C*. poorly differentiated carcinoma, *ONB* olfactory neuroblastoma, *SCC* squamous cell carcinoma, *ACC* adenoid cystic carcinoma

[a]Two FN ^{18}F-FDG PET/CT findings had resolved on the subsequent whole-body 18F-FDG PET/CT scan at 13 months in this patient

[b]Two FP ^{18}F-FDG PET/CT findings had resolved on the subsequent whole-body 18F-FDG PET/CT scan at 17 months in this patient

Table 5 Surveillance ^{18}F-FDG PET/CT examinations with false-negative (FN) and false-positive (FN) results for regional lymph-node metastases (LM)

Pt	Sex	Age	Tumor type	Site	T stage	Outcomes	Time of false PET/CT (mo)	Location of LM	Diagnostic method
1	F	51	SCC	Nasal cavity	T3	FN	3	Multiple cervical	PET/CT at 9 mo
2	M	66	M. Melanoma	Nasal cavity	T2	FN	10	Multiple cervical	PET/CT at 17 mo
3	M	53	ACC	Ethmoid sinus	T3	FP	16	Right level 2	FNA
4	F	64	SCC	Maxillary sinus	T4	FP	17	Bilateral level 1–2	PET/CT at 24 mo

Pt Patient, *m* male, *f* female, *mo* month, *FP* false positive, *FN* false negative, *FNA* fine needle aspiration, *M* melanoma, malignant melanoma, *SCC* squamous cell carcinoma, *ACC* adenoid cystic carcinoma, *LM* regional lymph-node metastasis

PET/CT in detecting DM was 81% (95% CI 64–97%), at a specificity of 99% (95% CI 85–100%), corresponding with PPV and NPV of 97% (95% CI 81–100%) and 96% (95% CI 81–100%), respectively (Table 3).

^{18}F-FDG-avid true-positive metastases were often found in the multiple sites ($n=13$), lungs ($n=8$), bones ($n=6$), liver ($n=1$), and adrenal gland ($n=1$).

^{18}F-FDG PET/CT studies revealed FP result for one patient in the lung which was followed up clinically and succeeding ^{18}F-FDG PET/CT was found to be negative for metastatic disease. ^{18}F-FDG PET/CT showed FN results for eight patients in the bone ($n=4$), lung ($n=2$) and colon ($n=1$). A recurrence of malignant melanoma at the colon was determined during a routine colonoscopy in a patient with previous false-negative ^{18}F-FDG PET/CT examination. Patients with bone metastases were negatively interpreted by ^{18}F-FDG PET/CT, but lesions were caught by subsequent follow-up ^{18}F-FDG PET/CT scan ($n=2$), bone scan (BS) ($n=1$) and lumbar MRI ($n=1$) (Table 6).

^{18}F-FDG PET/CT identified second primary tumors in four patients during the follow-up period (one patient with lymphoma, one patient with head and neck cutaneous squamous cell carcinoma, and two patients primary lung cancer).

Each of the patients with DMs was upstaged and had changes in the treatment regimen. Patients with DMs were referred to medical and radiation oncologists for nonsurgical treatment.

Out of a total of 197 whole-body ^{18}F-FDG PET/CT examinations, 9 scans were obtained at < 1 month (the accepted protocol was not followed), and 187 scans were obtained after 1 month following the protocol. Of the total of 26 false-positive and false-negative scans which was obtained considering the detection of recurrences, regional nodal metastasis, and distant metastases, three FP–FN ^{18}F-FDG PET/CT examinations were obtained in 1 month (3/9; 33%) and 23 FP–FN ^{18}F-FDG PET/CT examinations were obtained after 1 month (23/188; 12%). The overall accuracy of ^{18}F-FDG PET/CT conducted within 1 month (67%) was significantly inferior to that performed after 1 month (88%) ($p<0.05$).

Discussion

Posttreatment surveillance imaging for sinonasal malignancies is crucial for successful clinical management and for achieving higher long-term survival [19]. The presence of locoregional recurrences and distant metastases strongly affect both prognosis and treatment options [20]. Nevertheless, the rarity and the biologic variety of the

Table 6 Surveillance ^{18}F-FDG PET/CT examinations with false-negative (FN) and false-positive (FN) results for distant metastases (DM)

Pt	Sex	Age	Tumor type	Site	T stage	Outcomes	Time of false PET/CT (mo)	Location of DM	Diagnostic method
1	M	55	Adenocarcinoma	Ethmoid sinus	T4	FN	13	Bone	Bone scan
2	F	61	M. Melanoma	Nasal cavity	T1	FN	7	Lung	CT
3	F	70	M. Melanoma	Nasal cavity	T2	FN	6	Colon	Colonoscopy
4	M	65	Rhabdomyosarcoma	Nasal cavity	T3	FN	17	Bone	MRI
5	F	45	SCC	Maxillary sinus	T2	FN	8	Bone	PET/CT at 12 mo
6	M	54	SNUC	Ethmoid sinus	T3	FN	9	Lung	PET/CT at 12 mo
7	F	35	SCC	Sphenoid sinus	T4	FN	1	Bone	PET/CT at 4 mo
8	M	52	SCC	Sphenoid sinus	T4	FP	16	Lung	CT

Pt Patient, *m* male, *f* female, *mo* month, *FP* false positive, *FN* false negative, *SNUC* sinonasal undifferentiated carcinoma, *MRI* magnetic resonance imaging, *DM* distant metastasis, *M* melanoma, malignant melanoma, *SCC* squamous cell carcinoma, *ACC* adenoid cystic carcinoma

sinonasal tumors make it difficult to determine the optimum surveillance protocols [21].

The present study analyzed the performance variables of posttreatment whole-body ^{18}F-FDG PET/CT in a cohort of 80 asymptomatic patients with sinonasal malignancies to identify locoregional and distant recurrences. We found that surveillance imaging of sinonasal malignancies with whole-body ^{18}F-FDG PET/CT was highly accurate in the detection of recurrent disease at local, regional, and distant sites despite negative findings on endoscopy and clinical follow-up.

In this study population, ^{18}F-FDG PET/CT yielded positive results for DMs in a significant number of patients including multiple sites ($n=13$), lungs ($n=8$), bones ($n=6$), liver ($n=1$), and adrenal gland (n = 1). Furthermore, considering that 50% of patients with DMs had metastases to multiple organs, whole-body screening using ^{18}F-FDG PET/CT can determine most of the distant metastatic foci. For seven patients, ^{18}F-FDG PET/CT showed false-positive results at the primary site despite the absence of recurrent disease. ^{18}F-FDG uptake was possibly induced by local inflammation. On the other hand, false-negative results were identified in seven patients. These likely resulted from the small size of the recurrences, necrotic tissue around viable neoplasm or higher ^{18}F-FDG accumulation at the background tissue. Patients with negative scan can reasonably be followed up clinically only, whereas positive results on ^{18}F-FDG PET/CT necessitate verification by additional biopsies and imaging work-ups. This may be a disadvantage of ^{18}F-FDG PET/CT, raising the costs of confirming suspicious lesions. Nonetheless, we found that the NPV was very high 95% (95% CI 80–100%), indicating that ^{18}F-FDG PET/CT could be an efficient screening method for detecting locoregional recurrences. A negative posttreatment scan can guide the ongoing management of patients with sinonasal malignancies and probably minimize the need for more invasive diagnostic procedures.

Our results revealed that diagnostic accuracy was significantly inferior in ^{18}F-FDG PET/CT performed within 1 month as opposed to ^{18}F-FDG PET/CT performed after 1 month. We suggest that surveillance ^{18}F-FDG PET/CT should first be performed after 1 month following the conclusive treatment. When performed earlier, accumulation of ^{18}F-FDG may represent treatment-induced inflammatory changes in tissues. Furthermore, small traces of recurrent tumor may not be seen in ^{18}F-FDG PET/CT right after treatment, yet will become visible a couple weeks later. This contradicts with immediate diagnostics and salvage treatment of patients with recurrent disease. Further studies are needed to establish the ideal timing of the posttreatment ^{18}F-FDG PET/CT scans and to assess the impact of surveillance ^{18}F-FDG PET/CT on follow-up strategy and prognosis.

Despite that some studies exist with attention focused on head and neck cancer [22], a couple of studies [23] have evaluated the utilization of ^{18}F-FDG PET/CT in sinonasal malignancies. Gil et al. [24] examined skull base, middle and posterior cranial fossa tumors for both staging and restaging purposes in a prospective study of 57 examinations, which yielded a sensitivity, and specificity of 77% and 81%, respectively. However, our study focused on sinonasal malignancies for restaging purposes only and obtained a higher overall sensitivity and specificity of 84% and 98%, respectively. Wild et al. [25] studied particularly neoplasms of paranasal sinuses along with tumors extending to the orbit, infratemporal and pterygopalatine fossa. They evaluated 21 patients who underwent a total of 26 ^{18}F-FDG PET/CT scans. They concluded that ^{18}F-FDG PET/CT might offer further data contributory to conventional radiological methods if utilized just for restaging and not for staging purposes. In the study by Lamarre et al. [16], 77 scans were gathered from 31 patients for restaging purposes. The PPVs of the study for the LMs and DMs were 54% and 63%, respectively; NPVs were 100% and 98%, respectively. Nevertheless, the patient population in this study was different from ours. They included 13 out of 77 ^{18}F-FDG PET/CT scans of minor salivary gland carcinomas. In our study, the non-sinonasal neoplasms were excluded from the initial cohort. Khalili et al. [26] retrospectively assessed the usefulness of endoscopic examination as well as imaging surveillance of sinonasal malignancies. In their cohort of 100 patients, 30 patients were found to have locoregional and distant recurrences, with most of them were occurred in the primary site ($n=22$); besides, regional lymph-node metastases and distant metastases involved 17% and 10% of all recurrences, respectively. Workman et al. [27] examined a total of 111 posttreatment ^{18}F-FDG PET/CT scans which were conducted for 45 asymptomatic patients with sinonasal carcinoma. Overall specificity for ^{18}F-FDG PET/CT was 96%, with an NPV of 99%. Therefore, regarding their reference standard, the accuracy of ^{18}F-FDG PET/CT scan for the posttreatment surveillance of sinonasal malignancies was similar to our study.

The main difference in results from our versus previously reported studies is because of the inclusion of different cohorts. Our cohort solely involves patients without symptoms or suspected recurrence by routine follow-up. Furthermore, we did not utilize the SUV as a criterion for a positive result. Instead, we relied entirely on the qualitative interpretation of the ^{18}F-FDG PET/CT findings, visual interpretation of FDG uptake and comparison with the background. Even though our method needs a higher degree of radiological experience, we think that the usage of absolute SUV thresholds is limited in the posttreatment setting. Another strength of our study was the long-term follow-up. Most studies thus far compared ^{18}F-FDG PET/CT results (negative or positive) with clinical and histological findings without utilizing the follow-up period as a reference standard. With a minimum of 12 months of the follow-up period, our study examined the role of whole-body ^{18}F-FDG PET/CT to predict both locoregional recurrences and distant metastatic disease. Use of

subsequent ^{18}F-FDG PET/CT to define false-negative initial staging exams may increase false negatives if lesions arise subsequent to the initial study. As a result, the sensitivity of ^{18}F-FDG PET/CT for detecting metastases in our study seems to be lower than that in other studies.

Contrast-enhanced CT as part of the combined ^{18}F-FDG PET/CT examination offers further information in comparison with non-enhanced ^{18}F-FDG PET/CT. Because CT may yield anatomic background for an ^{18}F-FDG PET, the main advantage relates to more precise anatomic localization of pathology. CT contrast agents can be of additional benefit in ^{18}F-FDG PET-negative tumors by supporting lesion detection and characterization. Whole-body ^{18}F-FDG PET/CT acquired with CT contrast agent can provide morphologic and functional data in a single session, rendering additional diagnostic CT unnecessary. CT contrast agents and ^{18}F-FDG, as a result, do not compete but instead supplement each other in combined ^{18}F-FDG PET/CT imaging. Our results depend on specific ^{18}F-FDG PET/CT protocols for sinonasal malignancies, including the using intravenous contrast as well as experienced readers, and we strongly recommend the utilization of intravenous contrast to enhance the accuracy of ^{18}F-FDG PET/CT.

Overall, ^{18}F-FDG PET/CT has compared favorably to contrast-enhanced neck CT, and MRI in the assessment of sinonasal malignancies, and thus has been quickly adopted for both diagnosis and surveillance at many institutions. The use of whole-body ^{18}F-FDG PET/CT imaging easily enables examination of the whole body for metastatic disease as opposed to conventional CT and MRI locoregional scan protocols. In spite of these favourable outcomes, the absence of anatomical detail is the main drawback of ^{18}F-FDG PET/CT. Furthermore, ^{18}F-FDG PET/CT findings have to be confirmed by conventional diagnostic techniques. Given the retrospective nature of this study, both CT/MR imaging and ^{18}F-FDG PET/CT were not available for the entire study population, and thus, the prevalence of tumor extension and a side-by-side analysis of ^{18}F-FDG PET/CT and CT-MRI could not be assessed properly. These limitations of unstandardized imaging examinations may influence the results.

Even though ^{18}F-FDG PET/CT is a very accurate imaging method, it has some inherent limitations. There are a variety of malignant tumors in the sinonasal tract which could be ^{18}F-FDG-negative and subsequently missed by ^{18}F-FDG PET/CT [28]. Other potential causes of false-negative readings are due to small tumor size, necrotic tissue surrounding viable neoplasm and the high normal tissue background uptake. In our experience, the CT as a component of the ^{18}F-FDG PET/CT examination can partly aid to overcome this drawback. Moreover, ^{18}F-FDG PET/CT scan generates a significant number of FP results, particularly in areas, where physiological ^{18}F-FDG uptake is often observed, such as in the intestine [29]. This is a limitation of ^{18}F-FDG PET/CT imaging, because ^{18}F-FDG uptake is nonspecific for malignancy and related to the affinity of malignant cells for glucose due to increased metabolic activity. These drawbacks of ^{18}F-FDG PET/CT may result in further diagnostic, often invasive and expensive procedures, in addition to additional anxiety to the patient.

There are some limitations regarding the study protocol. As a result of the retrospective nature of the study, selection bias is unavoidable. Moreover, including various histological subtypes of sinonasal neoplasms with different propensities for the regional and distant recurrences might cause inefficient prediction of optimal surveillance protocol. Nevertheless, we believe that it is a representative sample of the patient population in routine clinical practice. The pathological confirmation was not available for all recurrent lesions, and some of the lesions were determined solely with clinical examination or imaging follow-up. Another drawback is that the pretreatment whole-body ^{18}F-FDG PET/CT was not evaluated in this retrospective study. There are some possible offerings when ^{18}F-FDG PET/CT is performed in the pre-treatment as well as posttreatment setting in sinonasal malignancies. Although infrequent, pretreatment ^{18}F-FDG PET/CT may establish that a certain tumor is not ^{18}F-FDG-avid. In this scenario, its utility in disease surveillance after therapy is limited and that knowledge may help to prevent a false-negative reading in posttreatment follow-up ^{18}F-FDG PET/CT scans. A second previously suggested value is the prognostic information given by the SUV parameters of the pretreatment ^{18}F-FDG PET/CT scans. This measurement, essentially, displays the metabolic activity of the tumor; in head and neck cancer, this has been shown to have some prognostic value and has been hypothesized to predict response to chemotherapy and radiation. ^{18}F-FDG PET/CT-based treatment response studies typically measure the change in SUV to quantify response. Typically, relative or percentage changes in SUVs are thought to be an index for drug efficiency or clinical response. In addition, the residual SUV, that is, the SUV from a single scan during or after therapy, may have predictive value. Our posttreatment cohort is not yet sufficient to determine any correlation between pre- and posttreatment SUV changes with treatment outcome, but this will certainly be an area of future interest. Finally, this study was performed at a university hospital with a high level of experience in ^{18}F-FDG PET/CT interpretation, cancer treatment, and clinical follow-up, which can influence the generalizability of our results.

Our data suggested that posttreatment whole-body ^{18}F-FDG PET/CT surveillance is beneficial for the detection of locoregional recurrences and distant metastases that may be missed by endoscopy and conventional radiological examinations of the nasal cavity and paranasal sinuses. For routine surveillance, the use of ^{18}F-FDG PET/CT scans at least 1 month after the completion of treatment may decrease the risk of false-negative readings, thus increasing detection sensitivity. Even

though a prospective comparative study would be necessary to determine the relative efficiency of the whole-body ^{18}F-FDG PET/CT imaging as opposed to other imaging modalities for the detection of locoregional and distant recurrences, this study proposes that ^{18}F-FDG PET/CT can be utilized for restaging of sinonasal malignancies. Even though this study demonstrates the benefits of whole-body ^{18}F-FDG PET/CT surveillance, further studies are required to optimize frequency and timing.

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Compliance with ethical standards

Conflict of interest All authors of this manuscript, Kerem Ozturk, Mehmet Gencturk, Emiro Caicedo-Granados, Faqian Li, Zuzan Cayci declare that they have no conflict of interest.

Ethical standards All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1983 revised Helsinki declaration and its later amendments or comparable ethical standards.

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