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Research article

Appropriate timing of surveillance intervals with whole-body ^{18}F-FDG PET/CT following treatment for sinonasal malignancies

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ABSTRACT

Purpose: To assess the ideal timing of posttreatment whole-body ^{18}F-FDG PET/CT examination as routine surveillance to determine local recurrence (R), lymph node metastasis (LM), and distant metastasis (DM) of sinonasal malignancies and to investigate the effect of ^{18}F-FDG PET/CT on survival.

Methods: An overall 80 patients who had undergone a total of 197 posttreatment whole-body ^{18}F-FDG PET/CT examinations for sinonasal malignancy were retrospectively examined after institutional review board approval. Patients were grouped regarding the time intervals (< 1 month, 1–3 months, 3–6 months, 6–12 months, 12–18 months and > 18 months) after the conclusion of treatment. Differences in diagnostic accuracy due to different follow-up intervals were calculated by receiver operator curves (ROC) and a Cox proportional hazards model was used to assess the prognostic value of surveillance ^{18}F-FDG PET/CT.

Results: Considering the time intervals of posttreatment ^{18}F-FDG PET/CT scans, the negative predictive value and positive predictive value of the ^{18}F-FDG PET/CT examinations to predict overall recurrence in 1–3 months (100 and 100%, respectively) and > 18 months (100 and 95%, respectively) were higher than for recurrence detection in < 1 month (50 and 100%, respectively), 3–6 months (81 and 93%, respectively), 6–12 months (79 and 87%, respectively), and 12–18 months (75 and 80%, respectively) ($p < 0.05$). Positive findings on ^{18}F-FDG PET/CT scans were also independent predictors of poorer overall survival (OS) ($p < 0.05$).

Conclusions: Whole-body ^{18}F-FDG PET/CT is capable of identifying recurrences following treatment, using an optimal time interval for scanning of 1–3 months and > 18 months after therapy.

1. Introduction

Sinonasal malignancies which represent only 3% of head and neck neoplasms [1], usually have a poor prognosis because of their advanced stage at initial presentation [2]. The early detection of the recurrent disease could provide an opportunity for a cure through early salvage treatment along with a potential survival benefit [3]. Although the vast majority of recurrences and metastases develop within 1–2 years following treatment, certain subtypes of sinonasal malignancies, including olfactory neuroblastoma and adenoid cystic carcinoma, tend to recur much later [4]. Given the diversity of pathologies, surveillance recommendations for head and neck neoplasms may not be relevant for nasal cavity and paranasal sinus pathologies [5].

Whole-body ^{18}F-Fluoro-deoxy-glucose positron emission computed tomography (^{18}F-FDG PET/CT) has an essential benefit in evaluating the primary tumor, regional lymph nodes and possible distant metastases (DMs), along with potential second primaries in a single examination compared to some other morphological imaging methods including magnetic resonance imaging (MRI) or computed tomography (CT) [6]. ^{18}F-FDG PET/CT can identify hypermetabolic foci of metastases that cannot be recognized on morphological imaging [7]. The potential benefits of surveillance whole-body ^{18}F-FDG PET/CT are rather high [5], yet there is no commonly approved protocol on the timing, and frequency of scans following curative treatment for sinonasal malignancies, resulting in the possible misapplication as well as excessive utilization of this method [8]. The standardized protocols and optimal timing of whole-body surveillance ^{18}F-FDG PET/CT examinations in the posttreatment setting are essential to reduce unnecessary expenses the radiation dose to patients while increasing the detection capability of the technique.

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We hypothesized that serial follow-up whole-body ^{18}F-FDG PET/CT for posttreatment surveillance in patients with asymptomatic sinonasal malignancies would allow accurate detection of subclinical lesions. The objectives of this study were to compare the performance of post-treatment surveillance whole-body ^{18}F-FDG PET/CT in the detection of local recurrence (R), regional lymph node metastases (LM), and DMs for the first and subsequent scans, to determine the optimal surveillance schedule and investigate the effect of surveillance ^{18}F-FDG PET/CT on survival.

2. Materials and methods

2.1. Patients and study design

This study was approved by the institutional review board at our institution before the collection of all patient information. This retrospective study includes 124 patients who had undergone surveillance posttreatment whole-body ^{18}F-FDG PET/CT examination for sinonasal malignancy from January 2009 through August 2017 prior to application of exclusion criteria. Patients were only included if they underwent primary surgery followed by adjuvant radiotherapy with or without chemotherapy and if they had no residual tumor within the immediate postoperative period. Treatment failure or the presence of residual disease in the immediate postoperative period was determined by surgical margins, endoscopy, and imaging (MRI and/or CT). Patients were excluded from the study if they had the distant metastatic disease at pretreatment staging (n = 21) and if patients had residual tumor present after conclusive treatment (n = 9). Patients diagnosed with sinonasal lymphoma (n = 11) were not included in the study due to the nonsurgical treatment as well as the different surveillance approach for this group of tumors. Of the remaining study population, two patients were excluded because they were lost to follow-up or did not have satisfactory reports (n = 1). The remaining 80 patients' medical records and post-treatment whole-body ^{18}F-FDG PET/CT scans were analyzed. Patients were staged by the American Joint Committee on Cancer (AJCC) criteria [9]; the University of California Los Angeles staging system was applied for olfactory neuroblastoma [10]. All patient data are described in Table 1. The 80 cases involved squamous cell carcinoma (SCC) (n = 30), olfactory neuroblastoma (n = 7), adenocarcinoma (n = 3), sinonasal undifferentiated carcinoma (SNUC) (n = 5), small cell carcinoma (n = 2), malignant melanoma (n = 8), rhabdomyosarcoma (n = 6), poorly differentiated carcinoma (n = 4), adenoid cystic carcinoma (n = 8), osteosarcoma (n = 2), neuroendocrine carcinoma (n = 4), clear cell carcinoma (n = 1), and carcinosarcoma (n = 2).

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	

2.2. Reference standard

The lesions that were suspected to be recurrent tumors on follow up ^{18}F-FDG PET/CT examinations were further investigated by endoscopic examination and/or biopsy. Histopathological examination of the biopsied sample or surgically resected mass, dissected neck nodes were determined as the reference standard whenever available. Patients without locoregional recurrences or distant metastasis were observed for a minimum of 12 months.

Whole-body ^{18}F-FDG PET/CT was regarded as true positive (TP) when the increased site of ^{18}F-FDG uptake was confirmed to be malignant by histological examination. Patients were considered as false positive (FP) for recurrence If ^{18}F-FDG PET/CT in surveillance screening was abnormal, but histological examination and imaging work-up was inconclusive. Screening by ^{18}F-FDG PET/CT was regarded as true negative (TN) in cases where the patients had negative test results, and no recurrences were detected in 12 months. If a patient had a negative ^{18}F-FDG PET/CT but developed recurrences within the 12 months follow-up period, screening was regarded as false negative (FN), supposing these lesions could exist at the time of screening.

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

Whole-body ^{18}F-FDG PET/CT scans were evaluated by a double-board-certified radiologist and nuclear medicine physician (Z.C.) having ten years of experience in interpretation of ^{18}F-FDG PET/CT in patients with head and neck cancer. The attenuation-corrected ^{18}F-FDG PET/CT images were utilized for analysis. No SUV cutoff value was utilized while interpreting the ^{18}F-FDG PET/CT scans. ^{18}F-FDG PET/CT images were mainly reviewed with visual analysis; focal and distant sites with ^{18}F-FDG uptake that exceeded the background activity were accepted to have tumor recurrence. While the main purpose was screening for locoregional recurrences or distant metastases, we also documented second primary tumors.

2.4. Influence of timing and surveillance protocol

We examined a total of 197 post-treatment ^{18}F-FDG PET/CT scans obtained for these 80 patients; 32 patients had one scan; 19 patients had two scans, 10 patients had three scans, 8 patients had four scans, 6 patients had five scans, and 5 patients had over five scans. Regardless of the clinical suspicion of recurrence, patients ideally get initial surveillance whole-body ^{18}F-FDG PET/CT scan at 3 months, then at 9 months and at 1 year after completion of curative therapy based on the determined protocol at our institution. The whole-body ^{18}F-FDG PET/CT scans were categorized into six groups according to time interval after treatment: < 1 months (group I), 1–3 months (group II), 3–6 months (group III), 6–12 months (group IV), 12–18 months (group V) and > 18 months (group VI). Patients with suspicious clinical and/or physical findings for recurrence were promptly further examined with ^{18}F-FDG PET/CT and were not included in the study cohort.

The choice of the time interval is determined by the marginal error encountered whenever scheduling a posttreatment ^{18}F-FDG PET/CT. It was not rare for a planned ^{18}F-FDG PET/CT to be acquired earlier or later than the planned time due to mostly patient factors. Additionally, overall there was rather non-homogeneity of the times of follow-up imaging; the surveillance whole-body ^{18}F-FDG PET/CT scan timing showed a relatively wide range. This might result from the retrospective nature of our study despite a systematic follow-up protocol established in our institution.

2.5. ^{18}F-FDG PET/CT imaging

All patients were imaged utilizing a standard clinical whole-body ^{18}F-FDG PET/CT protocol. Patients received an intravenous injection of 3.7 MBq/kg (0.1 mCi/kg) ^{18}F-FDG one hour prior to PET acquisition.

Table 2
Surveillance ^{18}F-FDG PET/CT examinations with false negative (FN) and false positive (FN) results for local recurrences (R), regional lymph node metastasis (LM), distant metastasİs (DM).

	Pt	Sex	Age	Tumor Type	Site	T stage	Outcomes	Time of False PET/CT (mo)
R	1	m	55	ACC	Ethmoid sinus	T4	FN	4,10
	2	m	58	ACC	Sphenoid sinus	T3	FN	1
	3	m	47	Adenocarcinoma	Nasal cavity	T2	FN	5
	4	m	68	Poorly D. C.	Nasal cavity	T3	FN	10
	5	m	62	Rhabdomyosarcoma	Nasal cavity	T3	FN	17
	6	f	61	SCC	Maxillary sinus	T4	FN	1
	7	m	81	ACC	Maxillary sinus	T3	FP	8
	8	m	46	ONB	Nasal cavity	T1	FP	8
	9	m	58	ONB	Nasal cavity	T2	FP	20
	10	m	60	SCC	Sphenoid sinus	T2	FP	6
	11	f	64	SCC	Maxillary sinus	T3	FP	7,13
	12	m	45	SCC	Nasal cavity	T3	FP	7
LM	1	f	51	SCC	Nasal cavity	T3	FN	3
	2	m	66	M. Melanoma	Nasal cavity	T2	FN	10
	3	m	53	ACC	Ethmoid sinus	T3	FP	16
	4	f	64	SCC	Maxillary sinus	T4	FP	17
DM	1	m	55	Adenocarcinoma	Ethmoid sinus	T4	FN	13
	2	f	61	M. Melanoma	Nasal cavity	T1	FN	7
	3	f	70	M. Melanoma	Nasal cavity	T2	FN	6
	4	m	65	Rhabdomyosarcoma	Nasal cavity	T3	FN	17
	5	f	45	SCC	Maxillary sinus	T2	FN	8
	6	m	54	SNUC	Ethmoid sinus	T3	FN	9
	7	f	35	SCC	Sphenoid sinus	T4	FN	1
	8	m	52	SCC	Sphenoid sinus	T4	FP	16

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; SNUC, sinonasal undifferentiated carcinoma; R, local recurrence; LM, regional nodal metastasis; DM, distant metastasis.

All patients fasted for a minimum of six hours prior to radiotracer injection and had blood glucose levels < 150 mg/dl as per standard institutional protocol. All data were obtained using a combined ^{18}F-FDG PET/CT in-line system (Biograph Sensation 16; Siemens Medical Solutions, Malvern, PA, USA) which was conducted through a continuous spiral technique utilizing a 16-slice helical CT with a gantry rotation speed of 0.8 s. The patients were scanned with a whole-body ^{18}F-FDG PET/CT from the vertex extending down to the patient's feet, accompanied by a dedicated head and neck PET from the vertex to the carina. Head and neck images were acquired with the arms down to limit attenuation artifacts, and body images were obtained with arms up. The CT acquisition protocol included a low-dose CT (variable milliampere settings, 120 kV tube voltage, 0.5 s per rotation, isotropic data set with resolution of 3 mm, helical pitch of 1.5, 16 × 1.5 collimation) performed using the same axial coverage as for ^{18}F-FDG PET for attenuation correction purposes and a dedicated head-neck CT (variable milliampere settings, 140 kV, section thickness of 3 mm, FOV of 20.9 cm, 256 × 256 matrix) performed from skull base to aortic arch with intravenous injection of 1.5 ml/kg body weight of non-ionic iodinated radiographic contrast medium for CT evaluation. ^{18}F-FDG PET images were reconstructed using CT data by an attenuation-weighted ordered-subsets expectation maximization algorithm (four iterations, eight subsets) followed by a post-reconstruction smoothing Gaussian filter (5-mm full width at half maximum) using a 128 × 128 matrix. Automated co-registration of the CT and PET scans data was conducted with commercially available software -Syngo.Via® (Siemens Healthcare Forchheim, Germany).

2.6. Statistical analysis

Continuous variables are presented as 'means and standard deviations' for normally distributed data and 'medians and ranges' for skewed data. Each ^{18}F-FDG PET/CT study was assessed for its capacity to determine the recurrence at the primary site, within the regional lymph nodes, and at distant sites. A ROC-curve was designed to determine an optimum time interval for scanning. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for each time interval were calculated. 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. The Kaplan-Meier method was used to estimate overall survival (OS). Log-rank testing and Cox proportional hazards modeling were used to examine the significance of any differences in survival outcomes according to the presence or absence of positive findings in the anytime surveillance ^{18}F-FDG PET/CT scan as well as between different follow-up time periods. Each calculation was carried out using SPSS 22.0 for Windows. All tests were two-sided, and P values < 0.05 were regarded as statistically significant.

3. Results

3.1. Clinical characteristics

Eighty patient underwent a total of 197 whole-body ^{18}F-FDG PET/CT scans during the study period (53 men, 27 women; mean age, 60 years). A total of 37 (46.2%) out of 80 patients developed recurrences in the follow-up period; 24 patients (30%) developed local recurrences, 13 patients (16%) developed regional LMs, and 18 patients (23%) developed DMs. The different site of recurrences (R, LM, DM) was overlapped in some patients. The incidence of locoregional and distant recurrences was not statistically different according to the T stages, mean age and sex distribution ($p > 0.05$). No significant differences were recognized between the subtypes of sinonasal malignancies regarding the incidence of local recurrences, DMs and LMs ($p > 0.05$). ^{18}F-FDG PET/CT determined second primary tumors in four patients throughout the follow-up period (one patient with lymphoma, one patient with head and neck cutaneous squamous cell carcinoma and two patients primary lung cancer). ^{18}F-FDG-avid true-positive metastases were commonly identified in the multiple sites (n = 13), lungs (n = 8), bones (n = 6), liver (n = 1), and adrenal gland (n = 1). Table 2 demonstrates false negative (FN) and false positive (FP) ^{18}F-FDG PET/CT

examinations. The diagnostic performance of whole-body ^{18}F-FDG PET/CT as a posttreatment surveillance tool of our cohort with sinonasal malignancies was reported in detail in our previous study [11].

3.2. Accuracy and optimal timing of follow-up ^{18}F-FDG PET/CT

Out of a total of 197 whole-body ^{18}F-FDG PET/CT examinations, 9 scans were obtained at < 1 month, 10 scans at 1–3 months, 31 scans at 3–6 months, 66 scans at 6–12 months, 36 scans at 12–18 months and 45 patients after 18 months.

Regarding the time intervals of posttreatment ^{18}F-FDG PET/CT scans, local recurrences developed in 5 scans at < 1 month, in 4 scans at 1–3 months, in 10 scans at 3–6 months, in 14 scans at 6–12 months, in 5 scans at 12–18 months and in 6 scans at > 18 months. Regional lymph node metastases developed in 0 scans at < 1 month, in 0 scans at 1–3 months, in 2 scans at 3–6 months, in 9 scans at 6–12 months, in 5 scans at 12–18 months and in 7 scans at > 18 months. Distant metastases developed in 1 scan at < 1 month, in 1 scan at 1–3 months, in 5 scans at 3–6 months, in 12 scans at 6–12 months, in 10 scans at 12–18 months and in 8 scans at > 18 months.

The accuracy of surveillance whole-body ^{18}F-FDG PET/CT for local recurrence, regional nodal metastasis and distant metastasis according to time intervals was revealed in Table 3.

The NPV and PPV of the whole-body ^{18}F-FDG PET/CT examination to predict overall recurrence in 1–3 months (100 and 100%, respectively) and > 18 months (100 and 95%, respectively) were higher than for recurrence detection in < 1 month (50 and 100%, respectively), 3–6 months (81 and 93%, respectively), 6–12 months (79 and 87%, respectively), and 12–18 months (75 and 80%, respectively) (Fig. 1) ($p < 0.05$). The diagnostic accuracy of ^{18}F-FDG PET/CT examinations did not differ significantly whether they were acquired in the < 1-month interval, the 3–6 months interval, the 6–12 months interval, or the 12–18 months interval ($p > 0.05$). The overall accuracy of ^{18}F-FDG PET/CT conducted within one month (67%) was significantly inferior to that performed after one month (87%) ($p = 0.001$).

Among the 24 patients with two consecutive negative scans for recurrences, there was only one recurrence, developing at 21 months following two consecutive negative scans (at 11 and 17 months). Therefore, two consecutive ^{18}F-FDG PET/CT scans with negative findings within 12 months provided a negative predictive value of 96%.

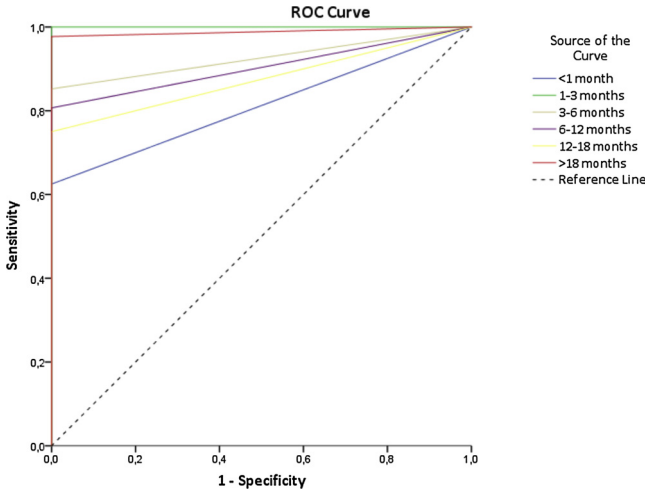

Fig. 1. Receiver operating characteristic (ROC) curve of the overall diagnostic accuracy of the whole-body ^{18}F-FDG PET/CT at different posttreatment time intervals.

3.3. Prognostic value of post-treatment ^{18}F-FDG PET/CT

The median survival of the study population was 40 months (range, 12–95) from the completion of treatment, and the overall survival (OS) rate was 75% at 3 years and 68% at 5 years. The Kaplan-Meier analysis based on ^{18}F-FDG PET/CT scan results showed a significant difference in time from the scan date to OS between those who had a positive ^{18}F-FDG PET/CT scan and those who had a negative ^{18}F-FDG PET/CT scan ($p = 0.011$), with a hazard ratio (HR) of 6.4; (95% CI, 2.05–25.6) (Fig. 2). A subgroup analysis investigating the impact of the various surveillance follow-up time periods was unable to demonstrate any significant differences for OS ($p > 0.05$).

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

		R	LM	DM	Overall	P values
< 1 months	*Sensitivity*	60 (38–90)	NA	NA	50 (32–75)	p = 0.046
	Specificity	100 (65–100)	100 (60–100)	100 (62–100)	100 (65–100)	
	PPV	100 (65–100)	NA	NA	100 (62–100)	
	NPV	66 (40–92)	100 (60–100)	89 (53–100)	50 (35–71)	
1–3 months	*Sensitivity*	100 (67–100)	NA	100 (58–100)	100 (68–100)	p = 0.0079
	Specificity	100 (64–100)	100 (62–100)	100 (61–100)	100 (68–100)	
	PPV	100 (67–100)	NA	100 (58–100)	100 (68–100)	
	NPV	100 (64–100)	100 (62–100)	100 (61–100)	100 (68–100)	
3–6 months	*Sensitivity*	80 (61–98)	100 (55–100)	80 (57–99)	82 (70–96)	p < 0.001
	Specificity	95 (78–100)	100 (74–100)	100 (82–100)	93 (81–100)	
	PPV	89 (63–100)	100 (55–100)	100 (76–100)	93 (80–100)	
	NPV	91 (65–100)	100 (74–100)	86 (70–100)	81 (68–93)	
6–12 months	*Sensitivity*	86 (70–100)	89 (72–100)	67 (41–93)	80 (69–92)	p < 0.001
	Specificity	92 (78–100)	100 (88–100)	100 (86–100)	87 (75–98)	
	PPV	75 (61–94)	100 (83–100)	100 (72–100)	87 (74–99)	
	NPV	96 (82–100)	98 (86–100)	93 (70–100)	79 (67–90)	
12–18 months	*Sensitivity*	80 (62–98)	80 (54–100)	80 (62–97)	80 (70–92)	p = 0.002
	Specificity	97 (85–100)	94 (80–100)	96 (84–100)	75 (64–86)	
	PPV	80 (62–98)	67 (41–90)	89 (73–100)	80 (68–90)	
	NPV	97 (85–100)	97 (82–100)	93 (81–100)	75 (64–87)	
> 18 months	*Sensitivity*	100 (87–100)	100 (69–100)	100 (64–100)	100 (88–100)	p < 0.001
	Specificity	97 (85–100)	100 (82–100)	100 (78–100)	96 (85–100)	
	PPV	86 (72–100)	100 (69–100)	100 (64–100)	95 (84–100)	
	NPV	100 (87–100)	100 (82–100)	100 (78–100)	100 (88–100)	

All values are expressed as percentage (%); 95% confidence intervals listed in parenthesis.
PPV, positive predictive value; NPV, negative predictive value; NA, not applicable.

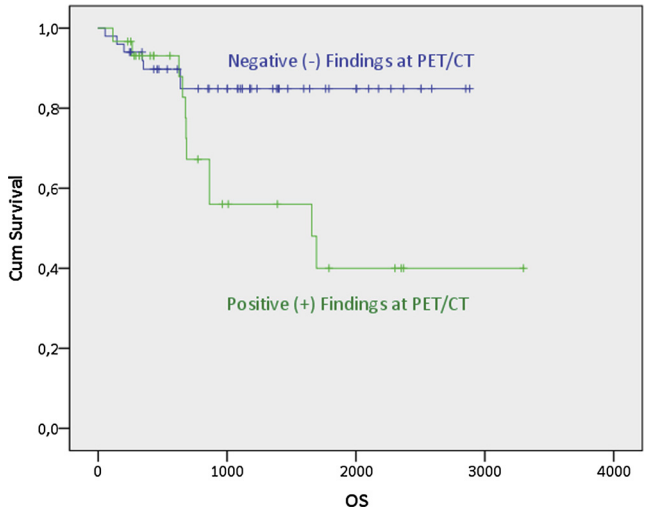

Fig. 2. Kaplan-Meier curves demonstrate the comparisons of overall survival (OS) according to the presence or absence of positive findings in the any time whole-body ^{18}F-FDG PET/CT scans after definitive treatment.

4. Discussion

The standard timing of whole-body surveillance ^{18}F-FDG PET/CT examinations in the posttreatment setting is essential to reduce unnecessary expenses while increasing the detection capability of the technique [12,13]. In the present study, we have assessed the optimal timing and frequency of posttreatment whole-body ^{18}F-FDG PET/CT to identify locoregional and distant recurrences in patients with sinonasal malignancies. In our study, diagnostic accuracy was significantly inferior in ^{18}F-FDG PET/CT performed within one month compared to ^{18}F-FDG PET/CT performed after one month. We suggest that surveillance ^{18}F-FDG PET/CT should first be performed 1–3 months following the conclusive treatment. When performed earlier, diffusely increased ^{18}F-FDG-uptake of surrounding tissue caused by inflammation can hinder the accurate detection of recurrent disease [14]. Furthermore, small traces of recurrent tumor may not be noticed in ^{18}F-FDG PET/CT shortly after treatment, yet will become noticeable a few weeks later [15]. This conflicts the need for prompt diagnostics (e.g., baseline ^{18}F-FDG PET/CT imaging) and salvage treatment of patients with recurrent disease. There is increased risk of disease progression after three months, as well as there will be the development of radiation-induced fibrosis [16]. Therefore, we think that delaying the first posttreatment surveillance scan after 3 months does not offer any additional data to assist clinical decision making.

Apart from the appropriate timing of initial whole-body ^{18}F-FDG PET/CT, the frequency of consecutive ^{18}F-FDG PET/CT examinations is another substantial parameter for optimal surveillance [17]. The patients in our study obtained slightly fewer than one ^{18}F-FDG PET/CT scan for each year. Half of the TP recurrences were identified on a second scan several months after an initial negative ^{18}F-FDG PET/CT examination. Even though the impact of a second ^{18}F-FDG PET/CT scan would be significantly lower than that of the first whole-body ^{18}F-FDG PET/CT scan, the appropriate timing of subsequent scan might be > 18 months after the conclusive treatment. Our study also implies that ^{18}F-FDG PET/CT surveillance could be terminated in a subset of patients who have two consecutive negative scans within 12 months, a conclusion that has a significant economic impact for the utilization of costly healthcare resources.

Our study has also revealed the potential prognostic role of post-treatment ^{18}F-FDG PET/CT surveillance. However, we couldn't determine any clear evidence of survival benefit of post-treatment ^{18}F-FDG PET/CT scan when acquired 1–3 months and > 18 months following the conclusive treatment. This result may be caused by a small number of included patients and needs to be elucidated by further prospective studies with large sinonasal malignancy population.

Few studies have shown that ^{18}F-FDG PET/CT could be beneficial to determine locoregional and distant recurrences in patients with sinonasal malignancy [18]. Khalili et al. [19] retrospectively assessed the efficiency of endoscopy and imaging for the surveillance of sinonasal malignancies. In their analysis of 100 patients, 30 patients developed recurrences, with 22 patients (73%) having recurrences at the primary site; LMs and DMs represented 17% and 10% of recurrences, respectively. Most of the patients (63%) were found to have recurrent disease within two years of the period. In our patient cohort, significant numbers of the recurrences were after 18 months. This may be conflicting with the result of Khalili et al. [19] which demonstrated that negative 3–18 months interval ^{18}F-FDG PET/CT scans could be a prognostic predictor. Our study revealed that ^{18}F-FDG PET/CT at > 18 months identified recurrences in all 36 patients (100%), supporting the usage of posttreatment ^{18}F-FDG PET/CT at > 18 months for the accurate detection of late recurrences. Harvey et al. [20] showed that ^{18}F-FDG PET/CT could have excellent sensitivity and NPV (100%), but its utility is hindered by poor specificity (40%) and PPV (53.8%) in the early surveillance period. They suggested that ^{18}F-FDG PET/CT scans could be acquired at a minimum of 3 months after treatment, however optimal time intervals for the subsequent scans could not be determined in their analysis. Additionally, Gil et al. [21] evaluated the role of ^{18}F-FDG PET/CT imaging for surveillance with specificity and PPV of 85% and 67%, respectively. They obtained the most of ^{18}F-FDG PET/CT scans (> 80%) 6 months after conclusive treatment. Contrary to the previous reports which examined the cross-sectional accuracy of ^{18}F-FDG PET/CT, Schwartz et al. [22] conducted a longitudinal analysis of ^{18}F-FDG PET/CT scans in the post-treatment setting. In their study, 76 patients were examined with ^{18}F-FDG PET/CT examination. The median time to recurrence was 20 months, with only four patients were found to have recurrences before five months, besides ten patients developed recurrences by 24 months. This result was similar to that of our study.

The main differences between ours and previously reported studies' are due to the inclusion of various cohorts. Our cohort only includes asymptomatic patients without suspected recurrence by clinical examination. Moreover, we did not use the SUV as a criterion for the positive result; rather, we relied on qualitative analysis. Although our method requires a higher degree of radiological expertize, we believe that the utilization of absolute SUV thresholds could be limited in the posttreatment setting [23]. The majority of studies to date compared to ^{18}F-FDG PET/CT results with clinical and histological findings without using the follow-up period as a reference standard. Our study analyzed the role of ^{18}F-FDG PET/CT to predict both locoregional and distant recurrences with a minimum of 12 months follow-up period.

Driven by the success of PET/CT, raising efforts are ongoing to develop PET/MRI to combine PET and MRI, and fully integrated PET/MRI scanners have been recently established. The combination of the high soft-tissue contrast derived from MRI and the metabolic information offered by PET shows promise, particularly in the evaluation of head and neck tumors [24]. A first prospective study on the value of PET/MRI in assessments for local tumor recurrence in head and neck SCC patients reported a sensitivity of 92% [25]. Based on these first results, PET/MRI appears to enhance therapy-response evaluation due to the combination of the high NPV (PET component) and the high sensitivity provided by the MRI component [26]. The true value of the combined PET/MR rather lies in the simultaneous acquisition of functional MRI parameters (e.g., MR spectroscopy and diffusion-weighted imaging) and metabolic PET information [27]. Therefore, the development of organ-specific PET/MRI protocols with unique radiotracers is a focus of the ongoing strategy of implementing this technique clinically.

There are several limitations to the current study. The heterogeneity of tumor subtypes restricts the broad applicability of the study results [28]. The risk of recurrence is determined by stage in addition to tumor

biology. A cohort of patients with various sinonasal neoplasms may have different outcomes. The limitation is not avoidable and is a result of the low incidence and prevalence of the disease. Moreover, the prevalence of the sinonasal malignancies is quite low, and the validity of proper cut-off points from ROC curves could not be determined. This research is hypothesis generating, and further studies are required to confirm our results and to assess the impact of surveillance ^{18}F-FDG PET/CT on follow-up strategy and prognosis.

In conclusion, whole-body ^{18}F-FDG PET/CT has an excellent diagnostic accuracy to identify locoregional and distant recurrences and to predict the survival following treatment of sinonasal malignancies. The optimal time interval for the initial scan is in between 1 and 3 months after the conclusion of therapy, enabling the resolution of inflammatory changes and reducing the false-positive rate. Nevertheless, a reevaluation is likely required > 18 months after treatment to detect late recurrences. In the future, prospective, multi-institutional surveillance studies for individual sinonasal neoplasms are required.

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Ethical standards

All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 2013 revised Helsinki declaration or comparable ethical standards.

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References

[1] H.B. Eggesbo, Imaging of sinonasal tumours, Cancer Imaging 12 (2012) 136–152.
[2] M.H. Jakobsen, S.K. Larsen, J. Kirkegaard, H.S. Hansen, Cancer of the nasal cavity and paranasal sinuses. Prognosis and outcome of treatment, Acta Oncol. 36 (1) (1997) 27–31.
[3] S.K. Haerle, P.J. Gullane, I.J. Witterick, C. Zweifel, F. Gentili, Sinonasal carcinomas: epidemiology, pathology, and management, Neurosurg. Clin. N. Am. 24 (1) (2013) 39–49.
[4] Y.B. Mahalingappa, H.S. Khalil, Sinonasal malignancy: presentation and outcomes, J. Laryngol. Otol. 128 (7) (2014) 654–657.
[5] E.D. Lamarre, P.S. Batra, R.R. Lorenz, M.J. Citardi, D.J. Adelstein, S.M. Srinivas, J. Scharpf, Role of positron emission tomography in management of sinonasal neoplasms–a single institution's experience, Am. J. Otolaryngol. 33 (3) (2012) 289–295.
[6] G. Xu, J. Li, X. Zuo, C. Li, Comparison of whole body positron emission tomography (PET)/PET-computed tomography and conventional anatomic imaging for detecting distant malignancies in patients with head and neck cancer: a meta-analysis, Laryngoscope 122 (9) (2012) 1974–1978.
[7] G.Z. Xu, D.J. Guan, Z.Y. He, (18)FDG-PET/CT for detecting distant metastases and second primary cancers in patients with head and neck cancer. A meta-analysis, Oral Oncol. 47 (7) (2011) 560–565.
[8] A.D. Workman, J.N. Palmer, N.D. Adappa, Posttreatment surveillance for sinonasal malignancy, Curr. Opin. Otolaryngol. Head Neck Surg. 25 (1) (2017) 86–92.
[9] S.B. Edge, C.C. Compton, The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM, Ann. Surg. Oncol. 17 (6) (2010) 1471–1474.
[10] B.A. Tajudeen, A. Arshi, J.D. Suh, M.F. Palma-Diaz, M. Bergsneider, E. Abemayor, M. St John, M.B. Wang, Esthesioneuroblastoma: an update on the UCLA experience, 2002-2013, J. Neurol. Surg. B Skull Base 76 (1) (2015) 43–49.
[11] K. Ozturk, M. Gencturk, E. Caicedo-Granados, F. Li, Z. Cayci, Performance of whole-body (18)F-FDG PET/CT as a posttreatment surveillance tool for sinonasal malignancies, Eur. Arch. Otorhinolaryngol. (2019).
[12] R. Abgral, S. Querellou, G. Potard, P.Y. Le Roux, A. Le Duc-Pennec, R. Marianovski, O. Pradier, Y. Bizais, F. Kraeber-Bodere, P.Y. Salaun, Does 18F-FDG PET/CT improve the detection of posttreatment recurrence of head and neck squamous cell carcinoma in patients negative for disease on clinical follow-up? J. Nucl. Med. 50 (1) (2009) 24–29.
[13] K. Shah, L. Te Marvelde, M. Collins, R. De Abreu Lourenco, I. D'Costa, A. Coleman, T. Fua, C. Liu, D. Rischin, E. Lau, J. Corry, Safety and cost analysis of an (18)FDG-PET-CT response based follow-up strategy for head and neck cancers treated with primary radiation or chemoradiation, Oral Oncol. 51 (5) (2015) 529–535.
[14] A. Digonnet, M. Hamoir, G. Andry, M. Haigentz Jr., R.P. Takes, C.E. Silver, D.M. Hartl, P. Strojan, A. Rinaldo, R. de Bree, A. Dietz, V. Gregoire, V. Paleri, J.A. Langendijk, V. Vander Poorten, M.L. Hinni, J.P. Rodrigo, C. Suarez, W.M. Mendenhall, J.A. Werner, E.M. Genden, A. Ferlito, Post-therapeutic surveillance strategies in head and neck squamous cell carcinoma, Eur. Arch. Otorhinolaryngol. 270 (5) (2013) 1569–1580.
[15] B.S. Purohit, A. Ailianou, N. Dulguerov, C.D. Becker, O. Ratib, M. Becker, FDG-PET/CT pitfalls in oncological head and neck imaging, Insights Imaging 5 (5) (2014) 585–602.
[16] P. Castaldi, V. Rufini, F. Bussu, F. Micciche, N. Dinapoli, R. Autorino, M. Lago, E. De Corso, G. Almadori, J. Galli, G. Paludetti, A. Giordano, V. Valentini, Can "early" and "late"18F-FDG PET-CT be used as prognostic factors for the clinical outcome of patients with locally advanced head and neck cancer treated with radio-chemotherapy? Radiother. Oncol. 103 (1) (2012) 63–68.
[17] J.W. Kim, J.L. Roh, J.S. Kim, J.H. Lee, K.J. Cho, S.H. Choi, S.Y. Nam, S.Y. Kim, (18) F-FDG PET/CT surveillance at 3-6 and 12 months for detection of recurrence and second primary cancer in patients with head and neck squamous cell carcinoma, Br. J. Cancer 109 (12) (2013) 2973–2979.
[18] A.D. Workman, J.T. Glicksman, A.K. Parasher, R.M. Carey, S.G. Brooks, D.W. Kennedy, S.A. Nabavizadeh, K.O. Learned, J.N. Palmer, N.D. Adappa, (18)FDG PET/CT in routine surveillance of asymptomatic patients following treatment of sinonasal neoplasms, Otolaryngol. Head. Neck Surg. 157 (6) (2017) 1068–1074.
[19] S. Khalili, D.M. Worrall, S. Brooks, S.M. Morris, D. Farquhar, J.G. Newman, K.O. Learned, P.H. Ahn, J. Craig, D.W. Kennedy, B.W. O'Malley, J.N. Palmer, N.D. Adappa, Endoscopy versus imaging: analysis of surveillance methods in sinonasal malignancy, Head Neck 38 (8) (2016) 1229–1233.
[20] R.J. Harvey, G. Pitzer, D.B. Nissman, L. Buchmann, Z. Rumboldt, T. Day, R.J. Schlosser, PET/CT in the assessment of previously treated skull base malignancies, Head Neck 32 (1) (2010) 76–84.
[21] Z. Gil, E. Even-Sapir, N. Margalit, D.M. Fliss, Integrated PET/CT system for staging and surveillance of skull base tumors, Head Neck 29 (6) (2007) 537–545.
[22] J.S. Schwartz, S.G. Brooks, V. Stubbs, A. Ghosh, B.A. Tajudeen, S. Khalili, J.N. Palmer, J.Y. Lee, S.A. Nabavizadeh, K.O. Learned, N.D. Adappa, Temporal patterns of (18) F-fluorodeoxyglucose positron emission tomography/computed tomography sinonasal uptake after treatment of sinonasal malignancy, Int. Forum Allergy Rhinol. 6 (12) (2016) 1301–1307.
[23] R. Hustinx, G. Lucignani, PET/CT in head and neck cancer: an update, Eur. J. Nucl. Med. Mol. Imaging 37 (3) (2010) 645–651.
[24] C. Buchbender, T.A. Heusner, T.C. Lauenstein, A. Bockisch, G. Antoch, Oncologic PET/MRI, part 1: tumors of the brain, head and neck, chest, abdomen, and pelvis, J. Nucl. Med. 53 (6) (2012) 928–938.
[25] Y. Nakamoto, K. Tamai, T. Saga, T. Higashi, T. Hara, T. Suga, T. Koyama, K. Togashi, Clinical value of image fusion from MR and PET in patients with head and neck cancer, Mol. Imaging Biol. 11 (1) (2009) 46–53.
[26] D.J. Loeffelbein, M. Souvatzoglou, V. Wankerl, A. Martinez-Moller, J. Dinges, M. Schwaiger, A.J. Beer, PET-MRI fusion in head-and-neck oncology: current status and implications for hybrid PET/MRI, J. Oral Maxillofac. Surg. 70 (2) (2012) 473–483.
[27] M. Becker, H. Zaidi, Imaging in head and neck squamous cell carcinoma: the potential role of PET/MRI, Br. J. Radiol. 87 (1036) (2014) 20130677.
[28] K. Ozturk, R. Gawande, M. Gencturk, K. Boegel, E. Caicedo-Granados, Z. Cayci, Imaging features of sinonasal tumors on positron emission tomography and magnetic resonance imaging including diffusion weighted imaging: a pictorial review, Clin. Imaging 51 (2018) 217–228.