RHINOLOGY

The value of ^{18}F-FDG-PET/CT imaging for sinonasal malignant melanoma

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Abstract The aim this study was to evaluate imaging findings using position emission tomography (PET) in combination with computed tomography (CT) and 18F-fluorodeoxyglucose (^{18}F-FDG) in sinonasal malignant melanoma (SNMM) of the head and neck in a retrospective analysis of a consecutive cohort of patients. ^{18}F-FDG-PET/CT examinations were performed for initial staging and compared with CT or magnetic resonance tomography (MRI), and ^{18}F-FDG-PET alone. Medical records were reviewed retrospectively with regard to the location and the size of the tumor. Furthermore, locoregional and distant metastases with a consecutive change in therapy detected by ^{18}F-FDG-PET/CT were assessed. Ten patients suffering from sinonasal malignant melanoma were staged and followed by ^{18}F-FDG-PET/CT imaging. A total of 34 examinations were obtained. ^{18}F-FDG-PET/CT depicted all primary tumors adequately. Aside from one cerebral metastasis all regional and distant metastases were truly identified by using this method. In summary, if available, ^{18}F-FDG-PET/CT is a valuable imaging modality for staging and re-staging sinonasal malignant melanoma to evaluate expansion of the primary tumor, locoregional disease, and distant metastases.

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Introduction

Mucosal malignant melanoma (MMM) is a very rare tumor counting for approximately 0.8–1.3% of all melanomas [1, 2]. The most common region for MMM is the head and neck, whereas other sites, such as the rectum and the anus, the urinary system, and the female genitalia may also be involved [1, 2]. The most prevalent sites of MMM in the head and neck are the nasal cavity, oral cavity, and the paranasal sinuses [1]. Sinonasal malignant melanoma (SNMM) accounts roughly for 4% of all head and neck melanomas and sinonasal malignancies alike [3]. Although the incidence of cutaneous melanoma is increasing, the incidence of MMM remains stable [1].

Positron emission tomography (PET) with 18F-fluorodeoxyglucose (^{18}F-FDG) is increasingly used for initial staging for head and neck malignancies. It is also an established tool for initial staging and follow-up imaging of cutaneous malignant melanomas [4]. In most centers, the standard imaging technique for MMM in the head and neck at initial staging is computed tomography (CT) or magnetic resonance imaging (MRI) if there is suspicion for skull base infiltration. The role of ^{18}F-FDG-PET in the management of MMM has been validated in a previous report by our institution [5]. Meanwhile, technology has evolved, and high-resolution multi-slice CT scanners are integrated in ^{18}F-FDG-PET- systems. The aim of this study was to elucidate imaging and the possible additional value of ^{18}F-FDG-PET/CT on therapeutic management of patients with MMM, particularly SNMM, when using it at initial staging or follow-up for locoregional or distant disease.

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Materials and methods

We retrospectively reviewed the charts of all patients treated for MMM of the head and neck at the Department of Otolaryngology-Head and Neck Surgery, University Hospital Zurich, Switzerland . We revealed 10 patients, with sinonasal involvement only, examined by ^{18}F-FDG-PET/CT since the introduction of this technique at the Division of Nuclear Medicine, University Hospital Zurich, Switzerland, has been introduced in March 2001. If patients were referred to our institution with a CT or MRI scan done by the referring institution, these data were blindly re-evaluated by our double board certified radiologist and nuclear physician. In case of patients without previous imaging, the CT part from the fused ^{18}F-FDG-PET/CT was evaluated in a blind way without looking at the ^{18}F-FDG-PET part. All suspicious lesions detected by physical examination (endoscopy) and imaging (CT, MRI or ^{18}F-FDG-PET/CT) were further investigated by histological work- up which served as the standard of reference. The study was conducted in accordance with the local guidelines established by the ethics committee for retrospective evaluations. Each patient was followed by imaging using ^{18}F-FDG-PET/CT at 6-month intervals.

^{18}F-FDG-PET/CT acquisition

For this study, we used a combined PET/CT system (Discovery STE or Discovery RX, GE Health Systems, Milwaukee, WI). This device integrates a PET scanner with a multi-slice helical CT (16 or 64 slices; slice thickness: 2.5 mm) and permits the acquisition of coregistered CT and PET images in the same session. Patients fasted for at least 4 h prior to scanning, which started approximately 60 min after the injection of a standard dose of approximately 350 MBq of ^{18}F-FDG. Patients were examined in the supine position. The CT scan was acquired during breath holding in the normal expiratory position. Immediately following the CT acquisition, the PET emission scan was acquired. The CT data were used for the attenuation correction and the images were reconstructed using a standard iterative algorithm (ordered subset expectation maximization (OSEM)) for 3D PET reconstruction. The acquired images were postprocessed with a dedicated software (AW workstation, GE Health Systems) providing multiplanar reformatted images of ^{18}F-FDG-PET alone, CT alone, and fused ^{18}F-FDG-PET/CT with linked cursors.

^{18}F-FDG-PET/CT evaluation

^{18}F-FDG-PET/CT images were retrospectively analyzed by a double board certified radiologist and nuclear physician with 6 years of experience (K. S.) in reading ^{18}F-FDG-PET/CT`s of head and neck cancer patients. The ^{18}F-FDG-PET images were evaluated with regard to the presence and nature of focal lesions with increased ^{18}F-FDG- uptake. Attenuation-corrected ^{18}F-FDG-PET images were used for analysis. Lesions were interpreted as a malignancy if the uptake was higher than the uptake of the surrounding background tissue. It was a visual interpretation and not based on standardized uptake value (SUV) measurements. Furthermore, morphological findings of suspicious lesions provided by the low-dose CT part were also used for interpretation. ^{18}F-FDG- uptake in muscles, glands, brown fat or pulmonary infiltration were not interpreted as tumor or metastases. Four patients were initially examined after resection and therefore attribution of ^{18}F-FDG-uptake and histological finding was either equivocal or no more uptake was observed. Two patients received intravenous and oral contrast agent (Ultravist 300, Gastrografin, Bayer AG Switzerland) for obtaining either a diagnostic CT of the neck or of the whole body.

Semiquantitative analysis of ^{18}F-FDG-uptake in all suspicious lesions was performed by measuring the maximum standardized uptake value (SUV max).

Results

Clinical and histopathologic findings

The charts of ten consecutive patients (4 males, 6 females) were reviewed. The median age was 65 years (range, 49–82 years). At initial staging, no patient had clinical evidence of a primary melanoma elsewhere in the body. The MMM involved the nasal cavity and/or the adjacent ethmoidal and maxillary sinus in all cases (Table 1). Most frequent symptoms at initial presentation were unilateral nasal hemorrhagic discharge, nasal obstruction, and facial pain. After clinical investigation including nasal endoscopy, a CT or MRI scan was acquired. In six patients (patient nos. 1, 3, 4, 5, 6, 7, Table 1), an additional ^{18}F-FDG-PET/CT scan for initial staging was obtained (Fig. 1a–d). In patient nos. 2, 8, 9, and 10 an additional ^{18}F-FDG-PET/CT after initial resection for re-staging was performed.

SNMM was confirmed histologically and immunohistologically in all patients. Four tumors (nos. 1, 5, 8, 10; Table 1) showed the histologic pattern of an amelanotic melanoma. The primary tumor was surgically removed in all patients; postoperative percutaneous radiotherapy (intensity modulated radiotherapy, IMRT) was given to all but one patient (patient no. 9, Table 1) with a mean of 58 Gy. Two patients underwent adjuvant chemotherapy because of distant metastases detected during follow-up (patient nos. 1, 3; patient no. 1 was included in a study protocol receiving interferon alpha (IFNa; 3MU s.c., three times a week) plus Dacarbazine (DTIC 850 mg/m2 via intravenous (i.v) infusion on
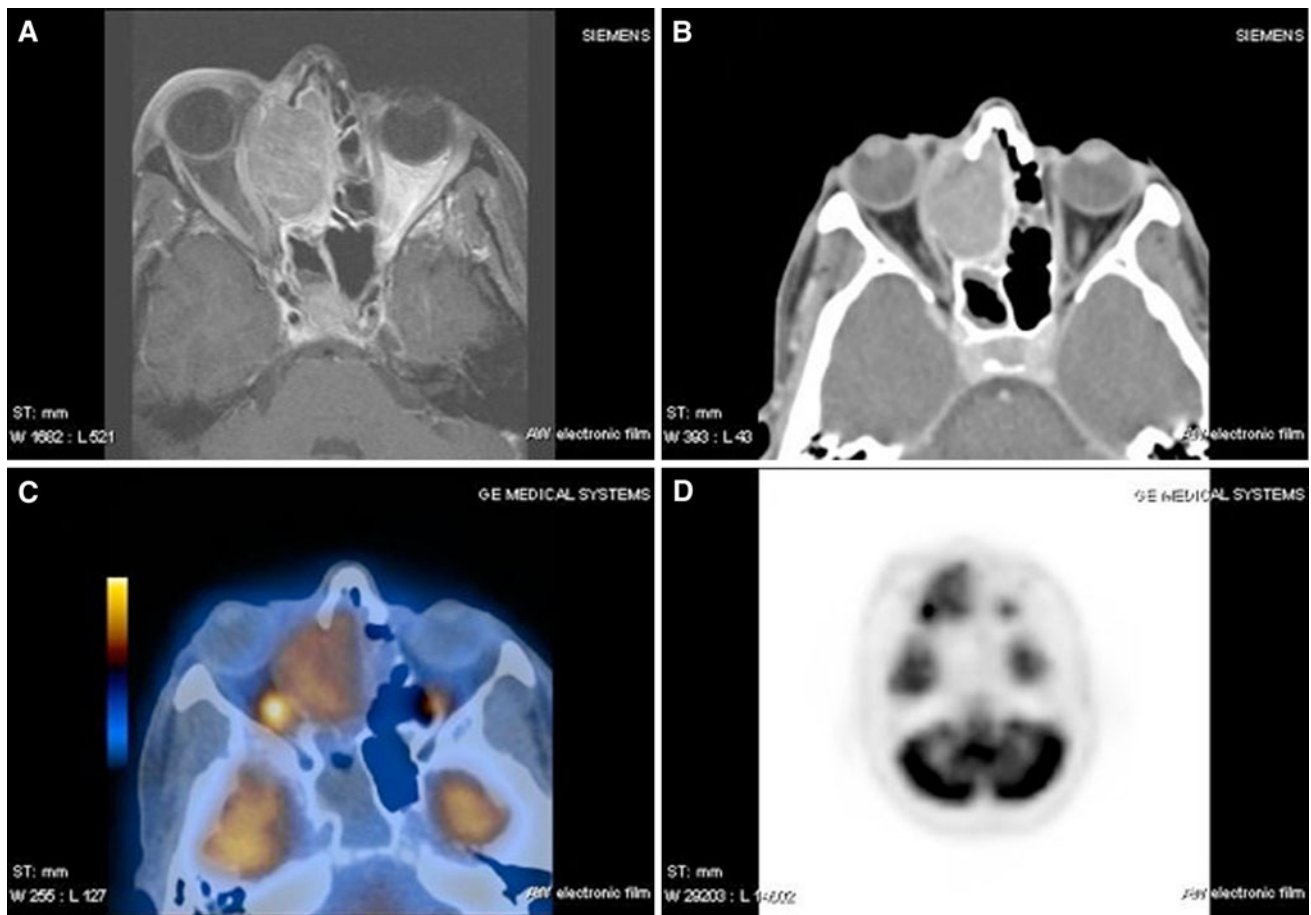
Fig. 1 56-year-old female suffering from a sinonasal malignant melanoma originating from the right nasal cavity involving the ethmoid sinus, the dura, and the periorbit. **a** T1 weighted MRI with Gadolinium, axial section. **b** Bone window CT with contrast agent, axial section. **c** Fused 18F-FDG-PET-CT, axial section. **d** 18F-FDG-PET, axial section

day 1 every 28 days during the first 6 months; patient no. 3 was included in a different study (SAKK 50/70) receiving Bevacizumab (Avastin® 10 mg/kg via i.v. infusion every 2 week) and Temozolomid (Temodal® 150 mg/m2 daily for 7 days every second week)). The median follow-up period was 17.5 months (range, 8–34 months). Five patients died as a result of locoregional recurrence and distant metastases (Table 2). Four Patients are alive with no evidence of disease, whereas one patient is known to have bone and pulmonary metastases (Table 2).

18F-FDG-PET/CT findings versus other imaging findings

18F-FDG-PET/CT was performed at the time of diagnosis before surgical resection in six patients, within 1 week after surgery (*n* = 4), and during follow-up (*n* = 24). A total of 34 18F-FDG-PET/CT were analyzed for this study.

The follow-up examinations were performed between 5 and 33 months after diagnosis. Increased 18F-FDG-uptake was observed in all patients with present tumors. All the 18F-FDG-PET/CT findings with regard to the detection of the primary tumor were also detected by CT or MRI-scans and were well correlated in size. The contrast-enhanced (ce) CT part of the 18F-FDG-PET/CT was able to approve the 18F-FDG-PET findings. One cerebral metastasis was not detected either by 18F-FDG-PET or by ceCT scanning and could only be found on MRI. Three suspicious lesions revealed by native CT (one osteolytic lesion in the spine; one small lesion in the lung; one enlarged lymph node in the mediastinum) showed none, or very little 18F-FDG activity. During follow-up, these lesions turned out to be false-positive lesions as no growth or onset of symptoms could be shown.

Increased activity in soft tissue was located in brown fat tissue in one patient. Patient no. 10 showed repeatedly local 18F-FDG activity at the site of resection (SUV 4.4-4.7). The fused CT did not approve a growing mass at this position and malignancy was finally ruled out by biopsy.

Table 1 Patient and tumor characteristics

No	Sex	Age	Localization	Histology	SUV max initial	Activity size in PET/CT	Preoperative size in MRI or CT	Therapy	Current status
1	m	52	Nasal cavity Ethmoidal sinus	NMC	7.1	0.76 × 0.65 × 0.9	n/a	Surgery RT & C	Dead of disease
2	f	51	Septum	MC	n/a[a]	n/a[a]	n/a	Surgery RT	Alive no disease
3	m	67	Maxillary sinus	MC	3.4	4.2 × 4.7 × .4.8	4.5 × 5.1 × 4.75	Surgery RT & C	Dead of disease
4	m	78	Nasal cavity	MC	10.8	3.7 × 3.8 × 3.2	4.8 × 5.4 × 2.5	Surgery RT	Dead of disease
5	f	82	Nasal cavity	NMC	4.2	1.7 × 1.6 × 0.9	3.1 × 3.2 × 1.3	Surgery RT	Alive with disease
6	f	49	Ethmoidal sinus	MC	11.5	3.2 × 3.4 × 3.5	3.4 × 3.3 × 2.8	Surgery RT	Dead of disease
7	f	56	Nasal cavity	MC	6.4	3.1 × 3.7 × 2.4	3.8 × 4.2 × 3.0	Surgery RT	Alive no disease
8	f	67	Middle turbinate	NMC	n/a[a]	n/a[a]	n/a	Surgery RT	Dead of disease
9	F	63	Inferior turbinate	MC	n/a[a]	n/a[a]	n/a	Surgery	Alive no disease
10	m	81	Spheno-ethmoidal	NMC	4.9[a]	1.4 × 2.2 × 2.0[a]	n/a	Surgery RT	Alive no disease

f Female, *m* Male, *NMC* non-melanotic melanoma, *MC* melanotic melanoma, *MRI* magnetic resonance imaging, *CT* computed tomography, *SUV* standardized uptake value, *RT* radiotherapy, *C* chemotherapy

Sizes indicated in anterio-posterior × cranio-caudal × right-left distances (in cm)

[a] After resection

Discussion

In general

Primary mucosal malignant melanoma (MMM) is a rare disease and occurs in older patients of both genders. Incidence of nasal cavity MMM was reported to be 0.018/10 [5] per year [6]. Only around 4% of all head and neck melanomas arise in the nasal cavity or adjacent paranasal sinuses [3]. The most common site of origin is the nasal septum, closely followed by the lateral nasal wall and the middle and inferior turbinates [3, 7]. Lymph node metastases are generally noted in about one-third of mucous membrane head and neck melanomas at initial presentation, implying a worse prognosis [1, 8]. The poorer prognosis for mucous membrane melanoma has been related to the tumor bulk (size), delay in diagnosis resulting from the non-specific nature of the presenting symptoms, difficult visual examination, and technical inaccessibility of the primary tumor [9].

Sinonasal malignant melanomas have, like cutaneous malignant melanomas, an increased glucose metabolism. The role of ^{18}F-FDG-PET in staging mucosal malignant melanomas of the head and neck has already been affirmed [5]. ^{18}F-FDG-PET imaging is also known to be more sensitive and specific than CT for the detection of metastasis in melanoma patients [10].

Advantages of ^{18}F-FDG-PET/CT

At initial staging, all our patients showed increased ^{18}F-FDG uptake at the tumor site and could thus be easily identified.

^{18}F-FDG-PET-only imaging is lacking anatomical information. Complementary anatomical imaging is often required, especially for surgical therapy planning in this complex anatomical area. Coregistred ^{18}F-FDG-PET/CT has been available for a few years and provides such anatometabolic datasets in a single examination. ^{18}F-FDG-PET/CT has been found to be superior to CT alone and PET alone in staging and evaluation of therapy response in several oncological diseases including malignant melanoma [11–13].

^{18}F-FDG-PET/CT as a functional and anatomical imaging method provides additional information for surgical therapy planning. Especially in the nasal cavity and paranasal sinuses, where anatomy is difficult and different vital structures are in close proximity, ^{18}F-FDG-PET/CT appears to be superior to ^{18}F-FDG-PET alone. Particularly in recurrent tumors it seems essential to distinguish scar-tissue from melanoma masses and predicts the extent of affection, which is not possible by CT alone. ^{18}F-FDG-PET without the additional information of the fused CT on the other hand is not able to give enough spatial resolution to perform exact surgical planning in the setting of the pre-operated nasal cavities and paranasal sinuses, where CT data add valuable information on fused images.

In a previous study by Department of Otolaryngology-Head and Neck Surgery, University Hospital Zurich, Switzerland, it could be shown that local tumor control in SNMM can be achieved in many cases and the majority of patients die from distant metastasis [7]. Hence, ^{18}F-FDG-PET/CT is in our opinion the imaging of choice during the follow-up period.

Table 2 Clinical and radiological information for every patient given at time of ^{18}F-FDG-PET/CT examinations

Patient number	^{18}F-FDG-PET/CT examinations	SUV max of the primary tumor	Locoregional recurrence	R0 resection at first intervention	All detected metastases
1	Initial staging	7.1		No	None
	1st follow-up	2.8	Yes		Neck
	2nd follow-up	6.3	Yes		Neck, bone
	3rd follow-up	4.5	Yes		Neck, bone, liver
	4th follow-up	n/a	No		Neck, bone, kidney
2	Initial staging	n/a		Yes	None
	1st follow-up	n/a	No		None
	2nd follow-up	n/a	No		None
	3rd follow-up	n/a	No		None
	4th follow-up	n/a	No		None
3	Initial staging	3.4		Yes	None
	1st follow-up	3.7	Yes		Adrenal gland
	2nd follow-up	4.7	Yes		Adrenal gland
4	Initial staging	10.8		Yes	None
	1st follow-up	n/a	No		Lungs
5	Initial staging	4.2		No	None
	1st follow-up	12.0	Yes		Lungs, bone
6	Initial staging	11.5		Yes	None
	1st follow-up	4.8	Yes		Lungs, brain (MRI)
7	Initial staging	4.8		No	None
	1st follow-up	n/a	No		None
	2nd follow-up	n/a	No		None
	3rd follow-up	2.8[a]	No		None
	4th follow-up	2.3[a]	No		None
	5th follow-up	n/a	No		None
8	Initial staging	n/a	Yes	No	Lungs, bone
9	Initial staging	n/a		Yes	None
	1st follow-up	n/a	No		None
	2nd follow-up	n/a	No		None
10	Initial staging	4.9		Yes	None
	1st follow-up	n/a	No		None
	2nd follow-up	4.4[a]	No		None
	3rd follow-up	3.8[a]	No		None
	4th follow-up	4.7[a]	No		None

R0 resection with neither macroscopic nor microscopic evidence of residual tumor, *SUV max* maximum standardized uptake value, *n/a*: no focal uptake

[a] False-positive uptake

Limitations of ^{18}F-FDG-PET/CT

A known limitation of ^{18}F-FDG-PET imaging is the identification of brain metastases due to the high background metabolism as well as small melanoma metastases, where the spatial resolution of ^{18}F-FDG-PET/CT- imaging is not small enough [14]. We, too, did encounter these difficulties, as one cerebral metastasis was not seen during follow-up ^{18}F-FDG-PET/CT scans and was only identified by MRI.

Fused ^{18}F-FDG-PET/MRI might possibly eliminate this problem in the future.

In a study by Gulec et al. [14] all of the 29 lesions larger than 1 cm showed ^{18}F-FDG uptake, whereas only two out of 15 lesions smaller than 1 cm were detected by ^{18}F-FDG-PET alone14. A theoretical three-dimensional spatial resolution of 4 mm can be achieved by modern ^{18}F-FDG-PET/CT scanners. However, due to motion and the tumor related uptake ratio, a spatial resolution of 6-8 mm can be expected realistically [15].

Veit-Haibach et al. [16] stated that ^{18}F-FDG-PET/CT show low sensitivities at initial staging of patients suffering from malignant cutaneous melanomas and therefore metabolic imaging should only be recommended as a first-line diagnostic tool for selected melanoma patients in high-risk groups. Although none of our patients was found to have regional or distant metastasis upon first imaging workup, all of the primary sites could be identified adequately. This is also due to late presentation of the oligosymptomatic patient in a late stadium with large tumor size, as stated above. As a rule, we believe it is advantageous performing the same follow-up imaging modality as that used for primary workup.

The cost-effectiveness of ^{18}F-FDG-PET/CT

Different authors have described the cost-effectiveness of ^{18}F-FDG PET/CT in staging head and neck squamous cell carcinoma (HNSCC) [17, 18]. The drawback of staging patients with ^{18}F-FDG PET/CT is the relatively high number of false-positive findings. Although many of the positive ^{18}F-FDG PET/CT findings will have an impact on the patient treatment, the costs of subsequent investigations and the burden caused to patients by additional investigations are considerable. Therefore, the indication for metabolic imaging should be handled reluctantly. A recent study showed ^{18}F-FDG PET/CT is the most effective pretreatment screening method for distant metastases in HNSCC patients with risk factors [19]. It is our opinion, that in future, when integrated ^{18}F-FDG PET/CT and MRI scanners become routine, this will be the most cost-effective imaging method for SNMM.

The role of CT

Three ^{18}F-FDG- negative lesions (spine, lung, and mediastinum) detected and found to be suspicious by native CT were shown to be unsuspicious on ^{18}F-FDG-PET scanning. All of these findings were proven not to be malignant upon follow-up examination. These lesions represent false-positive findings on native CT scans; therefore, CT scanning should be ultimately performed ce, and, furthermore, ^{18}F-FDG negativity shows the potential to identify unreliable CT findings. On the other hand it can be challenging, especially in the head and neck area, to distinguish physiological or inflammatory uptake from malignant tissue which can be downsized by the ceCT part [20].

As malignant mucosal melanoma is a very rare condition, it is difficult to show significant improvements in staging with ^{18}F-FDG-PET/CT because of the small number of patients. However, we know from previous reports on ^{18}F-FDG-PET/CT imaging that only few false-negative results are obtained, leading to a high negative predictive value,

which is also supported by the current study. As modern ^{18}F-FDG-PET/CT scanners are providing a better resolution of the added CT information, one can also expect less false-positive findings. As shown, it is important to perform a ceCT part, which is not routine in many centers.

The role of MRI

To evaluate dural or intracranial involvement, MRI seems to be indisputably the imaging modality of choice. However, the tumor's appearance is dependent on the amount of melanin found within. Melanotic tumors usually show hyperintensity on T1 images, whereas hypomelanotic or amelanotic melanomas may appear intermediate in signal intensities [21–23]. In our series 4/10 SNMM were amelanotic. In previous studies of mucosal melanoma, the frequency of amelanotic melanoma ranged from 25 to 42.9% [22]. All of the tumors in our series had increased ^{18}F-FDG uptake independent of their melanin contents which is in accordance with the literature.

Conclusion

In addition to the previously published experience concerning ^{18}F-FDG-PET imaging for the detection of MMM, the updated data presented in this study suggest that ^{18}F-FDG-PET/CT is superior to other imaging, e.g., CT or MRI scans, with its known limitations. Owing to the combined ^{18}F-FDG-PET and CT part, the visibility of SNMM is not solely dependent on ^{18}F-FDG activity anymore.

Therefore, if available, contrast-enhanced ^{18}F-FDG-PET/CT, in our opinion, is the adequate staging and restaging imaging modality to respond to the question of the expansion of the primary tumor, locoregional disease, or distant metastases.

If dural or intracranial involvement is clinically suspected, we believe that, additional MRI is required. However, it will never replace ^{18}F-FDG-PET/CT scanning as a staging modality unless MRI is fused with ^{18}F-FDG-PET.

Conflict of interest None.

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