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Whole-body hybrid positron emission tomography imaging yields clinically relevant information in the staging and restaging of sinonasal tumors

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Abstract

Background: Whole-body hybrid positron emission tomography (PET) imaging is increasingly used for sinonasal tumors. However, only empirical data exist on the additional, clinically relevant information derived from these techniques.

Methods: This study included 96 regionalized magnetic resonance imaging (MRI) of the sinonasal tract/neck and separate hybrid FDG-PET/CT or FDG-PET/MRI in 74 patients. Additional radiological information (ARI) obtained from each hybrid examination was analyzed and its clinically relevance was determined. Clinically relevant information (CRI) was categorized with regard to primary tumor site, regional lymph node metastases, distant metastases, second primary tumors, and non-neoplastic findings.

Results: A total of 45/96 (46.9%) hybrid PET examinations revealed ARI. CRI was found in 32/96 (33.3%) examinations and concerned the primary tumor site (6.1%), regional lymph node metastases (4.1%), distant metastases (14.3%), second primary tumors (7.3%), and non-neoplastic findings (5.1%).

Conclusions: Hybrid PET imaging yields additional radiological information translating into clinically relevant information in a substantial proportion of patients with sinonasal tumors.

Alexander Maurer and Christian M. Meerwein are co-first authors.

David Holzmann and Martin W. Huellner are co-last authors.

KEYWORDS

clinically relevant information, fluorodeoxyglucose F18, otorhinolaryngologic diseases, paranasal sinus neoplasms, positron emission tomography

1 | INTRODUCTION

Primary sinonasal malignancies represent 3%–5% of all head and neck cancers.[1] Their growth is associated with a potential affection of pivotal neural and vascular structures, such as the dura, brain, internal carotid artery, and optic nerve.[1–4] Typically, patients are seen at an advanced stage, since tumors tend to expand unnoticed for a long time and often lead to delayed symptoms.[3–6] Traditionally, both contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) were considered as first-line imaging modalities.[7–9] Computed tomography addresses the bony sinonasal system and provides a bony roadmap for surgery.[7] Magnetic resonance imaging helps to delineate tumor from surrounding tissue such as dura and periorbita and is capable to identify perineural spread, bone marrow infiltration, and local metastases.[8,9] In the last decades, 2-[^{18}F]-fluorodeoxy-D-glucose (FDG) positron emission tomography (PET)/CT (FDG-PET/CT) and more recently FDG-PET/MRI emerged as potential alternatives for the assessment of sinonasal tumors, providing information on both metabolic activity and local extent of the primary tumor and on the presence of regional and distant metastases (DM).[10,11] While various studies have investigated the diagnostic accuracy of hybrid PET imaging for squamous cell carcinoma (SCC) of the upper aerodigestive tract, only a few studies addressed its use for primary sinonasal malignancies.[10,12–16] In a recent study on the initial staging of sinonasal malignancies with hybrid PET, Meerwein et al. reported an excellent sensitivity in detecting primary tumors, lymph node (LN) metastases, and DM and identified the PET parameter total lesion glycolysis (TLG) as an independent prognosticator of complete remission.[10] Ozturk et al. demonstrated that FDG-PET/CT is an accurate diagnostic tool, providing a sensitivity of 81% and specificity of 99% for detection of DM, and 83% and 96% for LN metastases, respectively.[17] They also suggested that pretreatment diffusion-weighted MRI in combination with FDG-PET/CT parameters may serve as surrogate marker for the prognosis of sinonasal malignancies.[18] One important, but unanswered clinical question is, whether whole-body hybrid PET imaging can provide relevant additional radiological information (ARI) beyond the current imaging standard of reference (MRI and/or CT), which might justify its use in clinical routine. Today, only empirical data exist on the clinically relevant information of hybrid PET techniques compared to standalone MR imaging in sinonasal tumors. Thus, the aim of our study was to compare whole-body hybrid PET imaging with regionalized sinonasal/neck MRI in order to assess its clinically relevant information.

2 | METHODS

2.1 | Study design

This study received ethical approval from the local ethics committee (approval number: 2016-00162_amendment2019). Patients with documented unwillingness to contribute personal health-related data to research were not included. We retrospectively reviewed patients with primary malignant sinonasal tumors at the department of otorhinolaryngology/head and neck surgery at the University Hospital Zurich (Zurich, Switzerland) between November 2001 and October 2019. All patients underwent either whole-body FDG-PET/CT or FDG-PET/MRI and synchronous sinonasal/neck MRI (± 4 weeks). Restaging examinations were scheduled as part of the regular tumor surveillance and were performed at least 3 months after the end of primary treatment, in order to avoid false positive FDG-PET findings due to postinterventional inflammation.[19] Tumors were staged according to the seventh (until 2017) and eighth (from 2017 on) American Joint Committee on Cancer/Union for International Cancer Control staging system.[20] For histopathological tumor classification at initial diagnosis, patients underwent endonasal-endoscopic biopsy under general anesthesia. This procedure is of paramount importance for the workup of patients with sinonasal malignancies.[21] Treatment plans for every patient had been discussed at a multidisciplinary head and neck tumor board.

2.2 | Patient characteristics and treatment protocols

The following patient and tumor data were collected: age at diagnosis, sex, initial clinical classification (cT, cN, cM), and histopathological workup. Primary curative

treatment protocols consisted of either (1) surgical tumor resection +/− adjuvant intensity-modulated radiation therapy (RT) +/− concomitant chemo(immuno)therapy, or (2) primary radio(chemo)(immuno)therapy in intensity-modulated technique or proton beam therapy. Palliative therapy concepts consisted of palliative tumor debulking, palliative RT, chemo(immuno)therapy or best supportive care. From 2012 on, immunotherapy was available for sinonasal melanoma patients. Postoperatively, all patients were followed with (1) systematic nasal endoscopy every 6-8 weeks and (2) cross-sectional imaging with FDG-PET (PET/CT or PET/MRI) and synchronous sinonasal/neck MRI. The first radiological examination was scheduled 3 months after the end of primary treatment; the further regular examinations were performed every 3–6 months or upon clinical suspicion in terms of recurrence. In general, patients were followed for at least 10 years, except from particular low-risk tumors (e.g., low-grade, low-stage adenocarcinoma), which were monitored for 5 years.

2.3 | Imaging

FDG-PET/CT was acquired using a Discovery VCT scanner (GE Healthcare, Waukesha, WI), a Discovery 690 Standard scanner (GE Healthcare), a Discovery MI scanner (GE Healthcare), a Discovery ST scanner (GE Healthcare), or a Discovery LS scanner (GE Healthcare). FDG-PET/MRI was performed using a 3T SIGNA PET/MR scanner (GE Healthcare). A standardized dose of 3.5 MBq of FDG per kg body weight (PET/CT) or 3.0 MBq per kg body weight (PET/MRI) was injected, from 2017 on. BMI-adapted body weight-dependent dosage protocols were used.[22] For attenuation correction in PET/MRI, standard Dixon-based maps were used. Computed tomography (CT) consisted of a standardized protocol of high-resolution axial volume acquisition (0.6–1.0 mm) with reconstructions in coronal and sagittal planes in bone and soft tissue kernel, with and without contrast-enhancement. For the sinonasal/neck MRI dedicated regionalized T2-weighted and T1-weighted MR pulse sequences with and without gadolinium-based contrast agent were used.

2.4 | Image analysis

For the purpose of this study, all whole-body hybrid PET images and MRI examinations were reviewed by a double board-certified radiologist/nuclear medicine physician, with 9 years of experience in head and neck imaging. The additional radiological information (ARI) retrieved from whole-body hybrid PET imaging compared to regionalized MRI alone was extracted by the same person. The term "additional radiological information" (ARI) comprises all additional findings retrieved from whole-body hybrid PET imaging compared to regional MRI alone. The ARI was then categorized as follows: information on (1) primary tumor site, (2) regional lymph node metastases, (3) DM, (4) second primary tumors, and (5) non-neoplastic findings (e.g., pituitary (micro)adenoma detected by FDG uptake, metabolically active mediastinal lymphadenopathy suggesting sarcoidosis).

2.5 | Assessment of clinically relevant information

The ARI from every hybrid PET examination was presented on a PACS workstation to a board-certified ENT surgeon, with 7 years of clinical experience in head and neck cancer treatment. Based on the subsequent clinical course, including therapeutic decisions made, the ENT surgeon reviewed ARI for any clinically relevant information (CRI) beyond the MRI-derived information, which had an influence on the further course of the patient. The CRI retrieved from whole-body PET was then categorized as follows: (1) detection of local disease, regional disease, or DM and consecutive adjustment of treatment (curatively intended), (2) detection of local disease, regional disease, or DM and consecutive adjustment of treatment (palliatively intended), (3) detection of second primary tumors and consecutive treatment initiation, (4) induction of endoscopic biopsy of the primary tumor site or mediastinal/pulmonal lymph nodes (endobronchial ultrasound bronchoscopy) under general anesthesia, (5) prevention of invasive diagnostic procedures/therapies owing to information from whole-body PET, (6) benign findings with clinically relevant information, (7) no clinically relevant information. The clinically relevant information was determined for every single finding on whole-body PET (primary tumor site, regional lymph node metastases, DM, second primary tumors and other, non-neoplastic findings). The significance level was set to 10%. Thus, clinically relevant information (beyond the impact of sinonasal/neck MRI) needed to be present in ≥10% hybrid PET examinations in order to count as significant. Only procedures and findings with evident consequences for the patient or his/her treatment were rated as clinically relevant information (e. g., fine needle aspiration [FNA] of a LN, which did not reveal malignancy, was not rated as clinically relevant information).

2.6 | Statistical analysis and visualization

Ordinal nondichotomous variables were expressed as median (range) and interquartile range (IQR), and nominal nondichotomous variables were expressed as mode (percentage). The ARI and consecutive translation into clinically relevant information for all examinations were presented in bar charts. The hypothesis that ≥ 10% of all staging and/or restaging examinations showed a clinically relevant information compared with sinonasal/neck MRI was validated with the test for one proportion for all staging and/or restaging examinations. Consecutively, 95% confidence intervals (95% CI) of observed

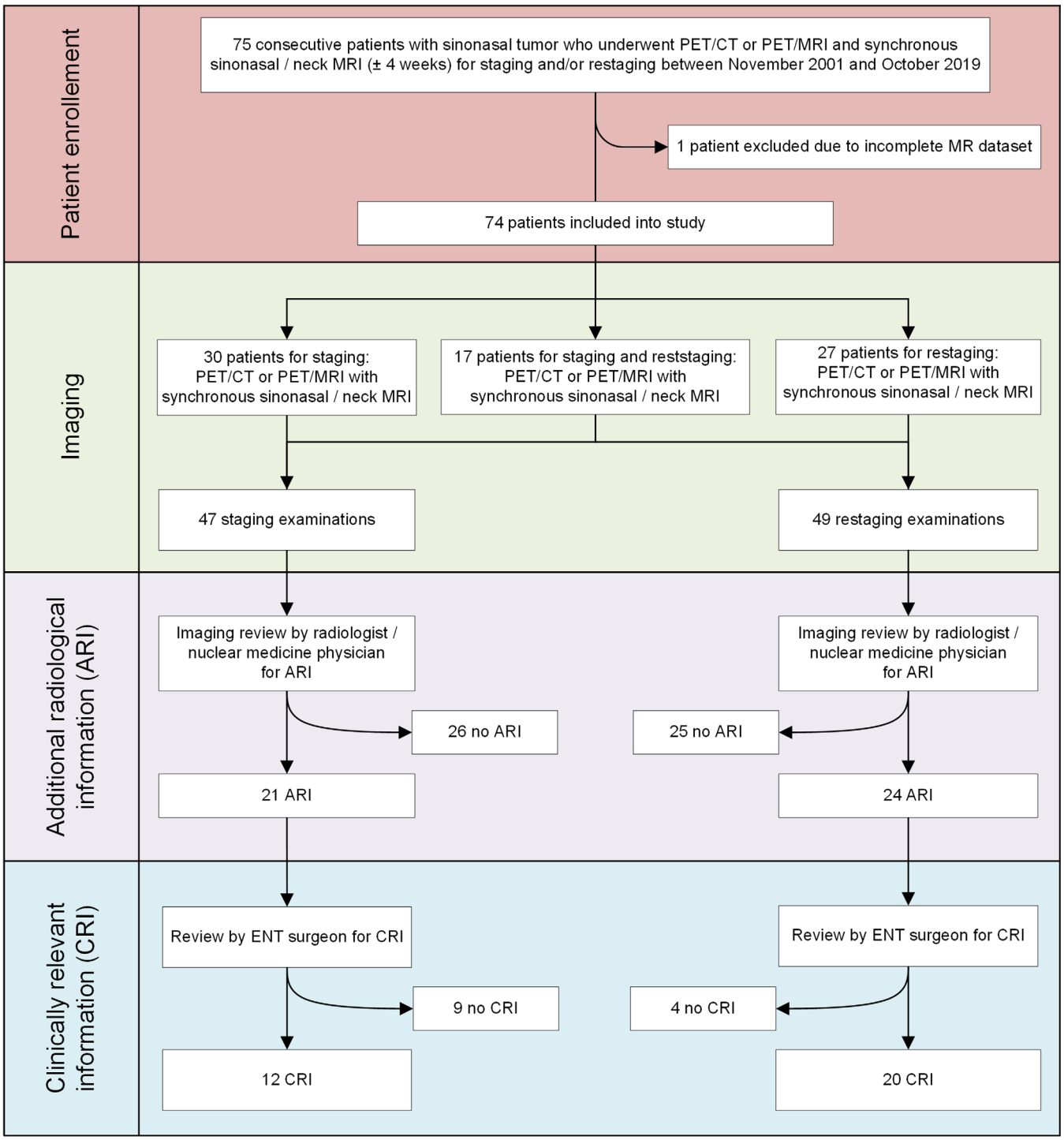

FIGURE 1 Details on patient enrollment and study design. ARI, additional radiological information; CRI, clinically relevant information; MRI, magnetic resonance imaging; PET/MRI, positron emission tomography/magnetic resonance imaging; PET/CT, positron emission tomography/computed tomography [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Patients and treatment characteristics

Number of patients (*n*)	**74**
Sex, *n* (%)	
Female	32 (43.2)
Male	42 (56.8)
Age at initial diagnosis (median, 1 and 3 IQR)	67 (IQR 53, 75)
Histopathology, *n* (%)	
Sinonasal mucosal melanoma	23 (31.1)
Sinonasal adenocarcinoma	13 (17.6)
Sinonasal undifferentiated carcinoma (SNUC)	12 (16.2)
Sinonasal adenoid cystic carcinoma	11 (14.9)
Sinonasal squamous cell carcinoma	11 (14.9)
Olfactory neuroblastoma	4 (5.4)
Initial clinical T classification according to clinical and radiological assessment, *n* (%)	
cT1	2 (2.7)
cT2	9 (12.3)
cT3	15 (20.6)
cT4a	19 (26.0)
cT4b	28 (38.4)
Initial N classification, *n* (%)	
cN0	68 (93.1)
cN+	5 (6.9)
Initial M classification, *n* (%)	
cM0	69 (94.5)
cM1	4 (5.5)
Primary treatment protocol, *n* (%)	
Surgical tumor resection	56 (75.7)
No adjuvant treatment	15
Adjuvant IMRT/adjuvant PBT +/− systemic therapy	40
Neoadjuvant chemotherapy	1
Primary radio(chemo)(immuno)therapy using IMRT or PBT	12 (16.2)
Palliative therapy	6 (8.1)
Surgical approach, $n = 56$ (%)	
Endoscopic endonasal only	37 (66.1)
Transfacial only	8 (14.3)
Craniofacial only	5 (8.9)
Combined endoscopic endonasal and transfacial/craniofacial	6 (10.7)

Abbreviations: IMRT, intensity-modulated radiation therapy; IQR, interquartile range; PBT, proton beam therapy.

proportions and z statistics were calculated. A p-value < 0.05 indicated significance and refused the null hypothesis. Sankey diagrams for visualizing clinically relevant information were designed with e!Sankey 5.2.1 (ifu Hamburg GmbH, Hamburg, Germany). Statistical analyses were performed using MedCalc Statistical Software version 19.1 (MedCalc Software bv, Ostend, Belgium).

3 | RESULTS

3.1 | Patient, tumor, and treatment characteristics and radiological workup

A total of 74 patients with 96 whole-body PET examinations were included. Thereof, 30/74 patients (40.5%)

underwent staging, 27/74 (36.5%) restaging, and 17/74 (23.0%) patients both staging and restaging examinations. Of all 96 examinations, 47/96 (49.0%) were performed for staging and 49/96 (51.0%) for restaging. Whole-body examinations consisted of 85/96 (88.5%) FDG-PET/CT examinations and 11/96 (11.5%) FDG-PET/MRI examinations. All patients underwent a synchronous sinonasal/neck MRI at each time-point (+/− 4 weeks). Details on patient enrollment and study design are given in Figure 1. Table 1 provides detailed information on patient demographics, histopathology, preoperative staging based on clinical and radiological assessment, and treatment protocols.

3.2 | Additional radiological information and evaluation of clinically relevant information

Of all included 96 whole-body hybrid PET examinations, 45/96 examinations (46.9%) yielded ARI. Among all 45 findings with ARI, 21/45 (46.7%) findings were seen on initial staging and 24/45 (53.3%) findings on restaging examinations. Clinically relevant information of PET was found in 32/96 (33.3%) examinations (initial staging 12/47 [25.5%], restaging 20/49 [40.8%]). Table 2 shows absolute numbers of whole-body PET findings rated as ARI and consecutive clinically relevant information, including an allocation to subcategories. Among the 11/96 examinations yielding ARI on the primary tumor, specific ARI on orbital or dural infiltration, intracranial tumor extension or perineural spread of tumor was not retrieved from hybrid PET in any case. However, by adding metabolic information on lesions, ARI obtained by hybrid PET helped distinguish treatment-related alterations and local recurrence. A second primary tumor was found in 6/96 (6.1%) examinations (thyroid carcinoma [$n = 1$], pleural tumor [$n = 1$] (histology could not be obtained), bronchial carcinoma [$n = 3$], intestinal lymphoma [$n = 1$]). Seven (7.1%) non-neoplastic findings on PET had clinically relevant information (thyroid nodules [$n = 2$], pulmonary sarcoidosis [$n = 2$], parathyroid adenoma [$n = 1$], pituitary adenoma [$n = 1$], terminal ileitis [$n = 1$]). Figure 2(A)–(C) represents overall ARI and clinically relevant information for staging and restaging examinations as bar charts, including a stratification by subcategories. Figure 2(D) indicates how ARI and clinically relevant information were distributed across different tumor entities. Absolute numbers and translation into clinically relevant information for every detected lesion rated as ARI are presented as Sankey diagram (Figure 3). Figure 4 demonstrates the clinically relevant information of all PET examinations demonstrated as Sankey diagram. The hypothesis that $\geq$ 10% of ARI translates into a clinically relevant information was accepted for all PET examinations and separately for staging and restaging examinations as well ($p < 0.0001$ for all examinations [observed proportion 33.3%, $n = 96$, z statistic 7.6, 95% CI 24.0–43.7], $p < 0.0004$ for initial staging examinations [observed proportion 25.5%, $n = 47$, z statistic 3.5, 95% CI 13.9–40.3], $p < 0.0001$ for restaging examinations [observed proportion 40.8%, $n = 49$, z statistic 7.2, 95% CI 27.0–55.8]).

4 | DISCUSSION

4.1 | Main findings

In this single-institution study on whole-body hybrid PET imaging of primary sinonasal malignancies, PET imaging yielded additional radiological information in 46.9% of all

TABLE 2 Absolute number of findings rated as ARI retrieved from whole-body FDG-PET/CT or FDG-PET/MRI, compared to MRI alone and translation into CRI

	All examinations ($n = 96$)		Initial staging examinations ($n = 47$)		Restaging examinations ($n = 49$)	
	ARI, *n* (%)	CRI, *n* (%)	ARI, *n* (%)	CRI, *n* (%)	ARI, *n* (%)	CRI, *n* (%)
Sinonasal malignancy						
Primary tumor site	11 (11.2)	6 (6.1)	2 (4.3)	0 (0)	9 (18.4)	6 (12.2)
Regional lymph node metastases	16 (16.3)	4 (4.1)	9 (19.1)	0 (0)	7 (14.3)	4 (8.2)
Distant metastases	15 (15.3)	14 (14.3)	5 (10.6)	5 (10.6)	10 (20.4)	9 (18.4)
Incidental findings						
Second primary tumors	6 (6.1)	5 (5.1)	2 (4.3)	1 (2.1)	4 (8.2)	4 (8.2)
Non-neoplastic findings	8 (8.2)	7 (7.1)	7 (14.9)	6 (12.7)	1 (2.0)	1 (2.0)

Abbreviations: ARI, additional radiological information; CRI, clinically relevant information; FDG-PET/CT, 2-[^{18}F]-fluorodeoxy-D-glucose positron emission tomography/computed tomography; FDG-PET/MRI, 2-[^{18}F]-fluorodeoxy-D-glucose positron emission tomography/magnetic resonance imaging.

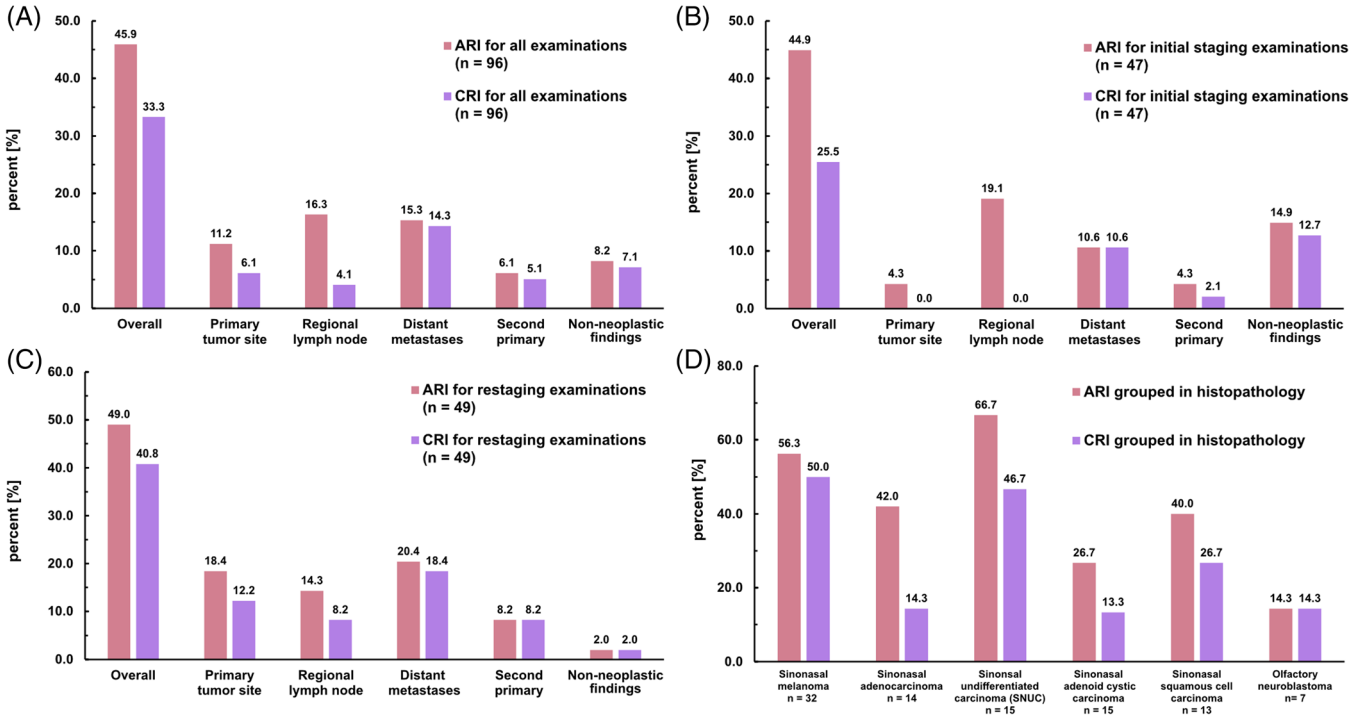

FIGURE 2 (A) Percentage of ARI and CRI in staging and restaging examinations, (B) in initial staging examinations only, (C) in restaging examinations only, and (D) stratified by histopathology of primary sinonasal tumors. ARI, additional radiological information; CRI, clinically relevant information [Color figure can be viewed at wileyonlinelibrary.com]

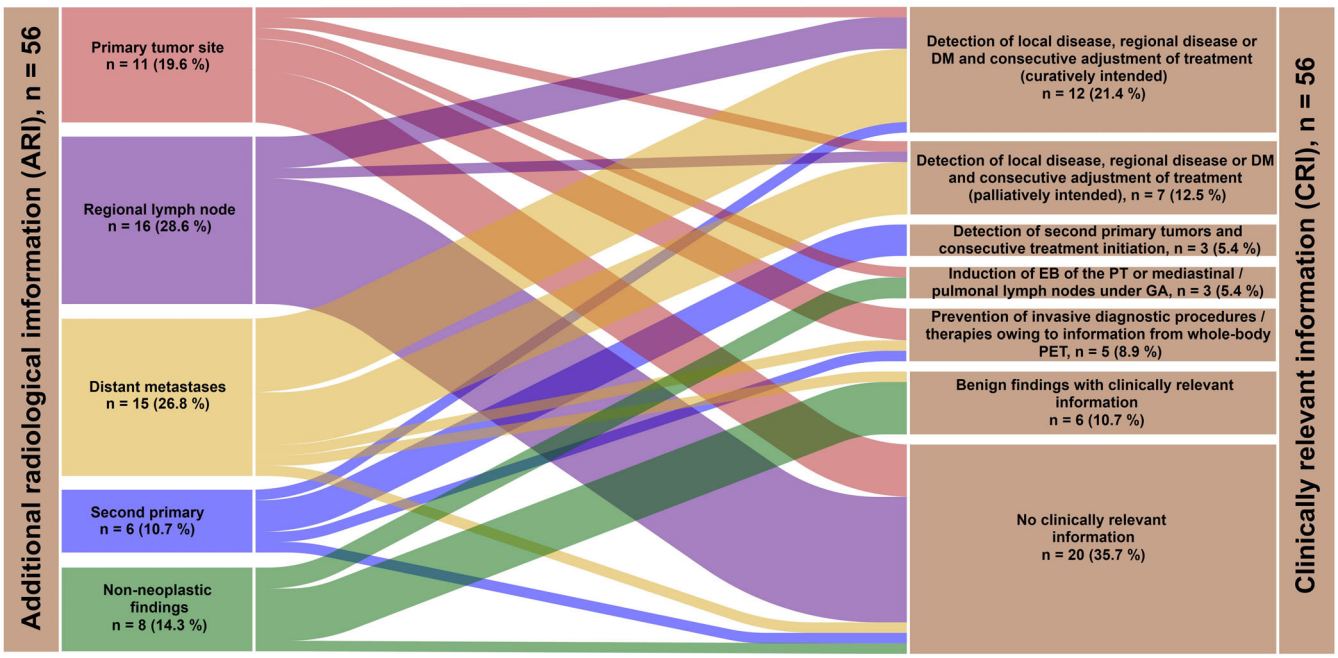

FIGURE 3 Sankey diagram shows translation of ARI into CRI in absolute numbers and percentages. ARI, additional radiological information; CRI, clinically relevant information; DM, distant metastases; EB, endoscopic biopsy; GA, general anesthesia, PET, positron emission tomography; PT, primary tumor [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 4 Sankey diagram demonstrates the CRI for all examinations in absolute numbers and percentages. CRI, clinically relevant information; DM, distant metastases; PET, positron emission tomography [Color figure can be viewed at wileyonlinelibrary.com]

examinations, compared to regional cross-sectional imaging with MRI alone, which translated into clinically relevant information in 33.3% of all examinations.

4.2 | Results in the context of available literature

This tertiary referral center series on primary sinonasal malignancies reflects two decades of hybrid PET imaging. Similar to other studies, our cohort consisted of locally advanced tumors in the majority of subjects (62/74 patients ≥ cT3, 83.8%) with a comparably low rate of LN metastases and DM at initial presentation.[12,23,24] Our series showed that 36/56 (64.2%) additional radiological findings retrieved from whole-body PET translated into clinically relevant information. As seen in Figure 2, there were more findings with clinically relevant information in the restaging setting compared to the initial staging. This might partially be explained by frequent FDG-avid LNs on PET imaging, which turned out negative on FNA (and were not considered to have clinically relevant information). In the available literature, only limited data on the additional value of PET imaging for clinical decision-making in sinonasal tumors is available. In a markedly smaller series of 21 subjects, Wild et al. investigated patients with sinonasal tumors undergoing FDG-PET/CT for staging (9/21 patients) and restaging (12/21 patients).[13] They found additional information by PET imaging in 11/21 patients, which translated into a change in clinical management in 9/21 patients.[13] Workman et al. investigated asymptomatic post-treatment patients with sinonasal tumors and found a total of three recurrences in 111 PET examinations, which consecutively lead to therapy adjustment.[25] They concluded that FDG-PET/CT is a valuable surveillance tool for patients with sinonasal malignancies, with the ability to detect treatable recurrences, which were missed with combination of endoscopy and traditional cross-sectional imaging with CT and MRI.[25] Ozturk et al. came to a similar conclusion with regard to regional and distant metastases from sinonasal malignancies in asymptomatic patients, leading to a change in management in 85% of all patients with recurrences (total of 104 recurrences).[26]

4.3 | Primary tumor

Adequate assessment of the primary tumor is pivotal for staging and restaging sinonasal tumors, since local

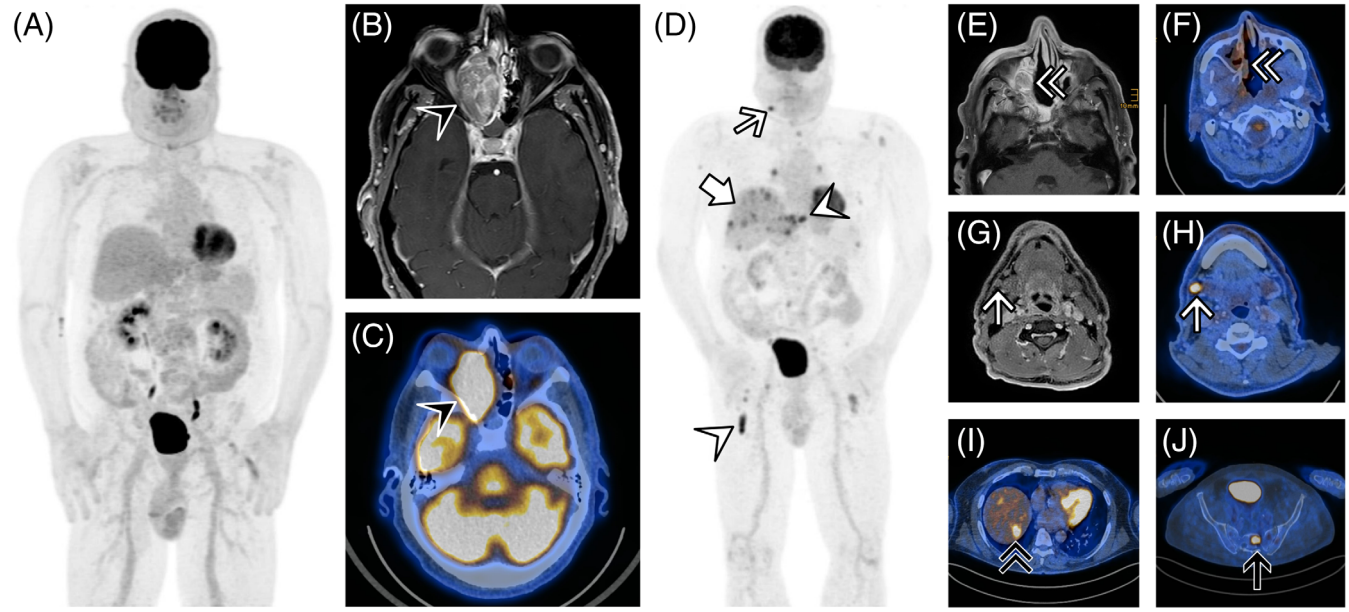

FIGURE 5 Seventy-six-year-old male patient with sinonasal mucosal melanoma. Initial FDG-PET/CT staging examination with synchronous sinonasal/neck MRI: (A) whole-body maximum intensity projection (MIP) shows no distant metastasis: (B) axial contrast-enhanced, fat-suppressed T1-weighted MR image and (C) fused FDG-PET/CT image show the large primary tumor in the right-sided nasal cavity, expanding into adjacent paranasal sinuses and bulging into the orbit (black arrow). FDG-PET/CT restaging examination with synchronous MRI 4 months after surgical tumor resection and adjuvant radiation therapy. (D) Whole-body MIP with an FDG-avid submandibular lymph node (white arrow), multiple liver metastases (white bold arrow), and numerous bone metastases, for example, in spinal column and femur (white arrow heads). (E) Axial contrast-enhanced, fat-suppressed T1-weighted image with an unclear contrast enhancing mass (white double arrow head), which turned out slightly FDG-avid on (F) fused FDG-PET/CT (white double arrow); the finding is consistent with local recurrence. (G) Axial contrast-enhanced, fat-suppressed T1-weighted MR image with a normal appearing submandibular lymph node (white arrow), intensely FDG-avid on (H) fused FDG-PET/CT, consistent with a lymph node metastasis (white arrow). (I) Fused axial FDG-PET/CT with FDG-avid liver metastases (black double arrow) and (J) fused axial FDG-PET/CT with sacral bone metastasis (black arrow). Owing to PET findings, the patient then underwent systemic immunotherapy. FDG-PET/CT, 2-[^{18}F]-fluorodeoxy-D-glucose positron emission tomography/computed tomography; MR, magnetic resonance; MRI, magnetic resonance imaging [Color figure can be viewed at wileyonlinelibrary.com]

extension and infiltration of adjacent structures—as represented the AJCC cancer staging system—determines the T category, one of the strongest prognosticators of outcome.[4,27–29] Despite state-of-the-art cross-sectional imaging with MRI and CT, a reliable statement in terms of dural or orbital invasion often requires an exploration of the tumor under general anesthesia.[21] To address this shortcoming of conventional imaging modalities, the use of hybrid PET imaging may generate added radiological value. Recent data, addressing the primary staging of sinonasal tumors, demonstrated that hybrid PET imaging yields an excellent sensitivity (95%–100%) for detecting the primary tumor.[10,12,30] However, a more thorough assessment of the primary tumor in PET imaging is complicated by the fact that different histopathological subtypes of sinonasal tumors may reveal different FDG-avidity and by the "spillover" of activity from normal brain tissue. Typically, sinonasal undifferentiated carcinoma (SNUC) and olfactory neuroblastoma tend to exhibit higher FDG uptake, compared to adenoidcystic carcinoma and sinonasal adenocarcinoma.[10,11,31,32] Furthermore, locally confined, and superficial tumors are a common challenge, since they may appear FDG-negative.[10,33] Kuhn et al. reported that PET/MRI is superior to PET/CT in differentiating tumor tissue from entrapped mucus secretions in sinonasal cavities and in the assessment of perineural spread, while maintaining adequate accuracy in the assessment of bony structures, such as the skull base.[34] Sekine et al. had a small number of sinonasal tumors in their study on head and neck cancer and found FDG-PET/MRI to yield at least equal diagnostic accuracy as FDG-PET/CT, with an additional advantage in soft-tissue contrast that is of particular importance for the assessment of dural and orbital involvement.[35] In our study, whole-body hybrid PET imaging revealed ARI concerning the primary tumor in 11.2% of all examinations, which revealed clinically relevant information in 6.1% (Table 2 and Figure 3). However, compared to MRI alone, hybrid PET imaging did not yield ARI on potential dural or orbital infiltration,

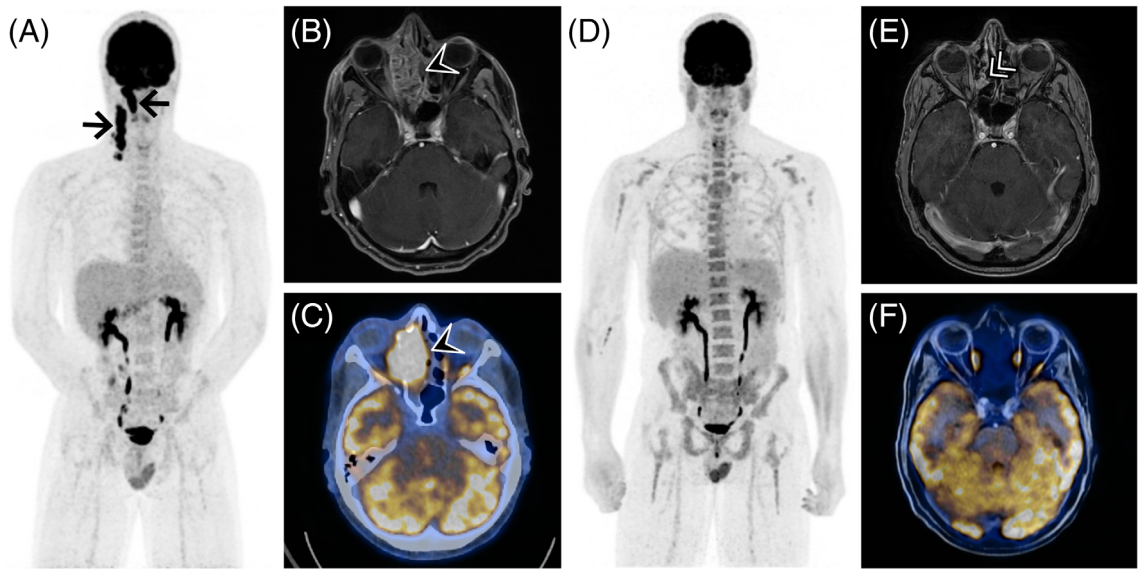

FIGURE 6 Thirty-five-year-old male patient with olfactory neuroblastoma. Initial FDG-PET/CT staging examination with synchronous MRI of the paranasal sinus and neck: (A) Whole-body maximum intensity projection (MIP) shows numerous, metabolically active lymph node metastases (black arrow). (B) Axial contrast-enhanced, fat-suppressed T1-weighted image and (C) fused FDG-PET/CT image show the FDG-avid tumor in the right-sided ethmoid with orbital infiltration (black arrow). FDG-PET/MRI restaging examination with synchronous sinonasal/neck MRI after 3 cycles of induction chemotherapy: (D) Whole-body MIP shows no distant metastasis, (E) axial contrast-enhanced, fat-suppressed T1-weighted MR image shows an unclear contrast enhancing structure in the right-sided nasal cavity (white double arrow). In (F) fused axial FDG-PET/MRI the structure is not metabolically active and thus rather consistent with scar tissue. The patient consecutively underwent transnasal-transcribriform tumor resection, with small vital remnants of olfactory neuroblastoma in the middle nasal turbinate. FDG-PET/CT, 2-[^{18}F]-fluorodeoxy-D-glucose positron emission tomography/computed tomography; FDG-PET/MRI, 2-[^{18}F]-fluorodeoxy-D-glucose positron emission tomography/magnetic resonance imaging [Color figure can be viewed at wileyonlinelibrary.com]

intracranial tumor extension or perineural spread of tumor. Hybrid PET imaging was useful in the restaging setting and helped distinguish treatment-related alterations and local recurrence by adding metabolic information on lesions (Figures 5 and 6). A distinct radiological statement on therapy response is particularly important, since negative findings on the first post-treatment PET/CT predict significantly longer overall survival.[36] As seen in the Sankey diagram (Figure 3), the addition of whole-body PET imaging guided clinicians by either discouraging from additional invasive diagnostic procedures, by advocating an endoscopic-endonasal biopsy under general anesthesia due to suspicious radiological findings at the primary tumor site, or by the detection of regional disease or DM, with either curatively intended or palliatively intended treatment adjustment.

4.4 | Lymph node metastases

FDG uptake by inflammatory LN is a frequent source of false-positives, reverting into comparably low positive predictive value and specificity of FDG-PET.[10,11] The additional value of PET in detecting LN metastasis is demonstrated by Figure 5. Since we did not classify FNA of FDG-avid LN as clinically relevant information, the vast majority of ARI retrieved from hybrid PET imaging did not have clinically relevant information (Figure 3). In our study, only 4/16 (25.0%) metabolically active lymph nodes revealed clinically relevant information. Lymph nodes were found with clinically relevant information only in restaging examinations. However, one might argue that the presence of FDG-avid lymph nodes might alert the clinician and promote a more thorough clinical staging of the neck.

4.5 | Distant metastases

Overall, approximately 13.8% of all patients with head and neck cancer have DM at initial presentation 13.8%.[37] Furthermore, approximately 10% of patients with head and neck cancer develop metachronous DM within 1 year after initial diagnosis, and 20% within 5 years.[11,37] For sinonasal tumors in particular, Ozturk et al. recently reported a 24% rate of DM at initial presentation, with lung, bone, and liver being mainly affected.[26] Examples are shown in Figures 5 and 7. Owing to dedicated MR pulse sequences,

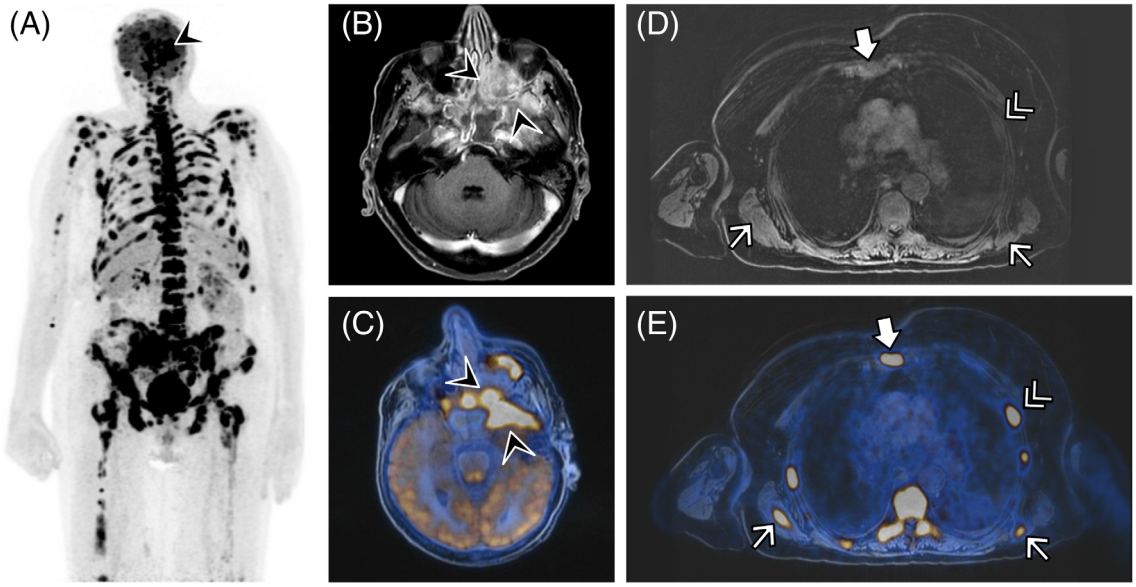

FIGURE 7 Initial FDG-PET/MRI and synchronous sinonasal/neck MRI staging examination of an 81-year-old female patient with sinonasal undifferentiated carcinoma (SNUC): (A) Whole-body maximum intensity projection of PET shows an intensely FDG-avid sinonasal tumor (black arrow) with FDG-avid soft tissue metastases and disseminated FDG-avid bone metastases. (B) Axial contrast-enhanced, fat-suppressed T1-weighted MR image and (C) FDG-PET/MRI show a large sinonasal tumor expanding into the orbit (black arrow). (D) Whole-body MRI and (E) fused FDG-PET/MRI demonstrate an FDG-avid soft tissue metastasis in bilateral latissimus dorsi muscles (white arrows), a bone metastasis in the sternum (bold white arrow) and bone metastasis in the sixth left rib (white double arrow). Owing to PET findings, the patient then underwent best supportive care. FDG-PET/MRI, 2-[^{18}F]-fluorodeoxy-D-glucose positron emission tomography/magnetic resonance imaging [Color figure can be viewed at wileyonlinelibrary.com]

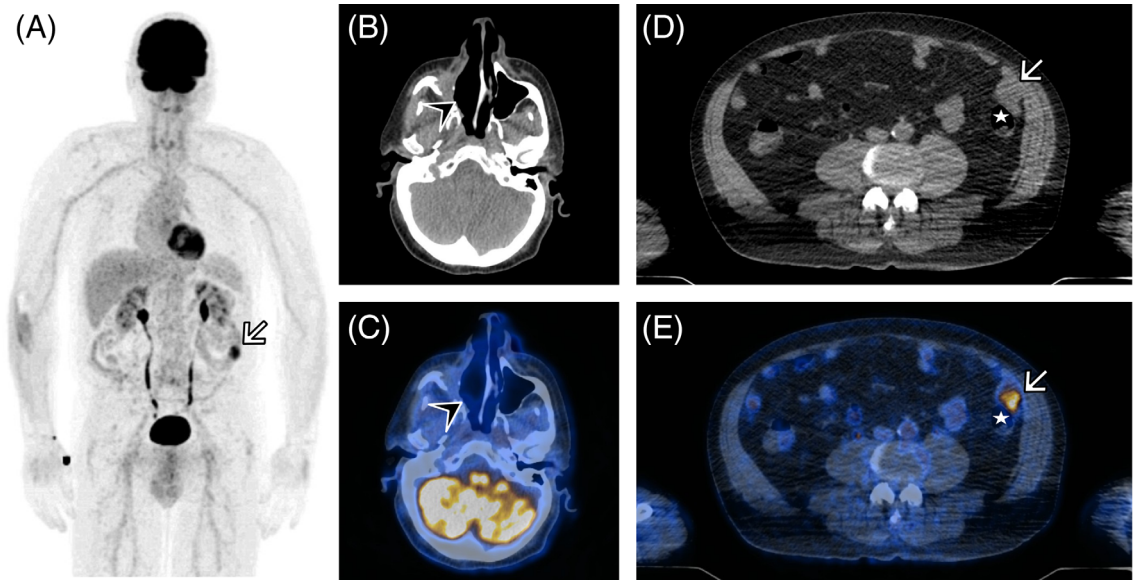

FIGURE 8 FDG-PET/CT restaging examination of a 67-year-old man with maxillary sinus squamous cell carcinoma after surgical tumor resection and adjuvant radiation therapy: (A) whole-body maximum intensity projection of PET shows a metabolically active tumor in the left-sided abdomen (white arrow). (B) nonenhanced CT and (C) axial fused FDG-PET/CT show no evidence of local recurrence of the sinonasal tumor (arrowhead), (D) nonenhanced CT and (E) axial fused FDG-FDG-PET/CT demonstrate a metabolically active tumor in the small bowel (white arrow), located anterior to the descending colon (white asterisk). This incidental finding turned out to be follicular lymphoma. CT, computed tomography; FDG-PET/CT, 2-[^{18}F]-fluorodeoxy-D-glucose positron emission tomography/computed tomography [Color figure can be viewed at wileyonlinelibrary.com]

detecting lung metastases with PET/MR is no longer problematic and has an increasing relevance in clinical routine in our center.[14,38,39] However, the incidence of DM in sinonasal tumors heavily depends on the histological entity, with sinonasal melanoma typically yielding the highest rate.[40] Unsurprisingly, detection of DM translated into clinically relevant information with adjustment of treatment (Figure 3). Of note, owing to immunotherapy, the detection of DM in patients with sinonasal melanoma does not always prompt a palliative treatment concept.[41]

4.6 | Second primary tumors and additional non-neoplastic findings

In a large recent meta-analysis addressing the risk of second primaries in 456 130 patients with head and neck cancer, Coca-Pelaz et al. found more than 5% synchronous second primaries (most often upper aero-digestive tract cancers, followed by lung cancer) and 13% metachronous second primaries within 2 years after initial diagnosis.[42] However, data on how exactly these second primaries were diagnosed (panendoscopy vs. imaging vs. clinical examination) were missing in 61% of all cases.[42] Wang et al. investigated FDG-PET/CT restaging examinations for different cancers and reported an overall rate of 8% proven synchronous second primaries.[43] For head and neck cancer, Britt et al. and Casselden et al. found synchronous second primaries in 3.2% (3/93) and 4.1% (12/293), respectively.[44,45] In our study, a second primary was found in 6.1% (6/96) of all PET examinations. Similar to the study by Gosh et al., lung cancer was the most common entity.[46] An example of a second primary (lymphoma) is given in Figure 8. The overall rate of incidental findings (second primary tumors and non-neoplastic incidental findings) in PET imaging is reported between 32.3% and 35.2%.[44,45] In our study, this rate was considerably lower (14.3%).

4.7 | Strengths and limitations

To the best of our knowledge, our study represents the largest one on ARI and clinically relevant information of whole-body hybrid PET imaging in the staging and restaging of primary sinonasal malignancies. Compared to regionalized neck MRI, whole-body hybrid PET imaging revealed complementary diagnostic information. The subcohort of patients undergoing PET/MRI, which offers whole-body imaging and regionalized neck MRI in one single examination (11/96 examinations), corroborates the feasibility of this new hybrid imaging modality in such a specific population. However, we are aware of some noteworthy limitations. First, a retrospective evaluation of ARI and clinically relevant information of PET imaging incorporates a significant risk of bias, since no tumor board simulation was performed. Second, our cohort was somewhat heterogeneous concerning histopathological tumor types, some being represented only by a few cases. Third, a study duration over two decades and PET examinations on different scanners harbor the risk of a natural evolution of knowledge over time. Fourth, the indication for restaging PET examinations included both symptomatic and asymptomatic patients, which leads to a blurred pretest probability. However, on the one hand, this limitation is only valid for 49/96 examinations (restaging group), and on the other hand, a heterogeneous profile of indications for restaging PET examinations reflects the clinical reality. And lastly, 17/74 patients underwent both staging and restaging examinations.

5 | CONCLUSIONS

PET imaging generated ARI and yielded clinically relevant information in a substantial proportion of patients. Clinically relevant information reflected a broad spectrum of therapeutic decisions, ranging from avoiding invasive procedures to commencing palliative treatment. Based on our findings, hybrid PET imaging should be encouraged in all patients with sinonasal tumors in addition to the mandatory regional sinonasal/neck MRI. Whole-body PET/MRI including such a regionalized MRI may be the optimal approach, integrating both examinations into a single one.

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Data available on request from the authors.

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