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Increased [⁶⁸Ga]Ga-SST uptake in the uncinata pancreatic process in new digital PET/CT machine and potential association with clinical and histologic factors in NET patients

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Abstract

Introduction: A physiological increase in the uptake of [⁶⁸Ga]Ga-labeled somatostatin analogues ([⁶⁸Ga]Ga-SST) PET tracers has been reported in the uncinata pancreatic process (UP) and might be even higher in latest generation of PET/CT scanners and might be falsely interpreted as NET. We aimed to investigate the uptake of UP in a large population of NET patients who underwent [⁶⁸Ga]Ga-SST PET/CT with digital SiPM detectors. We also explored potential associations between UP uptake and various clinical, imaging, and pathological factors routinely assessed in NET patients.

Methods: We analyzed all consecutive NET patients from July 2018 to June 2022 in this retrospective, single-center study. All patients underwent a [⁶⁸Ga]Ga-SST PET/CT scan on a digital SiPM PET/CT scanner. On visual analysis, we distinguished between normal linear and homogenous UP uptake or abnormal if otherwise. We compared SUV_{max/mean} in patients with normal UP uptake to those with abnormal UP uptake with suspicious NET lesions on contrast-enhanced CT (ce-CT) and according to the site of the primary NET (pancreatic NET vs. other), patient gender (female vs. male) and tumor grade (grade 1–2 vs. 3) using a Mann–Whitney test. We also assessed the correlation between SUV_{max/mean} values in UP with patients' age, primary NET Ki-67 counting, and its SUV_{max/mean}, TLA and MTV values.

Results: We included 131 NET patients with a total of 34 [⁶⁸Ga]Ga-DOTATATE PET/CT and 113 [⁶⁸Ga]Ga-DOTATOC PET/CT scans. An abnormal UP uptake was seen in 32 patients with 65.7% of suspicious NET lesion or extrinsic compression on morphological imaging. Normal UP uptake SUV_{max/mean} were measured in 115 [⁶⁸Ga]Ga-SST scans (78.2%) with normal UP uptake and without suspicious lesion on morphological imaging. We found an average SUV_{max} of 12.3 ± 4.1 for [⁶⁸Ga]Ga-DOTATATE and 19.8 ± 9.8 g/ml for [⁶⁸Ga]Ga-DOTATOC, hence higher than those reported in the literature [SUV_{max} 5 ± 1.6 to 12.6 ± 2.2 g/ml] with significant difference with abnormal UP uptake and between both PET tracers (both *p* < 0.01). Significant results were a higher

UP uptake on [⁶⁸Ga]Ga-DOTATOC in male patients ($p=0.02$) and significant associations between UP uptake on [⁶⁸Ga]Ga-DOTATOC and $SUV_{\text{max/mean}}$ of the primary tumor (ρ [0.337–0.363]; p [0.01–0.02]).

Conclusion: We confirmed a higher and very frequent UP uptake in latest SiPM-detector [⁶⁸Ga]Ga-SST PET/CT with an even higher uptake in patients that had [⁶⁸Ga]Ga-DOTATOC PET/CT. $SUV_{\text{mean/max}}$ were significantly higher in abnormal UP uptake but there were overlaps with UP SUV values for both [⁶⁸Ga]Ga-SST and a correlation to morphological imaging is crucial. Besides, significant associations between UP uptake and $SUV_{\text{mean/max}}$ of the primary NET as well as patients' gender were seen in the larger cohort of [⁶⁸Ga]Ga-DOTATOC patients suggesting that both physiological and pathological parameters could affect UP uptake.

Keywords: [⁶⁸Ga]Ga-DOTATOC, [⁶⁸Ga]Ga-DOTATATE, [⁶⁸Ga]Ga-SST PET/CT, Uncinate pancreatic process, NET, Physiological uptake, Digital SiPM PET/CT scanner

Introduction

[⁶⁸Ga]Ga-labeled somatostatin analogues PET tracers are routinely used in patients with neuroendocrine tumors (NET) to detect the primary tumor, to assess the extent of the disease, tumor heterogeneity or before peptide receptor radionuclide therapy to assess patients' eligibility (Bauckneht et al. 2020). Indeed, it is well-known that NET patients especially those with well-differentiated tumors have a higher expression in somatostatin receptor (SSTR) (Falconi et al. 2012). Various [⁶⁸Ga]Ga-labeled somatostatin analogues ([⁶⁸Ga]Ga-SST) PET tracers are available in routine practice, mainly [⁶⁸Ga]Ga-DOTATATE, [⁶⁸Ga]Ga-DOTATOC and [⁶⁸Ga]Ga-DOTANOC with different affinity for SSTR receptors (SSTR) (Johnbeck et al. 2014). For instance, [⁶⁸Ga]Ga-DOTATATE present a higher affinity for SSTR-2 whereas [⁶⁸Ga]Ga-DOTATOC has a higher affinity for SSTR-5 (Johnbeck et al. 2014). The increased physiological uptake of [⁶⁸Ga]Ga-SST in the uncinate pancreatic process (UP) has been confirmed in a recent meta-analysis which included six studies with a total of 684 patients and 829 PET/CT scans (Boughdad et al. 2021). This increased [⁶⁸Ga]Ga-SST activity in the head and the UP of the pancreas is related to differences in pathology with in particular a higher density in pancreatic polypeptide cells in comparison to the rest of the gland which express SSTR 1 to 4 (Wittingen and Frey 1974; Brabander et al. 2017). This finding should be accounted for when reporting abnormal finding in NET patients to avoid false positive and unnecessary investigations (Jacobsson et al. 2012). This is especially important since previous studies were done using older generation PET/CT scanners (Al-Ibraheem et al. 2011; Kunikowska et al. 2012) and latest-generation PET/CT with silicon photomultiplier (SiPM), time-of-flight and more efficient reconstruction algorithms that could affect [⁶⁸Ga]Ga-SST uptake of the UP (Ferretti et al. 2018). Therefore, in that setting we investigated the physiological uptake of UP in NET patients that underwent [⁶⁸Ga]Ga-SSTR PET/CT with either [⁶⁸Ga]Ga-DOTATATE or [⁶⁸Ga]Ga-DOTATOC PET tracers on a new digital SiPM PET/CT scan. We also explored associations between UP uptake for both PET tracers and various clinical, imaging, and pathological factors.

Materials and methods

Population

In this retrospective and single-center study, we included consecutive NET patients with biopsy proven that had [⁶⁸Ga]Ga-SST PET/CT scan from July 2018 to June 2022. For

patients that had multiple [^{68}Ga]Ga-SST PET/CT scans during the recruitment period only the first PET/CT for each PET radiotracer was assessed. Patients without a biopsy proven NET or for whom [^{68}Ga]Ga-SST PET/CT scan was of poor quality were not included in this study. The study was approved by the local IRB as pointed out below. Patients were recruited with respect to the general consent for the collection of clinical data. PET-CT image acquisition.

Imaging protocol

All patients had their PET/CT on a SiPM-detector PET/CT (Biograph VISION 600, Siemens Healthineers, Erlangen, Germany) either 60 or 90 min after injection of 2 MBq/kg of [^{68}Ga]Ga-DOTATATE or [^{68}Ga]Ga-DOTATOC respectively. PET/CT acquisition parameters were as follow: PET acquisition was done at 1.4 mm/s in flow mode with a low-dose CT scan (40mAs, 100 keV, 500 mm FoV, 1.4 mm increment, 2.0 mm slice thickness). PET/CT reconstruction parameters were as follow: TrueX and TOF (ultraHD-PET) reconstruction 4i5S, 440 image size and 2.00 mm Gaussian filter as per our institution protocol, all patients underwent a diagnostic contrast-enhanced CT (ce-CT) at the same time than the PET/CT scan, with arterial and portal acquisition times with technical parameters are as follow: 120 mAs, 120 kV, 1.00 mm slice thickness, Bv38 Kernel, 500 mm FoV, 0.6 mm increment. In patients that had a recent (< 1 month) dynamic contrast-enhanced abdominal MRI (DCE-MRI) or diagnostic ce-CT scan, concomitant ce-CT to [^{68}Ga]Ga-SST PET/CT scan was not systematically done as to limit patient radiation exposure.

PET-CT image analysis

For each patient and for both [^{68}Ga]Ga-SST PET tracers, UP uptake was assessed first on visual analysis classifying the uptake as either normal in case of linear and homogenous uptake regardless of its intensity or abnormal if otherwise. All UP uptakes were further investigated on ce-CT (or DCE-MRI) by a trained radiologist (MF), abnormal findings on morphological imaging were collected (lesion suspicious for pancreatic NET, tumor invasion in extensive pancreatic body tumor, extrinsic compression, post-surgical status with missing uptake or local inflammation). For all patients with normal uptake on visual analysis and without abnormal finding on morphological imaging, we measured SUV_{max} and SUV_{mean} ($\text{SUV}_{\text{max/mean}}$) in the UP. For patients with suspicious findings on morphological imaging such as a lesion suspicious of NET, extensive pancreatic body tumor, or extrinsic compression we also measured $\text{SUV}_{\text{max/mean}}$ for comparison to patients with normal UP uptake. We also collected data in cases where we were not able to measure UP uptake (post-surgery, etc.).

Statistical analysis

We used Mann–Whitney (M–W) test to compare $\text{SUV}_{\text{max/mean}}$ values between patients with normal UP uptake and those with suspicious findings after imaging analysis. We used M–W test to compare UP uptake according to the site of the primary NET (pancreatic NET vs. other), patient gender (female vs. male) and tumor grade (grade 1–2 vs. 3). Additionally, we used M–W test to compare patients' age between genders for both radiotracers. We also assessed the correlation between $\text{SUV}_{\text{max/mean}}$ values in UP

with patients' age, primary NET Ki-67 counting and $SUV_{max/mean}$, metabolic tumor volume (MTV) and tumor lesion activity (TLA) measured in the primary NET tumor using Spearman correlation. All statistical analyses were done using IBM SPSS statistics 27.0.1.0 (IBM® SPSS® Statistics) with p-value below 0.05 considered statistically significant.

Ethics

Our study was done according to the ethical standards stated in the Helsinki declaration and its later amendments. The "Commission cantonale d'éthique de la recherche sur l'être humain" (CER-VD) which is our internal review board for ethics approved this retrospective study with informed consent waiver allowing the inclusion of all patients that did not explicitly refuse their consent as per the local legislation at the time of the study (registration number: CER-VD-2018-01513).

Results

We included 131 NET patients in this retrospective study with a total of 34 [^{68}Ga]Ga-DOTATATE PET/CT and 113 [^{68}Ga]Ga-DOTATOC (Fig. 1). Sixteen patients had both a [^{68}Ga]Ga-DOTATATE and a [^{68}Ga]Ga-DOTATOC PET/CT scans. Patients' characteristics were similar for both radiotracers with a majority of midgut and pancreatic NETs (Table 1). On the initial visual analysis, we found 5/34 (15%) and 27/113 (23.9%) patients with abnormal UP uptake on a [^{68}Ga]Ga-DOTATATE and [^{68}Ga]Ga-DOTATOC respectively. On morphological imaging (ce-CT or DCE-MRI) 21 out of those 32 patients (65.7%) corresponded to suspicious NET lesion in or extending to the UP (43.8%) or had extrinsic compression (21.9%; Table 2, Figs. 2, 3). Additionally, 9 out of those 32 (28.1%) patients with abnormal missing uptake had pancreatic surgery. We should also note that one patient had active pancreatitis and one patient had no measurable uptake of the UP on [^{68}Ga]Ga-DOTATOC PET/CT. Ultimately, 29 out of 34 patients had a measurable normal uptake of the UP on [^{68}Ga]Ga-DOTATATE PET/CT and 86 out of 113 on [^{68}Ga]Ga-DOTATOC PET/CT (85.3% and 76.1% respectively; Table 2). All patients

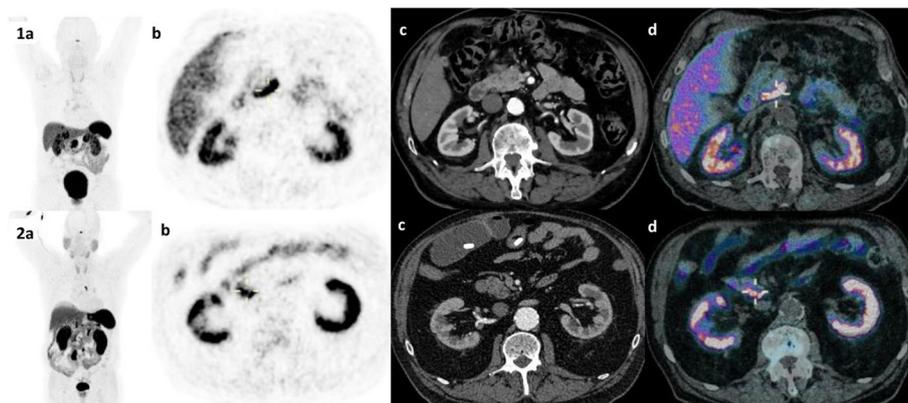


Fig. 1 **a** and **b** ^{68}Ga -DOTATOC and ^{68}Ga -DOTATATE PET/CT images showing normal uptake of the uncinate process of the pancreas in a 84-year man and 79-year man with both grade II mesenteric NET with metastatic spread [top (1) and bottom (2) images respectively]: **a** MIP image, **b** Axial PET slice, **c** Axial CE-CT slice and **d** fused axial PET/CT slice

Table 1 Patients' characteristics

Radiotracers	⁶⁸ Ga-DOTATATE	⁶⁸ Ga-DOTATOC
Number of patients	34	113
Gender	15 Females and 29 males	50 Females and 63 males
Age	63.2 yo [25.1–79.3]	62.2 yo [17.4–85.7]
Tumor grade	Grade 1 = 10 Grade 2 = 14 Grade 3 = 1 Unknown = 9	Grade 1 = 50 Grade 2 = 42 Grade 3 = 5 Unknown = 16
Ki-67%	6.1% [1–35]*	6.7% [1–35]*
Tumor type	Pancreatic NET = 13 Midgut NET = 14 Lung carcinoid tumor = 6 Other = 1	Pancreatic NET = 48 Midgut NET = 39 Lung carcinoid tumor = 12 Other = 14
TNM status	Metastatic spread = 24 LN involvement = 3 Isolated tumor = 6 Unknown = 1	Metastatic spread = 60 LN involvement = 14 Isolated tumor = 37 Unknown = 2

*[minimum–maximum value]

Table 2 Comparison of imaging findings on visual analysis and SUVmean/SUVmax measurements between ⁶⁸Ga-DOTATATE and ⁶⁸Ga-DOTATOC PET tracers

⁶⁸ Ga-SST PET tracers	⁶⁸ Ga-DOTATATE Mean ± SD [min–max]	⁶⁸ Ga-DOTATOC Mean ± SD [min–max]
Normal uptake on visual analysis	29	86
Abnormal uptake or missing	5 (2 absent post-surgery/1 LN extrinsic compression/2 Tumor extension*)	27 (7 absent post-surgery/6 extrinsic compression/12 Tumor with 1 tumor extension*/1 non measurable and 1 pancreatitis)
Uncinate process of the pancreas uptake	SUVmax	12.3 ± 4.1 [6.2–20.5]
	SUVmean	6.6 ± 2.1 [3.4–10.2]
Primary NET uptake	SUVmax	37.7 ± 25.4 [0–77]
	SUVmean	21.1 ± 14.6 [0–43]

*Patients with large pancreatic body NET that infiltrated the UP

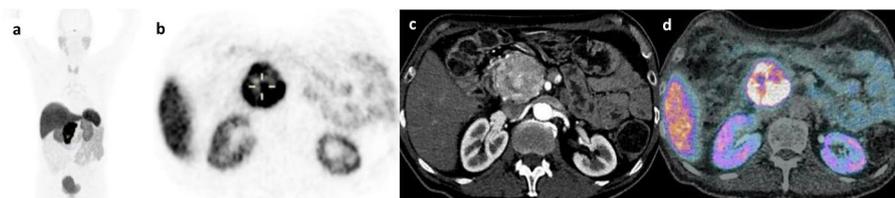


Fig. 2 ⁶⁸Ga-DOTATATE PET/CT images showing intense uptake of a grade II pancreatic NET of the uncinate pancreatic process in a 73 year man with; **a** MIP image, **b** Axial PET slice, **c** Axial CE-CT slice and **d** fused axial PET/CT slice

with normal UP uptake on visual analysis had no suspicious lesion on morphological imaging (ce-CT or DCE-MRI) When comparing $SUV_{max/mean}$ between patients with normal UP uptake and those with suspicious NET lesion for both [⁶⁸Ga]Ga-DOTATATE and [⁶⁸Ga]Ga-DOTATOC PET/CT scans we found significant differences (Fig. 4a–d; all $p < 0.001$; M-W test). Overall, there were significant differences between [⁶⁸Ga]

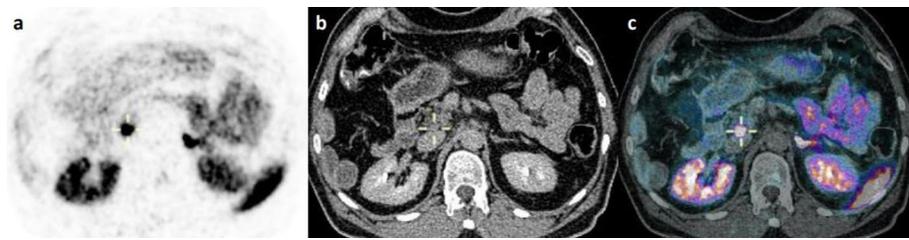


Fig. 3 ⁶⁸Ga-DOTATATE PET/CT images showing extrinsic compression of the uncinate process of the pancreas by a pre-cave adenopathy in a 55-year man with grade I midgut NET with metastatic spread; **a** Axial PET slice, **b** Axial CT slice and **c** Fused axial PET/CT slice

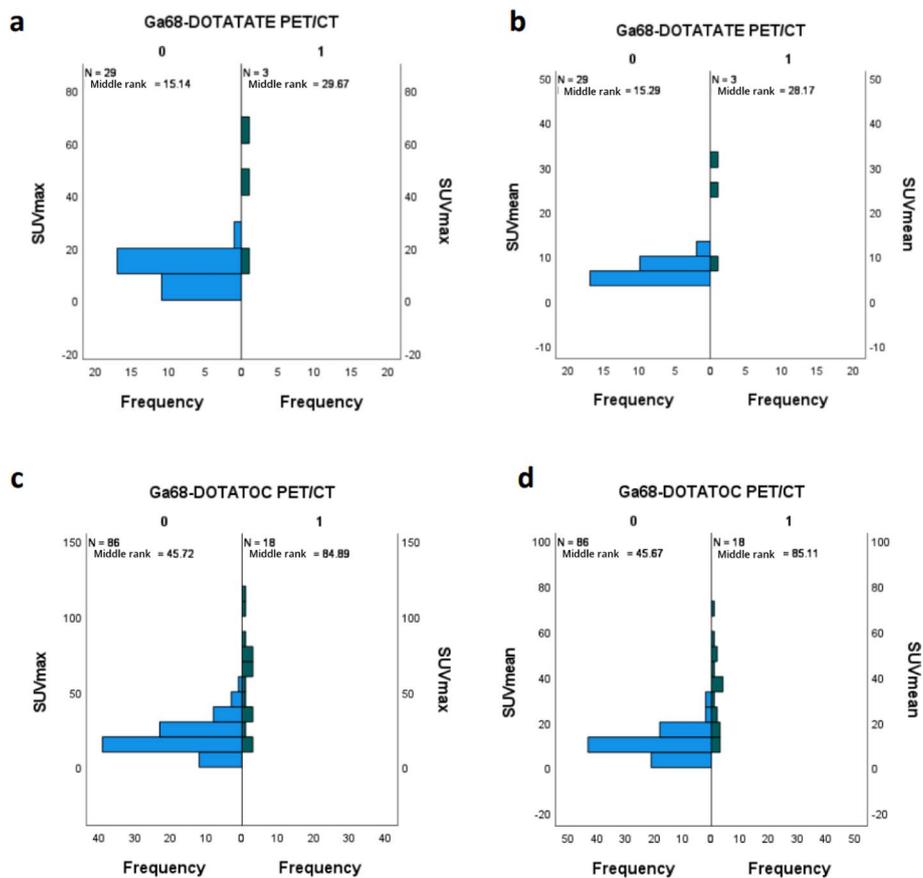


Fig. 4 **a, b, c** and **d** Graphs showing differences in SUVmax (**a/c**) and SUVmean (**b/d**) values between NET patients that had a ⁶⁸Ga-DOTATATE PET/CT (**a/b**) and those who had ⁶⁸Ga-DOTATOC PET/CT (**c/d**) scans

Ga-DOTATATE and [⁶⁸Ga]Ga-DOTATOC for UP SUV_{mean/max} with significantly higher values in patients that had a [⁶⁸Ga]Ga-DOTATOC PET/CT scan (Table 2, Fig. 5a, b; *p* < 0.001). This was confirmed in the 16 patients had both [⁶⁸Ga]Ga-DOTATATE and [⁶⁸Ga]Ga-DOTATOC PET/CT with 13 patients having normal UP on visual analysis without suspicious lesion on morphological imaging. Indeed, UP uptake was significantly higher when those patients underwent a [⁶⁸Ga]Ga -DOTATOC PET/CT with a mean SUV_{max} of 18.2 ± 7.4 [8.9–32.8] g/ml versus 11.1 ± 2.9 [6.8–16.5] g/ml on a [⁶⁸Ga] Ga-DOTATATE and 9.4 ± 3.9 [4.8–17.2] g/ml versus 6.0 ± 1.5 [3.9–8.5] g/ml for SUV

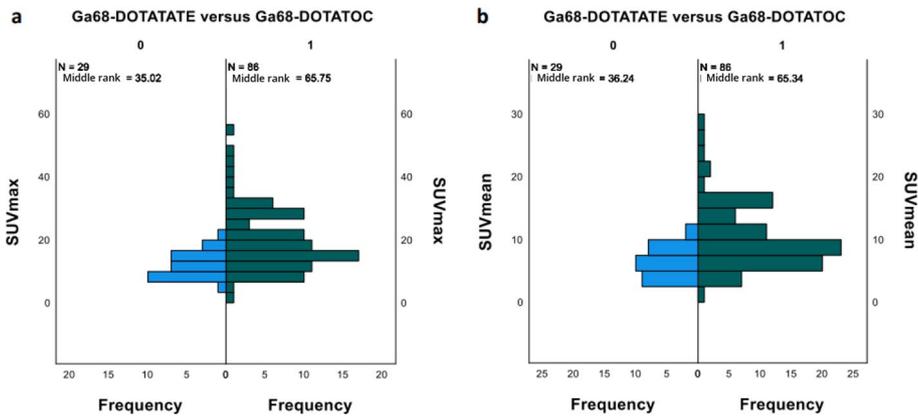


Fig. 5 **a** and **b** Graphs showing differences in SUVmax (**a**) and SUVmean (**b**) values between NET patients that had a ⁶⁸Ga-DOTATATE PET/CT and ⁶⁸Ga-DOTATOC PET/CT scans

SUV_{mean} ($p=0.04$ and $p=0.007$ respectively). There were no significant differences for SUVs according to patient gender for [⁶⁸Ga]Ga-DOTATATE though male patients had higher SUV_{mean} = 7.0 ± 2.2 [3.7–10.2] versus $6.0 \pm SD$ [3.4–9.6] and SUV_{max} = 13.4 ± 4.3 [7.1–20.1] versus 11 ± 3.6 [6.2–16.8] ($p=0.7$ and $p=0.5$ respectively). Conversely, significant differences in SUVs were found on [⁶⁸Ga]Ga-DOTATOC PET/CT with higher SUVs in male patients SUV_{mean} = 11.1 ± 4.9 [0.9–24] versus 9.5 ± 5.4 [3.8–28.6] and SUV_{max} = 21.4 ± 9.3 [1.8–45.3] versus 18.1 ± 10.2 [6.4–54] ($p=0.03$ and $p=0.02$ respectively). Interestingly, though no significant correlation was between UP SUV_{max/mean} and patients’ age males’ for both radiotracers, we noticed that male patients tended to be older than female patients in the [⁶⁸Ga]Ga-DOTATOC PET/CT cohort with a mean age of 65.4 [30.8–85] years versus 60 [17.4–85.7] years ($p=0.17$; M-W test). There were no significant differences for UP SUV_{max/mean} according to the location of the primary NET or tumor grade for both radiotracers ($p>0.05$). Additionally, there were no significant correlations between UP SUV_{max/mean} and Ki67 counting of the primary NET for both radiotracers ($p>0.05$). Conversely, on [⁶⁸Ga]Ga-DOTATOC PET/CT there were significant associations between UP SUV_{max/mean} and primary NET SUV_{max/mean} (ρ [0.337–0.363]; p [0.01–0.02]) but not with MTV or TLA ($p>0.05$).

Discussion

In this study we analyzed the uptake of the uncinate pancreatic process in a large population of NET patients using [⁶⁸Ga]Ga-DOTATATE or [⁶⁸Ga]Ga-DOTATOC on a digital SiPM PET/CT scanner. To our knowledge this is the first analysis being done in modern state-of-the-art ultrafast PET/CT scanners. We found that UP uptake was measurable in most patients that had [⁶⁸Ga]Ga-SST PET/CT scan, with 85.3% normal and measurable UP uptake on [⁶⁸Ga]Ga-DOTATATE and 76.1% on [⁶⁸Ga]Ga-DOTATOC. In our study, UP uptake was first assessed on visual analysis for both radiotracers and ultimately classified as either normal or abnormal based on ce-CT results as described above, confirming the usefulness of combining morphological and metabolic information (Bauckneht et al. 2020). Indeed, most patients with abnormal UP uptake on visual analysis that is 27.1% had a lesion suspicious of NET on ce-CT or presented with an extrinsic compression. As expected, SUV_{max/mean} values in abnormal UP, hence suspicious NET lesions

were significantly higher than in normal UP but overlaps between $SUV_{\max/\text{mean}}$ values were seen with a wide variation in SUVs values in UP, ranging for instance from 1.8 to 54 for SUV_{\max} in patients that underwent a ^{68}Ga Ga-DOTATOC PET/CT. In that setting, a combined reporting of findings on CT, especially ce-CT remained essential to confirm the absence of suspicious lesion especially additional NET lesion in agreement with recent guidelines (Bauckneht et al. 2020). Looking at the comparison of UP uptake according to the PET tracers we found significantly higher $SUV_{\max/\text{mean}}$ values in patients that had ^{68}Ga Ga-DOTATOC PET/CT scans. This finding could be explained by the differences in affinity for SST receptors previously reported in the literature but also in differences between acquisition times (Calabrò et al. 2020; Poeppel et al. 2011; Kabasakal et al. 2012). Indeed, per our institution protocols there was a difference in acquisition time after radiotracer injection between ^{68}Ga Ga-DOTATATE and ^{68}Ga Ga-DOTATOC with an earlier acquisition at 60 min for the former and 90 min for the latter, which likely affected the intensity of the uptake, hence $SUV_{\max/\text{mean}}$ values for both UP and the primary NET lesion (Novruzov et al. 2021; Nakamoto et al. 2016). In the subgroup of 16 patients that had both a ^{68}Ga Ga-DOTATATE PET/CT and a ^{68}Ga Ga-DOTATOC significantly higher $SUV_{\max/\text{mean}}$ values were also found in the latter. Looking at the immunochemistry, it has been reported that SSTR2 expression is low in pancreatic peptide cells present in the UP which might explain the lower uptake of ^{68}Ga Ga-DOTATATE which has a higher affinity for SSTR2 in comparison to ^{68}Ga Ga-DOTATOC (Portela-Gomes et al. 2000). However, SSTR5 which present a higher affinity for ^{68}Ga Ga-DOTATOC was almost absent in pancreatic polypeptide cells and thus could not explain the differences in uptake (Portela-Gomes et al. 2000). We should however mention that those immunochemistry findings were reported in an older study using rabbit polyclonal antibodies and though they were specific for each human STTR, it might be interesting to reassess those findings with current methods (Portela-Gomes et al. 2000). Nevertheless, those differences should be accounted for in NET patients during the follow-up as they tend to have multiple ^{68}Ga Ga-SST PET/CT scans and the PET tracer might vary within and across institutions. Besides, we investigated which factors could influence UP uptake in NET patients as this is the main population of patients referred for ^{68}Ga Ga-SST PET/CT scans in routine practice (Bauckneht et al. 2020; Chen et al. 2018). We did not find significant correlation between UP uptake and patients' age in both ^{68}Ga Ga-SST tracers though due to an atrophy of the acinar tissue with age leading to a higher density of pancreatic polypeptide cells' islets with an appearance of pseudo-hyperplasia in the UP which could hypothetically expect an increase ^{68}Ga Ga-SST UP uptake (Portela-Gomes et al. 2000). By contrast, patients' gender did significantly affect UP uptake with significantly higher $SUV_{\max/\text{mean}}$ UP values in male patients in comparison to female patients on ^{68}Ga Ga-DOTATOC PET/CT scans. It would be interesting to assess if it relates to difference of SST receptor on immunohistochemistry according to patients' gender though no data was available in the literature. Additionally, we should also point out that although it was not significant male patients also tended to be older than female patients and maybe in a larger cohort of patients a significant association between UP uptake could be seen (Wittingen and Frey 1974). The lack of difference found on ^{68}Ga Ga-DOTATATE might be also explained by the small number of patients in this cohort. Besides, the only significant associations found with $SUV_{\max/\text{mean}}$ in the

UP were moderate but significant correlations with $SUV_{\max/\text{mean}}$ in the primitive NET. The significance of this association is still unclear, but it would be interesting to confirm this association in future cohorts of NET patients.

We previously investigated the uptake of UP in a recent meta-analysis which assessed the incidental uptake of UP and included 4 studies with [^{68}Ga]Ga-DOTATOC and [^{68}Ga]Ga-DOTATATE tracers with 59.1% and 13.9% incidental UP uptake respectively (Boughdad et al. 2021; Jacobsson et al. 2012; Al-Ibraheem et al. 2011; Kunikowska et al. 2012; Mapelli et al. 2014). The lower incidence of UP uptake in those studies might be explained by the difference in PET/CT scanner technology as all those studies were done in older generation whereas all scans in our study were acquired in a new digital SiPM PET/CT (Boughdad et al. 2021). Indeed, a detectable uptake of UP was visible and measurable on all patients with both [^{68}Ga]Ga-SST PET tracers except for 11 patients including 9 patients that surgery with a total 78.2% of physiological uptake and 14.3% abnormal uptake with a suspicious NET lesion on ce-CT. Looking, at SUV values we had in the [^{68}Ga]Ga-DOTATOC cohort a mean SUV_{\max} value of 19.9 ± 9.8 g/ml versus $SUV_{\max} = 9.8 \pm 12.5$ g/ml in the study by Al-Ibraheem et al. (Boughdad et al. 2021; Al-Ibraheem et al. 2011). Similarly, in the [^{68}Ga]Ga-DOTATATE cohort the mean SUV_{\max} value was of 12.3 ± 4.1 g/ml versus in the study $SUV_{\max} 9.2 \pm 3.3$ g/ml in the study by Kunikowska et al. (Boughdad et al. 2021; Kunikowska et al. 2012). The increased detection of UP uptake on [^{68}Ga]Ga-SST PET/CT scans is likely explained in our study by the implementation of better detector resolution, faster time-of-flight, and better sensitivity of the latest-generation of SiPM-detector PET/CT leading to improved recovery coefficient and increased uptake seen both on visual analysis and semi-quantitative SUVs measurements (Ferretti et al. 2018; Calabrò et al. 2020; Ashrafinia et al. 2017). Thus, as previously mentioned, the intensity of the UP uptake should not be used alone to distinguish between physiological and pathological UP uptake but in addition to ce-CT. Nevertheless, our findings should be useful to nuclear physicians in routine practice by providing a range for $SUV_{\text{mean}/\text{max}}$ values in normal UP for [^{68}Ga]Ga-DOTATATE and [^{68}Ga]Ga-DOTATOC PET/CT in the absence of morphological abnormalities on ce-CT, as SiPM-detector PET/CT scanners are spreading across institutions. UP uptake may no longer have to be considered as an incidental finding but a caveat that should be accounted for when reporting [^{68}Ga]Ga-SST PET tracers scans in NET patients as it was seen in 78.2% of the patients in our study. The combined assessment of molecular imaging and ce-CT is essential to guide additional investigations in case of visually abnormal or excessively high [^{68}Ga]Ga-SST UP uptake especially if a biopsy is required.

We should also mention some limitations in our study. The first limitation was the smaller numbers of patients who had [^{68}Ga]Ga-DOTATATE in comparison to a [^{68}Ga]Ga-DOTATOC PET/CT, but patients' characteristics were similar with predominantly male patients with pancreatic and midgut NETs, with similar Ki-67 counting and comparison of UP $SUV_{\max/\text{mean}}$ was statistically significant. Indeed, only patients that had their scans on a new SiPM-detector PET/CT were included and we had a change in [^{68}Ga]Ga-SST PET tracer used in routine practice in our institution, leading to a limited time of 9 months for the recruitment of patients that had [^{68}Ga]Ga-DOTATATE PET tracer before we started using [^{68}Ga]Ga-DOTATOC. Indeed, [^{68}Ga]Ga-DOTATOC was produced by our radiopharmacists in a dedicated facility in our

institution. Secondly, in patients with abnormal UP uptake and with suspicious NET lesions seen on CE-CT no follow-up pathological data was collected as most patients had a history of biopsy proven NET and were at a metastatic stage at the time of PET/CT, that was 70.6% of the patients that had a [⁶⁸Ga]Ga-DOTATATE PET/CT scan and 53.1% of the patients that had [⁶⁸Ga]Ga-DOTATOC PET/CT scan. Finally, several parameters were thought to be outside of the scope of this study and were not explored such as the impact on the Krenning score according to the tumor grade, presence of a tumor predisposition syndrome and whether the primary NET lesion was secretory or not. Indeed, the data collection was retrospective and some of this information were missing but it might be interesting to investigate their influences on prospective studies.

Conclusion

We confirmed the higher and very frequent UP uptake in new SiPM-detector PET/CT scanners for both [⁶⁸Ga]Ga-DOTATATE and [⁶⁸Ga]Ga-DOTATOC in comparison to older generation PET/CT scanners. This is of interest, as we found that SUV values could be very high without any suspicious lesions seen on morphological imaging. Indeed, though abnormal UP uptake with suspicious NET lesions on ce-CT had significantly higher $SUV_{max/mean}$ than those measured in the UP there were overlaps for both [⁶⁸Ga]Ga-SST tracers. Thus, a high SUV_{max} value in the UP is not sufficient to suspect the presence of NET and a correlation to morphological imaging is crucial. This should be clearly understood by nuclear medicine physician while reporting [⁶⁸Ga]Ga-SST PET/CT imaging to limit unnecessary investigations in NET patients. Besides, significant associations between UP uptake and $SUV_{max/mean}$ of the primary NET as well as patients' gender were found in the largest cohort of [⁶⁸Ga]Ga-DOTATOC patients suggesting that both physiological and pathological parameters could affect UP uptake.

Abbreviations

[⁶⁸ Ga]Ga-SST	[⁶⁸ Ga]Ga-labeled somatostatin analogues
ce-CT	Contrast-enhanced CT
DCE-MRI	Dynamic contrast-enhanced abdominal–Magnetic resonance imaging
MTV	Metabolic tumor volume
NET	Neuroendocrine tumors
SSTR	Somatostatine receptor
SiPM	Silicon photomultiplier
TLA	Tumor lesion activity
UP	Uncinate pancreatic process

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Author contributions

The authors confirm contributions to the paper as follows: study conception: SB; data collection: MF and SB; analysis and interpretation of results: SB. The first draft of the manuscript was written by SB and all authors are responsible for reported research and have participated in the drafting or revising this manuscript as submitted.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Our study was done according to the ethical standards stated in the Helsinki declaration and its later amendments. The “Commission cantonale d'éthique de la recherche sur l'être humain” (CER-VD) which is our internal review board for ethics approved this retrospective study with informed consent waiver allowing the inclusion of all patients that did not explicitly refuse their consent as per the local legislation at the time of the study (registration number: CER-VD-2018-01513).

Consent for publication

Informed consent waiver allowing the inclusion of all patients that did not explicitly refuse their consent as per the local legislation at the time of the study (registration number: CER-VD-2018-01513).

Competing interests

The authors declare no competing interests.

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References

- Al-Ibraheem A, Bundschuh RA, Notni J, Buck A, Winter A, Wester HJ, Schwaiger M, Scheidhauer K (2011) Focal uptake of ⁶⁸Ga-DOTATOC in the pancreas: pathological or physiological correlate in patients with neuroendocrine tumours? *Eur J Nucl Med Mol Imaging* 38:2005–2013
- Ashrafinia S, Mohy-ud-Din H, Karakatsanis NA, Jha AK, Casey ME, Kadrmas DJ, Rahmim A (2017) Generalized PSF modeling for optimized quantitation in PET imaging. *Phys Med Biol* 62(12):5149
- Bauckneht M, Albano D, Annunziata S, Santo G, Guglielmo P, Frantellizzi V, Branca A, Ferrari C, Vento A, Mirabile A, Nappi AG, Laudicella R (2020) Somatostatin receptor PET/CT imaging for the detection and staging of pancreatic NET: a systematic review and meta-analysis. *Diagnostics* 10(8):598
- Boughdad S, Meyer M, Prior JO, Fernandes V, Allenbach G, Kamani C, Jreige M, Albano D, Bertagna F, Nicod-Lalonde M, Schaefer N, Treglia G (2021) Prevalence of physiological uptake in the pancreas on somatostatin receptor-based PET/CT: a systematic review and a meta-analysis. *Clin Transl Imaging* 9(4):353–360
- Brabander T, Teunissen J, Kwekkeboom D (2017) Physiological uptake in the pancreatic head on somatostatin receptor scintigraphy using [¹¹¹In-DTPA] octreotide: incidence and mechanism. *Clin Nucl Med* 42(1):15–19
- Calabrò D, Argalia G, Ambrosini V (2020) Role of PET/CT and therapy management of pancreatic neuroendocrine tumors. *Diagnostics* 10(12):1059
- Chen SH, Chang YC, Hwang TL, Chen JS, Chou WC, Hsieh CH, Yeh TS, Hsu JT, Yeh CN, Tseng JH, Chen TC, Yen TC (2018) ⁶⁸Ga-DOTATOC and ¹⁸F-FDG PET/CT for identifying the primary lesions of suspected and metastatic neuroendocrine tumors: a prospective study in Taiwan. *J Formosan Med Assoc* 117(6):480–487
- Falconi M, Bartsch DK, Eriksson B, Klöppel G, Lopes JM, O'connor JM, Salazar R, Taal BG, Vullierme MP, O'toole D (2012) ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms of the digestive system: well-differentiated pancreatic non-functioning tumors. *Neuroendocrinology* 95(2):120–134
- Ferretti A, Chondrogiannis S, Rampin L, Bellan E, Marzola MC, Grassetto G, Gusella S, Maffione AM, Gava M, Rubello D (2018) How to harmonize SUVs obtained by hybrid PET/CT scanners with and without point spread function correction. *Phys Med Biol* 63(23):235010
- Jacobsson H, Larsson P, Jonsson C, Jussing E, Grybäck P (2012) Normal uptake of ⁶⁸Ga-DOTA-TOC by the pancreas uncinuate process mimicking malignancy at somatostatin receptor PET. *Clin Nucl Med* 37(4):362–365
- Johnbeck CB, Knigge U, Kjær A (2014) PET tracers for somatostatin receptor imaging of neuroendocrine tumors: current status and review of the literature. *Future Oncol* 10(14):2259–2277
- Kabasakal L, Demirci E, Ocak M, Decristoforo C, Araman A, Ozsoy Y, Uslu I, Kanmaz B (2012) Comparison of ⁶⁸Ga-DOTA-TATE and ⁶⁸Ga-DOTANOC PET/CT imaging in the same patient group with neuroendocrine tumours. *Eur J Nucl Med Mol Imaging* 39:1271–1277
- Kunikowska J, Królicki L, Pawlak D, Zerizer I, Mikolajczak R (2012) Semiquantitative analysis and characterization of physiological biodistribution of ⁶⁸Ga-DOTA-TATE PET/CT. *Clin Nucl Med* 37(11):1052–1057
- Mapelli P, Tam HH, Sharma R, Aboagye EO, Al-Nahhas A (2014) Frequency and significance of physiological versus pathological uptake of ⁶⁸Ga-DOTATATE in the pancreas: validation with morphological imaging. *Nucl Med Commun* 35(6):613–619
- Nakamoto Y, Ishimori T, Sano K, Temma T, Ueda M, Saji H, Togashi K (2016) Clinical efficacy of dual-phase scanning using ⁶⁸Ga-DOTATOC-PET/CT in the detection of neuroendocrine tumours. *Clin Radiol* 71(10):1069–e1
- Novruzov F, Aliyev A, Wan MYS, Syed R, Mehdi E, Aliyeva I, Giammarile F, Bomanji JB, Kayani I (2021) The value of [⁶⁸Ga]Ga-DOTA-TATE PET/CT in diagnosis and management of suspected pituitary tumors. *Eur J Hybrid Imaging* 5(1):1–13
- Poeppel TD, Binse I, Petersenn S, Lahner H, Schott M, Antoch G, Brandau W, Bockisch A, Boy C (2011) ⁶⁸Ga-DOTATOC versus ⁶⁸Ga-DOTATATE PET/CT in functional imaging of neuroendocrine tumors. *J Nucl Med* 52(12):1864–1870
- Portela-Gomes GM, Stridsberg M, Grimelius L, Öberg K, Janson ET (2000) Expression of the five different somatostatin receptor subtypes in endocrine cells of the pancreas. *Appl Immunohistochem Mol Morphol* 8(2):126–132
- Wittingen J, Frey CF (1974) Islet concentration in the head, body, tail and uncinuate process of the pancreas. *Ann Surg* 179(4):412

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