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Imaging of small intestine neuroendocrine neoplasms: Is SSTR PET the holy grail?

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Management of patients with neuroendocrine neoplasms (NENs) is a complex task and warrants referral of these patients to high volume centers with appropriate expertise in order to ensure favorable outcomes and appropriate follow-up. PET/CT becomes increasingly important in almost every step of patient management and outcomes. In the recent years, somatostatin receptor (SSTR) PET/CT using [^{68}Ga]-labeled somatostatin analogs ([^{68}Ga]Ga-SSAs) has proven to be successful in the evaluation of well-differentiated GEP-NENs, and it is also tightly connected to the use of targeted radiotherapy (PRRT) in inoperable and progressive metastatic cases. Therefore, it has been deemed as a first « grab » tracer in many consensus and position statements made by expert panels (*1, 2*). There has been global enthusiasm and excitement surrounding [^{68}Ga]Ga-SSA, including its added value compared to previously used ^{99m}Tc- or ^{111}In-based somatostatin receptor scintigraphy, its worldwide availability, and on-site production. This, however, has thrown the baby out of the bathwater in regard to [^{18}F]FDOPA PET. SSTR PET is clearly superior to [^{18}F]FDOPA PET for certain NENs and should be positioned at the forefront of pancreatic NENs (except for insulinomas, where data are still scarce and GLP1-receptor imaging appears to be more promising). However, is this also the case for small intestine NENs (SI-NENs)?

The selection of a specific radiopharmaceutical is important in distinguishing between diagnostic and theranostic settings. In a theranostic setting (a time and cost-effective approach), SSTR PET is used as an evidence-based companion diagnostic for selecting candidates who will likely benefit from PRRT, regardless of tumor origin. ^{18}F-FDG also has great potential for predicting outcomes to PRRT. What is the role [^{18}F]FDOPA in the evaluation of NENs if it cannot be used in a theranostic setting and has the potential to be more costly? Is the data, usage, and popularity of [^{68}Ga]Ga-SSAs enough to disqualify or abandon [^{18}F]FDOPA in countries where it is approved, available, and previously used? Can we truly abandon [^{18}F]FDOPA when we have seen it be more specific, have higher resolution, and have less SI activity compared to [^{68}Ga]Ga-SSA? Are both tracers similar in terms of sensitivity? Until recently, no study has specifically addressed this issue. Three historical studies have compared [^{18}F]FDOPA PET/CT and SSTR PET/CT in a small case series (*3-5*). Although interesting, each study is hampered by mixing NENs of various origins with a very small number of pathologically proven SI-NETs that may have decreased the performance of [^{18}F]FDOPA.

More recently, three studies have compared [^{18}F]FDOPA PET/CT and SSTR PET/CT in GEP-NENs, focusing on SI-NENs (*6-8*). Although retrospective, these studies provide novel insights and analysis on optimal evaluation of patients with rare diseases. Our group retrospectively evaluated [^{68}Ga]Ga-DOTATOC and Carbidopa assisted [^{18}F]FDOPA PET/CT in 41 patients with well differentiated ileal NETs (*7*). All patients' primary tumors were previously resected and all were investigated by PET for restaging. [^{18}F]FDOPA PET/CT had a better detection rate than [^{68}Ga]Ga-DOTATOC (96% vs 80%, $p<0.001$). In a total of 605 lesions, 458 (76%) were positive on both modalities, 25 (4%) by [^{68}Ga]Ga-DOTATOC only, and 122 (20%) by [^{18}F]FDOPA PET/CT only, corresponding to liver, peritoneal or lymph node metastases. Due to recruitment of patients with extensive metastases, both examinations yielded a similar management plan. Ansquer *et al*. have compared [^{18}F]FDOPA PET/CT (without Carbidopa premedication) and [^{68}Ga]Ga-DOTANOC in a series of 30 patients with SI-NENs (*6*). PET/CT studies were performed for initial staging in 9 cases and restaging in the remaining cases. [^{18}F]FDOPA PET/CT detected significantly more lesions than [^{68}Ga]Ga-DOTANOC with sensitivities of 95.5% and 88.2%, respectively. [^{18}F]FDOPA PET/CT detected more lesions in 9 cases with 22 additional lesions from variable locations. [^{68}Ga]Ga-DOTANOC was superior to [^{18}F]FDOPA PET/CT in only 3 cases with a limited number of additional lesions. In concordant liver metastases, tumor-to-liver uptake ratio was superior in [^{18}F]FDOPA compared to [^{68}Ga]Ga-DOTANOC in 63% of cases. A more favorable uptake ratio in [^{18}F]FDOPA could potentially explain the higher detection rate of liver metastases. It is expected that SSTR antagonists could perform better than agonists in this setting. Lastly, Veenstra *et al.* have compared [^{18}F]FDOPA (under Carbidopa) and [^{68}Ga]Ga-DOTATOC PET/CT in 45 NEN patients, including 23 (51%) SI-NENs, followed by pancreatic, large intestine, lung, ovarium, and NENs of unknown origin. Considering the subgroup of SI-NENs, [^{18}F]FDOPA detected more lesions than [^{68}Ga]Ga-DOTATOC in 16/23 patients (70%) whereas [^{68}Ga]Ga-DOTATOC detected more lesions than [^{18}F]FDOPA in only 4/23 patients.

Taken collectively, these results show that both SSTR PET/CT and [^{18}F]FDOPA PET/CT are excellent for disease staging and restaging, although [^{18}F]FDOPA PET/CT is frequently the most sensitive tracer. Therefore, there is no reason to disqualify its use in the face of simplifying paradigms. This conclusion aligns with the 2017 EANM guidelines for PET/CT imaging of NENs (*9*). Additionally, [^{18}F]FDOPA PET/CT provides a specific molecular signature linked to serotonin secretion and potential underlying biological characteristics. This has been illustrated in pheochromocytoma and paraganglioma, where imaging phenotype is tightly linked to tumor location (sympathetic versus parasympathetic paraganglia; adrenal versus extra-adrenal), genetic status, biochemical phenotype, and size, with all being intimately interconnected (*10*). In conclusion, [^{18}F]FDOPA PET/CT can perform better than SSTR PET in SI-NETs. These findings could be important in a diagnostic setting, prior to major operations such as hepatic cytoreductive surgery or liver transplantation.

Compliance with ethical standards

NA

Conflicts of interest

The authors have nothing to disclose.

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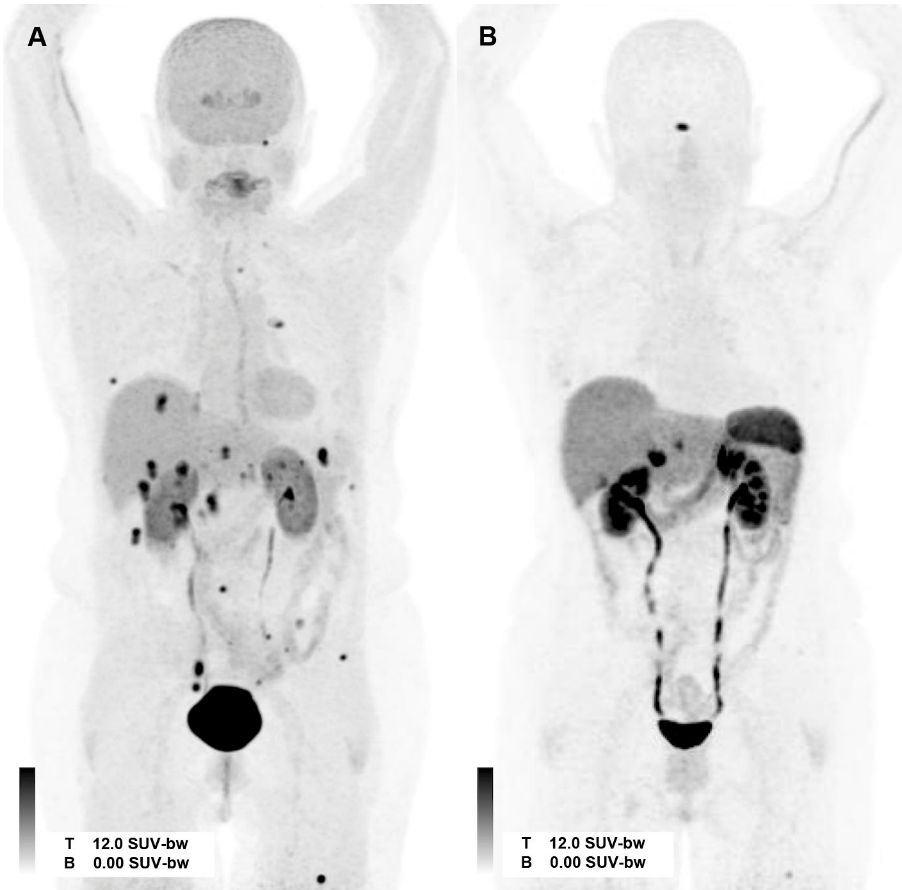

Figure 1. Illustrative image showing the superiority of [^{18}F]FDOPA (A) over [^{68}Ga]Ga-DOTATOC (B) in a patient with SI-NET.

SUV scale: SUV-bw for body weight normalized SUV, T for top, B for bottom.