Clinical Imaging 56 (2019) 146–154

Contents lists available at ScienceDirect

Clinical Imaging

journal homepage: www.elsevier.com/locate/clinimag

Molecular Imaging and Nuclear Medicine

Molecular imaging and therapy of somatostatin receptor positive tumors

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ARTICLE INFO

Keywords:
Neuroendocrine tumors
Somatostatin receptors
^{68}Ga-DOTATATE PET/CT

ABSTRACT

Somatostatin receptors (SSTR) are upregulated in the cells of origin that define numerous neuroendocrine neoplasms. PET imaging with ^{68}Ga-DOTATATE allows specific targeting of SSTR2A, a single species of SSTR receptor, which is commonly overexpressed in a variety of gastroenteropancreatic neuroendocrine tumors, as well as pulmonary carcinoid and head and neck tumors. Due to more specific targeting of SSTR2 as well as lower radiation dose, shorter study length, ability to quantify uptake, and lower cost, ^{68}Ga-DOTATATE has demonstrated superior imaging attributes when compared to ^{111}In-pentetreotide. As with any novel imaging modality, dedicated training, increasing experience and staying up-to-date with scientific publications are required to provide optimal patient care. The purpose of this review is to summarize the current state of the art in SSTR-targeted molecular imaging and discuss ongoing and future potential diagnostic and therapeutic applications.

1. Introduction: SSTR targeted radionuclides for molecular imaging

Somatostatin is a peptide hormone playing a role in neurotransmission, hormone secretion, and cell proliferation [1]. Somatostatin receptors (SSTR) are widely expressed on the surface of neuroendocrine cells. Molecular imaging targeting SSTR has been used since the 1980s to evaluate neuroendocrine tumors. In recent years, important developments have been made allowing the transition from gamma imaging to positron emission tomography (PET) and molecular therapy [2].

Octreotide is an 8-amino-acid synthetic somatostatin analog [2] and pentetreotide is a DTPA conjugate of octreotide. Indium-111 (^{111}In) pentetreotide has been widely used for SSTR-targeted gamma imaging since 1983. The imaging protocol includes planar whole-body and SPECT/CT at 24 h and optional imaging at 4 and 48 h following intravenous injection of 222 MBq (6 mCi) of ^{111}In-pentetreotide in adults [3]. Significant disadvantages of ^{111}In-pentetreotide imaging include the cumbersome protocol necessitating multiple acquisitions over several days, high radiation dose [4], and relatively poor resolution [1].

Gallium-68 (^{68}Ga) labeling of somatostatin analogs has allowed the advent of SSTR targeted PET/CT [5]. Important advantages of PET/CT over gamma imaging include greater convenience for patients with image acquisition at 1 h following injection due to shorter half-life of 68 min for ^{68}Ga (compared to 2.8 days for ^{111}In), improved resolution resulting in higher sensitivity and specificity, and decreased radiation dose [6]. Additionally, while bowel cleansing for patients is recommended to utilize octreotide, this is not required for imaging with ^{68}Ga. Furthermore, imaging with ^{68}Ga-labeled SSTR-targeted tracer is more cost-effective compared to ^{111}In-pentetreotide gamma imaging [6].

The compound 1,4,7,10-tetraazacyclododecane-1,4,7,10- tetraacetic acid (DOTA) has been used to chelate ^{68}Ga to the peptide hormone. Various ^{68}Ga-labeled somatostatin analogs have entered clinical practice worldwide, including DOTATATE, DOTATOC, and DOTANOC. The three radiotracers differ in their affinity to SSTR subtypes. While all have good affinity for SSTR subtypes 2 and 5, ^{68}Ga-DOTANOC also has high affinity for SSTR3 [7]. ^{68}Ga-DOTATATE exhibits the highest binding affinity for SSTR2 (100 times higher than that of ^{111}In-Octreotide), which is the receptor most often expressed in tumors of neuroendocrine origin [8]. The U.S. Food and Drug Administration approved ^{68}Ga-DOTATATE for clinical use in June 2016, while ^{68}Ga-DOTATOC is currently under review as of this writing. ^{68}Ga-DOTATOC has been approved by the European regulatory bodies and has been used clinically throughout the European Union for the past ten years [9].

Distinct foci of ^{68}Ga-DOTATATE avidity on PET imaging are considered positive for the expression of somatostatin receptors [10], and may represent tumors of neuroendocrine origin. ^{68}Ga-DOTATATE also has specific limitations that need to be taken into account in its

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https://doi.org/10.1016/j.clinimag.2019.04.006
Received 13 March 2019; Accepted 13 April 2019

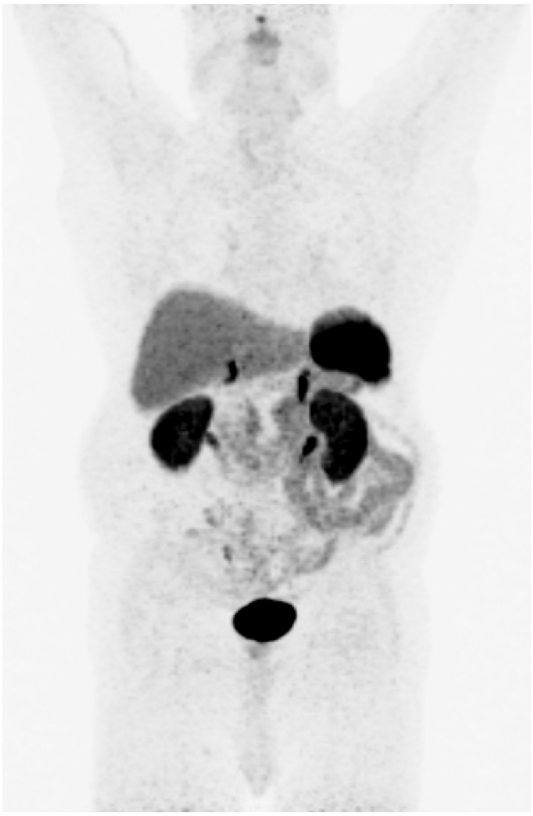

Fig. 1. Physiologic distribution of ^{68}Ga-DOTATATE PET as visualized on a 3D Maximum intensity projection (MIP) image. Physiologic avidity is expected in organs with a high density of somatostatin receptor type 2 (SSTR2). Highest avidity is visualized in the spleen, adrenal glands, kidneys and pituitary gland. Moderate avidity is visualized in the liver, thyroid and salivary glands. There is variable avidity throughout the gastrointestinal tract.

interpretation. Physiologic avidity in organs with a high number of SSTR2 such as the pituitary gland, spleen, adrenal glands, liver, kidneys, and urinary bladder (Fig. 1) can often make it difficult to distinguish benign from malignant areas [11]. The head of the pancreas, particularly the uncinate process, has been frequently cited as a potential source of misinterpretation [12]. The high number of pancreatic polypeptide cells in this region can lead to increased physiologic uptake of either a focal or diffuse pattern; this can be problematic as neuroendocrine tumors often arise in the pancreas and duodenum. Other important causes of false-positives on ^{68}Ga-DOTATATE imaging include inflammation or infection [11]. Activated lymphocytes or macrophages in areas of radiation pneumonitis, gastritis, sequelae of surgeries, reactive lymphadenopathy, granulomatous disease, thyroiditis or thyroid nodular disease can exhibit increased uptake. Uptake of accessory spleens or splenules could also be interpreted as lymph nodes of a worrisome nature [10].

A number of false-negatives can be detected on ^{68}Ga-DOTATATE imaging as well. Some high-grade neuroendocrine tumors do not exhibit any SSTR expression [10]. Chemotherapy can significantly modify receptor expression as well. Increased physiologic uptake in certain organs throughout the body can also conceal a mild pathologic SSTR uptake. Because of the possible difficulties in the interpretation of benign versus malignant SSTR uptake, correlation of PET imaging with that of CT imaging is often necessary to ensure more conclusive diagnosis of neuroendocrine tumors [13].

2. ^{68}Ga DOTATATE PET/CT in the imaging of neuroendocrine tumors

A number of studies have demonstrated high diagnostic accuracy of ^{68}Ga-DOTATATE PET/CT in the imaging and diagnosis of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) [5]. ^{68}Ga-DOTATATE was found to be superior to octreotide as well as conventional imaging at localization and extent-of-disease evaluation of primary neuroendocrine tumors [14]. In a separate systematic review and meta-analysis, ^{68}Ga-DOTATATE revealed numerous additional tumor foci on a per-lesion basis [1], and influenced the choice of treatment. These findings suggest that ^{68}Ga-DOTATATE represents a superior imaging approach as the primary evaluation tool in patients with suspected neuroendocrine malignancy, allowing improved extent-of-disease evaluation and guiding management [9].

2.1. ^{68}Ga-DOTATATE PET/CT in the imaging work-up of gastroenteropancreatic neuroendocrine tumors

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are the second most common digestive malignancy [15], and include pancreatic neuroendocrine tumors, and carcinoid tumors in the small intestine, rectum, colon, pancreas, and appendix. The age-adjusted incidence of these tumors increased from 1.09 per 100,000 in 1973 to 6.98 per 100,000 in 2012 [16]. While many GEP-NETs occur spontaneously, many can also be part of inherited familial syndromes such as multiple endocrine neoplasia (MEN) type 1, Von-Hippel Lindau syndrome (VHL), tuberous sclerosis, and neurofibromatosis type 1 (NF-1). GEP-NETs may be hormonally functioning or nonfunctioning, and can have a particular clinical presentation based on where they originate. While distal colonic and rectal tumors are commonly clinically silent, carcinoid tumors within the jejunum, ileum, and cecum can present with features of the classic carcinoid syndrome [17]. Symptoms often include watery diarrhea, flushing, and right-sided heart disease. Pancreatic neuroendocrine tumors may secrete peptide hormones, that can cause clinical syndromes such as insulinoma syndrome, gastrinoma syndrome, and glucagonoma syndrome [18]. The TNM staging classification is used to approximate the survival outcomes. While early-stage GEP-NETs generally carry a favorable long-term prognosis, the prognosis of patients with metastatic GEP-NETs is largely determined by tumor grade and primary site [19]. Surgery is the primary treatment for localized tumors [15]. Cross-sectional imaging including both CT and MRI is widely used in clinical practice throughout the abdomen and pelvis [20]. Although ^{111}In-pentetreotide has been used to evaluate for tumor SSTR expression in the past, recent studies have demonstrated the superiority of ^{68}Ga-DOTATATE PET/CT over other imaging modalities. Thus, while ^{68}Ga-DOTATATE had a primary GEP-NET detection rate of 95.2%, octreotide and conventional imaging detection rates were much lower (30.9% and 45.6%, respectively) [21]. Patient management decisions were significantly affected in approximately 33% of patients who received ^{68}Ga-DOTATATE imaging [2]. ^{68}Ga-DOTATATE was also demonstrated to be helpful in identifying GEP-NETs in patients who had no evidence of disease on anatomical imaging or endoscopic evaluation, and had no biochemical evidence of malignancy [22]. Additionally, ^{68}Ga-DOTATATE has been shown to be highly accurate in the identification of recurrent GEP-NETs [8], and has proven particularly useful in our own institutional experience (Figs. 2 and 3). In summary, these findings have prompted the revision of the Society of Nuclear Medicine and Molecular Imaging practice guidelines, recommending ^{68}Ga-DOTATATE as the initial imaging modality for the diagnosis of GEP-NETs [23].

2.2. ^{68}Ga-DOTATATE PET/CT in the imaging work-up of pulmonary neuroendocrine tumors

Tumors of neuroendocrine origin comprise 20% of all lung

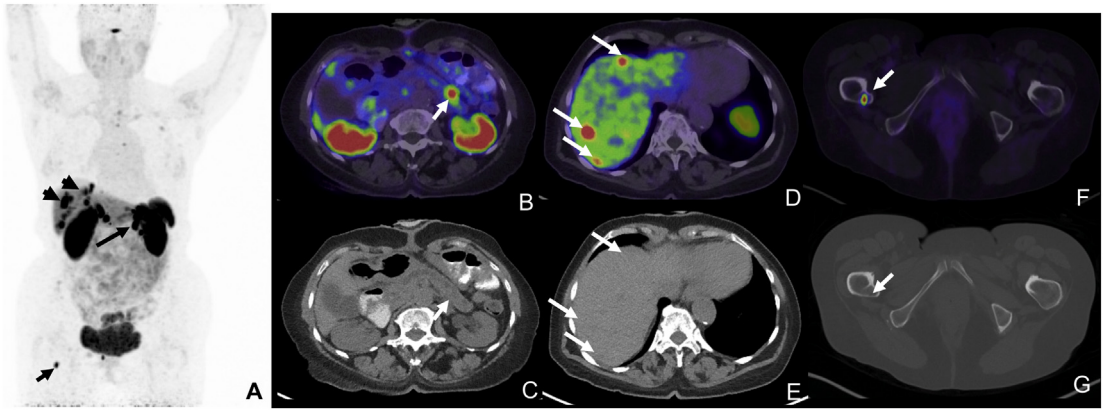

Fig. 2. 74 year-old woman with history of colorectal neuroendocrine carcinoma previously treated with right hemicolectomy, now with abdominal pain and suspected recurrence, who underwent ^{68}Ga DOTATATE PET/CT. A, 3D Maximum intensity projection image demonstrates a focus of intense DOTATATE avidity at the level of the pancreas (long arrow), as well as hepatic (arrowheads) and osseous (short arrow) lesions, suspicious for metastases. Fused axial PET/CT at the level of the pancreas localizes the intensely DOTATATE avid focus to the pancreatic tail (arrow in B) without definite lesion and stable main pancreatic duct dilatation on nonenhanced CT (arrow in C). Fused axial PET/CT at the level of the liver demonstrates intensely DOTATATE avid bilobar hepatic lesions suspicious for metastases (arrows in D), poorly delineated on noncontrast CT (arrows in E). An intensely DOTATATE avid lesion in the right femoral lesser trochanter (F) demonstrates no definite CT correlate (G) and is suspicious for metastasis.

malignancies in adults [24]. These include low-grade typical carcinoid, intermediate-grade atypical carcinoid, high-grade large cell neuroendocrine carcinoma, and small cell lung carcinoma [25]. There is strong literature evidence demonstrating that tobacco smoking is the most common cause of lung cancer, and both small cell and large cell neuroendocrine carcinomas are found almost entirely in patients with a strong smoking history [26]. Patients typically present with recurrent pneumonia, cough, hemoptysis, and chest pain [27]. While typical carcinoid tumors are indolent with a favorable prognosis, atypical carcinoid tumors are associated with an increased risk for metastasis [28]. Surgery is the mainstay of treatment for these tumors. Large cell neuroendocrine carcinomas and small cell lung cancers can demonstrate early local invasion, as well as locoregional and distal metastatic spread, conveying worse prognosis [29]. Pathology is the gold standard in the diagnosis of pulmonary neuroendocrine tumors [25]. Conventional imaging is particularly limited in the differentiation between typical and atypical carcinoid tumors. While ^{111}In-pentetreotide has been used in the past for diagnosis of pulmonary neuroendocrine tumors, PET/CT with ^{68}Ga-DOTA-peptides offers several advantages including an increased affinity for SSTR2, improved resolution, and decreased examination time [30]. In one study, ^{68}Ga-DOTATATE PET/CT detected 100% of typical carcinoid tumors, while atypical carcinoid tumors and high-grade large cell neuroendocrine tumors had less ^{68}Ga-DOTATATE avidity [27]. Furthermore, ^{68}Ga-DOTA-NOC detected a higher number of malignant lesions compared to CT scan only and thus provided additional information in approximately 82% of patients [31]. By and large, ^{68}Ga-DOTA-peptides have a very high detection rate for pulmonary neuroendocrine carcinomas, and have added clinical value in our own institutional experience (Fig. 4).

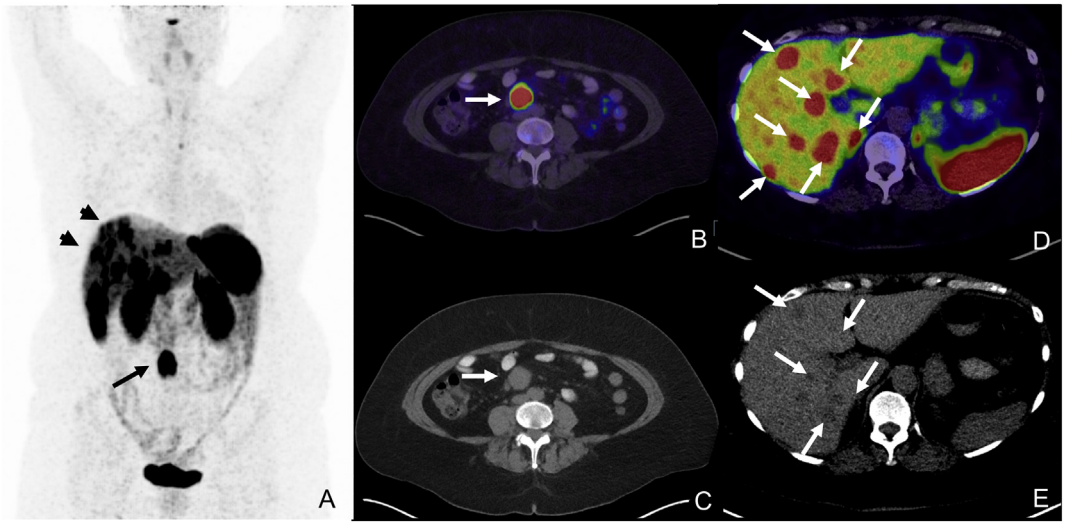

Fig. 3. 53 year-old woman who initially presented with epigastric pain was found to have metastatic well differentiated carcinoid tumor after liver biopsy. Due to elevated levels of serum chromogranin A, serotonin and urine 5-Hydroxyindoleacytic acid, a ^{68}Ga DOTATATE PET/CT was performed for further evaluation A, 3D Maximum intensity projection image demonstrates an intensely DOTATATE avid mid abdominal mass (arrow), as well as hepatic lesions suspicious for metastases (arrowheads). Fused axial PET/CT and noncontrast axial CT at the level of the mid abdomen localize the intensely DOTATATE avid soft tissue mass to the mid mesentery (arrows in B and C). Fused axial PET/CT and noncontrast axial CT at the level of the liver demonstrate intensely DOTATATE avid bilobar hepatic foci (arrows in D), some of them without clear CT correlate while others correlate to ill-defined hypodense lesions on noncontrast CT (arrows in E), compatible with metastatic involvement.

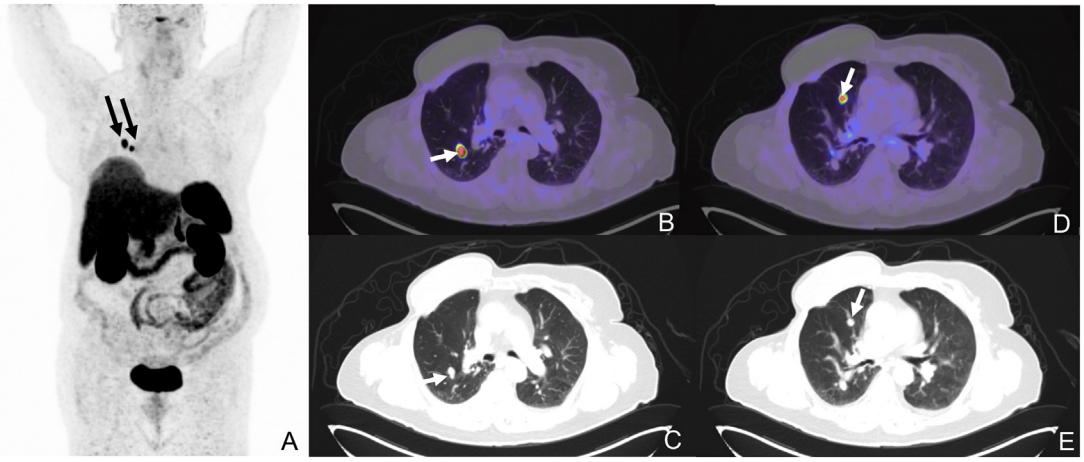

Fig. 4. 76 year-old woman, former heavy smoker, with history of adenocarcinoma of the lung and atypical pulmonary carcinoid status post right upper lobectomy, remote history of bilateral mastectomies for breast cancer and thyroid cancer status post thyroidectomy, with enlarging lung nodules who underwent ^{68}Ga DOTATATE PET/CT for further evaluation. A 3D Maximum intensity projection image demonstrates two intensely DOTATATE avid right pulmonary nodules (arrows in A). Fused axial PET/CT and noncontrast axial CT localize the intensely DOTATATE avid nodules to the right middle lobe (arrow in B and C) and right lower lobe (arrows in D and E), suspicious for recurrent atypical pulmonary carcinoid.

2.3. ^{68}Ga-DOTATATE PET/CT in the imaging work-up of pheochromocytoma

Pheochromocytomas are neuroendocrine tumors that originate from the adrenal medulla [32]. They have an incidence of 2 to 8 per million, occur in 0.2% to 0.6% of hypertensive patients and constitute up to 5% of adrenal incidentalomas [33]. Although only about 25% of these tumors are malignant, even benign pheochromocytomas are linked with high morbidity and mortality rates due to hypertension and cardiovascular disease. Patients with classic tumor syndromes such as NF-1, MEN2, VHL disease syndromes are at higher risk to develop a pheochromocytoma [34]. Patients may present with the classic triad of headache, diaphoresis, and palpitations along with hypertension, though many patients actually remain asymptomatic [35]. In terms of diagnosis, plasma-free metanephrines are the first-line screening test [36]. Once biochemical hypersecretion is detected, imaging is then used to locate the tumor. While CT is recommended as the modality of choice for anatomic imaging, MRI is suggested for children, pregnant women, or patients with the truly biochemical silent phenotype or metastatic disease [37]. When the risk of metastasis or recurrent disease is high, or when treatment with radiotherapy is being considered, functional imaging with Iodine-123 (^{123}I) metaiodobenzylguanidine (MIBG) scintigraphy is used. If metastatic disease is confirmed in a patient, the use of Fluorine-18 fluorodeoxiglucose (^{18}F-FDG) PET/CT is utilized [36]. In our institutional experience, ^{68}Ga-DOTATATE PET/CT had superior clinical utility in a case of recurrent metastatic pheochromocytoma (Fig. 5). In adult patients with a pheochromocytoma due to a mutation in the succinate dehydrogenase (SDH) gene, ^{68}Ga-DOTATATE had a 96.8% overall detection rate which proved to be superior to anatomic imaging with CT/MRI and other functional imaging scans (^{18}F-FDG, ^{18}F-FDOPA, and ^{18}F-FDA PET/CT) [38]. ^{68}Ga-DOTATATE had a similar detection rate of 97.6% in sporadic adult tumor cases and in patients with the truly biochemically silent phenotype [39]. Yet, ^{68}Ga-DOTATATE PET/CT proved to be inferior to ^{18}F-FDOPA PET/CT and ^{18}F-FDA PET/CT in the detection rate of pheochromocytoma in adult patients related to polycythemia or due to FH or MAX mutations. Based on these results, ^{18}F-FDOPA PET/CT and ^{18}F-FDA PET/CT are still considered the molecular imaging modality of choice for those specific tumoral subtypes. Studies comparing ^{68}Ga-DOTATATE PET/CT and ^{18}F-FDA PET/CT in the pediatric population have also produced variable results, and the utilization of more than one functional imaging modality is recommended for these patients [40]. Additional studies in this arena are needed to further define the appropriate tools for diagnosis of pheochromocytoma and paraganglioma.

2.4. ^{68}Ga-DOTATATE PET/CT in the imaging work-up of meningioma

Meningiomas are the most common primary intracranial tumor, accounting for 36.8% of all primary brain tumors with an incidence rate of 8.14 per 100,000 and a median age of 66 years. Meningiomas are classified based on histologic criteria established by the World Health Organization (WHO) into grade I (benign), grade II (atypical) and grade III (anaplastic). While grade 1 meningiomas carry a favorable prognosis, WHO grade II and III meningiomas are more aggressive with associated 5-year survival rates of 78% and 44%, respectively. Surgical resection constitutes the standard of care, and outcomes are graded using the Simpson classification. Gross-total resection (Simpson Grades 1–3) remains the prevalent objective of surgery for meningioma and has been demonstrated in approximately 50%–66% of patients in surgical series. Subtotal resection (Simpson Grades 4 and 5) has been found to convey substantially higher rates of progression, even in benign meningioma, and is associated with poorer progression-free survival (PFS) and overall survival (OS). Postoperative MRI appearance is the gold standard for adjuvant treatment planning, specifically stereotactic radiosurgery (SRS), in patients in whom gross total resection cannot be achieved and/or the tumor is classified as WHO grade II/III by histopathologic criteria. However, MR imaging can have limited sensitivity and specificity in cases of infiltrative or “en plaque” lesions, in cases of osseous or parenchymal invasion, as well as in cases of recurrent meningioma with presence of postsurgical/post-treatment scarring. In our institutional experience, ^{68}Ga-DOTATATE PET/MRI improved extent-of-disease evaluation in patients with meningioma, particularly in patients who had previously undergone radiation, and was superior to ^{18}F-FDG PET (Figs. 6, 7 and 8). Imaging with SSTR ligands has been demonstrated to have utility in the detection and target volume definition in meningiomas, specifically prior to radiation therapy, however has not yet entered clinical practice. ^{68}Ga-DOTATATE PET/CT has been shown to be far superior to ^{111}In-Octreotide scintigraphy imaging due to its improved target-to-background ratio and improved specificity, as ^{68}Ga-DOTATATE specifically targets SSTR2. Furthermore, ^{68}Ga-DOTATATE PET/CT was found to have an improved detection rate of transosseous meningiomas utilizing ^{68}Ga-DOTATATE PET/CT as compared to contrast-enhanced MRI, with higher sensitivity and accuracy [41].

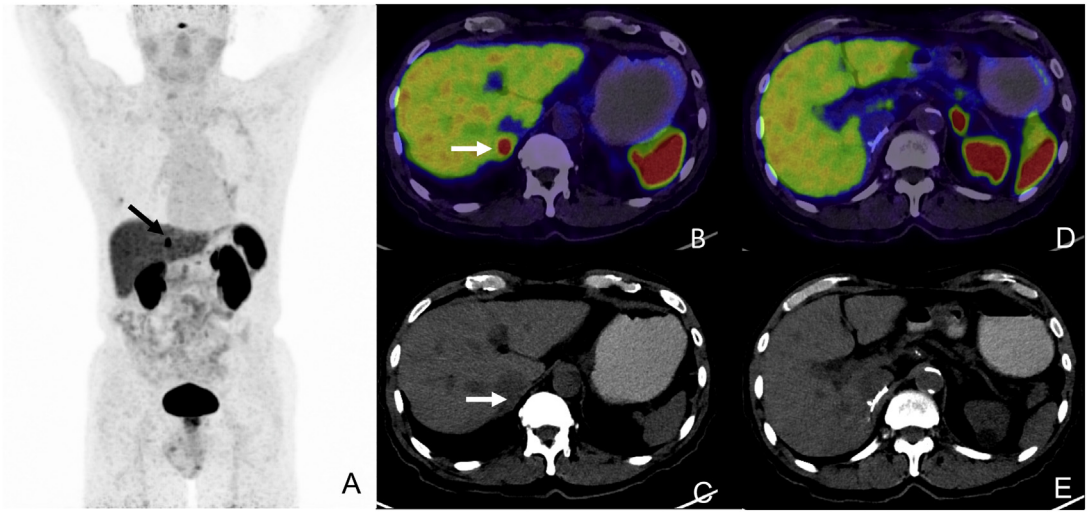

Fig. 5. 78 year-old man with remote history of pheochromocytoma of the right adrenal gland status post resection, multiple resections of recurrence in the retroperitoneum, and rising levels of plasma metanephrines who underwent ^{68}Ga DOTATATE PET/CT for follow-up evaluation. A, 3D Maximum intensity projection image demonstrates an intensely DOTATATE avid focus in the right upper quadrant of the abdomen (arrow in A). Fused axial PET/CT at the level of the upper abdomen localizes this lesion posterior to the right diaphragmatic crus (arrow in B), correlating to soft tissue density inseparable from the right posterior hepatic lobe on nonenhanced CT (arrow in C), highly suspicious of tumor recurrence. Fused axial PET/CT and nonenhanced CT images (D and E) of the abdomen more caudally in the region of surgical clips demonstrate no evidence of DOTATATE avidity or residual soft tissue respectively in the adrenalectomy bed.

2.5. ^{68}Ga-DOTATATE PET/CT in the imaging work-up of esthesioneuroblastoma

Esthesioneuroblastoma (ENB) is an exceedingly rare malignant neuroectodermal tumor arising from the olfactory neuroepithelium in the superior nasal cavity. The incidence of ENB is estimated at 0.4 cases per million in the general population, accounting for about 3% of sinonasal tumors. While ENB can occur at any age, a bimodal distribution is typical with maximum incidences in the second and sixth decades of life. Clinically, ENB commonly presents with epistaxis, nasal obstruction, and nasal discharge, with less common clinical manifestations including diplopia, proptosis, visual and olfactory disturbances, and headaches. ENB is known to have a slow onset of symptoms, favorable 5-year survival ranging between 57 and 93%, and propensity for delayed locoregional recurrence, for which long-term follow-up is warranted. Cervical nodal metastases are known to occur in 10–44% of patients. Staging is determined by the Kadish classification: Stage A for patients presenting with tumor restricted to the nasal cavity, Stage B for patients presenting with tumor involving the nasal cavity and at least one sinus, Stage C for patients presenting with tumor extending beyond the paranasal cavities and modified Kadish Stage D for patients presenting with cervical lymph node metastases. Grading is determined by the Hyams system, in which ENB is stratified into four grades ranging from most differentiated (grade I) to least differentiated (grade IV) on the basis of mitotic activity, nuclear pleomorphism, rosette formation, necrosis, disorganized architecture, and sparse fibrillary matrix. Pseudorosettes (Homer Wright) are present in 30% of cases. The risk of recurrence is highest amongst those with poor prognostic factors such as high Hyams grade, advanced Kadish staging, intracranial extension, and positive resection margins. Current treatment options include resection, adjuvant radiotherapy and/or chemotherapy; however, due to its rarity and location, determining the optimal treatment for ENB has been challenging, and no standardized treatment guidelines have been established to date. ^{68}Ga-DOTATATE avidity has been reported in a case of ENB [42] as well as its treatment with ^{177}Lu-DOTA-analogs [43] [44]. In our institutional experience, ^{68}Ga-DOTATATE PET/CT improved detection of nodal metastases in metastatic ENB (Fig. 9).

2.6. ^{68}Ga-DOTATATE PET/CT in the imaging work-up of hemangioblastoma

Hemangioblastoma (HBM) is a highly vascular tumor which occurs both sporadically and in patients with VHL. HBMs are WHO grade 1 tumors, most commonly found in the cerebellum, brainstem and spinal

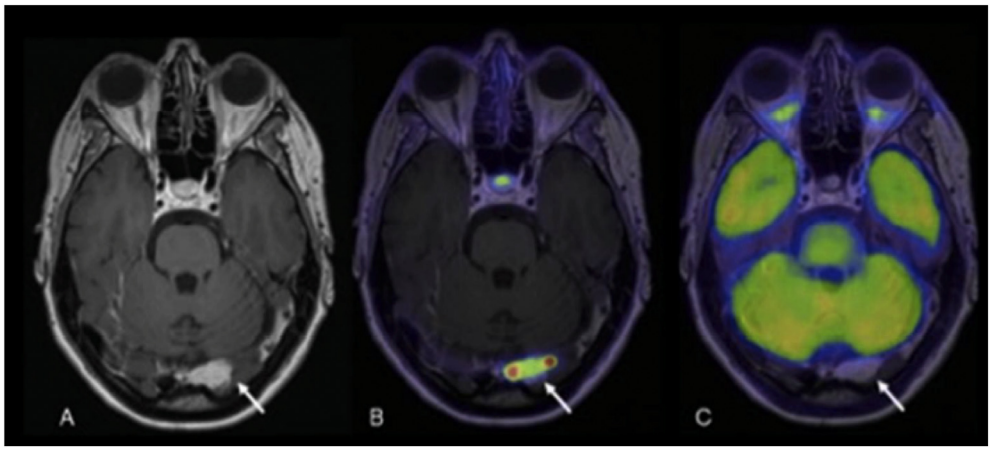

Fig. 6. 53 year-old woman with a history of resected left cerebellar hemangioblastic meningioma and subsequent recurrence. A. Postcontrast T1-weighted MRI demonstrates an enhancing mass in the left transverse sinus (arrow in A). B. ^{68}Ga-DOTATATE PET/MRI confirms this mass to be intensely avid (arrow in B), C. This mass demonstrates only minimal uptake on ^{18}F-FDG PET/MR (arrow in C), thus illustrating the limitations of ^{18}F-FDG PET in the distinction of recurrent meningioma from post-treatment change.

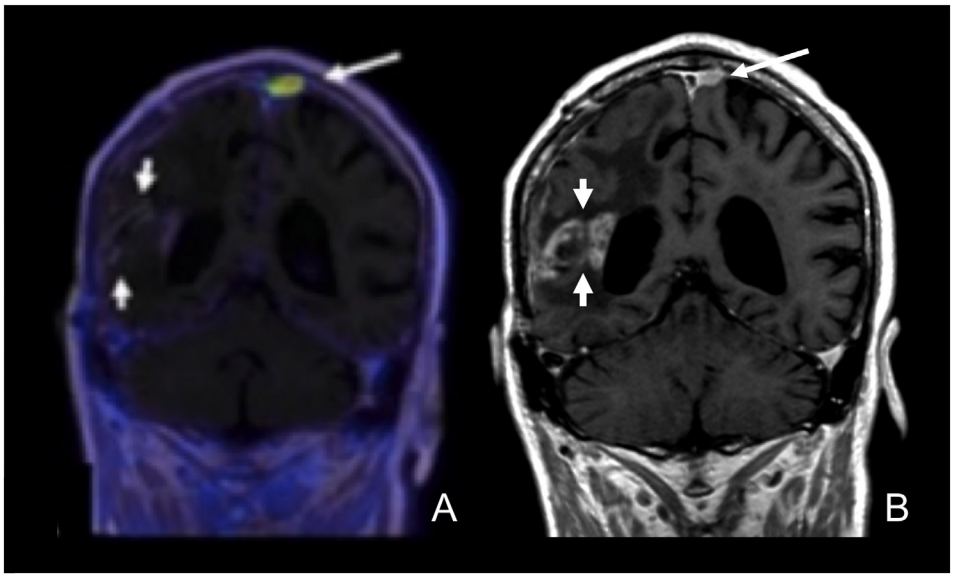

Fig. 7. 76 year-old man with a history of right frontotemporal atypical meningioma status post resection and subsequent stereotactic radiosurgery who presented with left-sided numbness and left-sided peripheral field cut. A. Fused PET/T1-postcontrast MRI B. T1-postcontrast MRI alone. There is an intensely ^{68}Ga-DOTATATE avid, vividly enhancing extra-axial mass along the left high parietal convexity, compatible with a meningioma (long arrow in A and B). Multifocal ill-defined enhancement (short arrows) demonstrated minimal associated DOTATATE avidity, thus most compatible with postradiation change.

cord, as well as elsewhere in the body, including the kidneys, liver and pancreas. HBMs are the most common posterior fossa primary tumor in middle-aged or older adults, with headache as the most common presenting symptom. Surgery represents the primary therapeutic approach. ^{68}Ga-DOTATATE avidity has been reported in a case of VHL-related retinal HBM [45], and further studies are needed to evaluate clinical utility.

2.7. ^{68}Ga-DOTATATE PET/CT in the imaging work-up of medulloblastoma

Medulloblastoma (MB) is the most common malignant pediatric brain tumor, with 75% occurring in patients under 10 years of age and most diagnosed by 5 years of age. MBs are invasive, highly cellular, embryonal tumors with four distinct recognized molecular subgroups: WNT (wingless), SHH (sonic hedgehog), group 3 and group 4, each with distinct cells of origin, molecular features, clinical features, therapeutic approaches, and locations. WNT tends to occur in the cerebellar peduncle or cerebellar pontine angle cistern. SHH tends to occur at the lateral cerebellar hemispheres and groups 3 and 4 tend to arise in the midline at the 4th ventricle. These tumors are WHO grade IV with four distinct histologic subtypes: classic, desmoplastic, MB with extensive nodularity, and large cell/anaplastic. MBs most commonly present with ataxia, signs of increased intracranial pressure and macrocephaly in infants with open sutures. ^{68}Ga-DOTATATE avidity has been reported in a case of cerebellar medulloblastoma [46], and further studies are needed to evaluate clinical utility.

2.8. ^{68}Ga-DOTATATE PET/CT in the imaging work-up of paraganglioma

Paragangliomas are rare neuroendocrine tumors arising from paraganglia, clusters of neuroendocrine cells dispersed throughout the body and closely related to the autonomic nervous system, with either parasympathetic or sympathetic function [47]. Sympathetic paragangliomas, which generally arise in paraganglia below the level of the neck, often present with features of catecholamine-release, including headaches, palpitations, diaphoresis and hypertension. Parasympathetic paragangliomas often arise within paraganglia of the head and neck in association with the glossopharyngeal and vagus nerves and are generally non-secretory; therefore, they commonly present with symptoms of mass-effect such as cranial nerve palsies, tinnitus or a neck mass [47]. Head and Neck Paragangliomas (HNPGLs), also known as glomus tumors, arise from a number of locations along the carotid sheath and middle ear, and are named on the basis of their location, such as the carotid bifurcation (glomus caroticum paraganglioma),

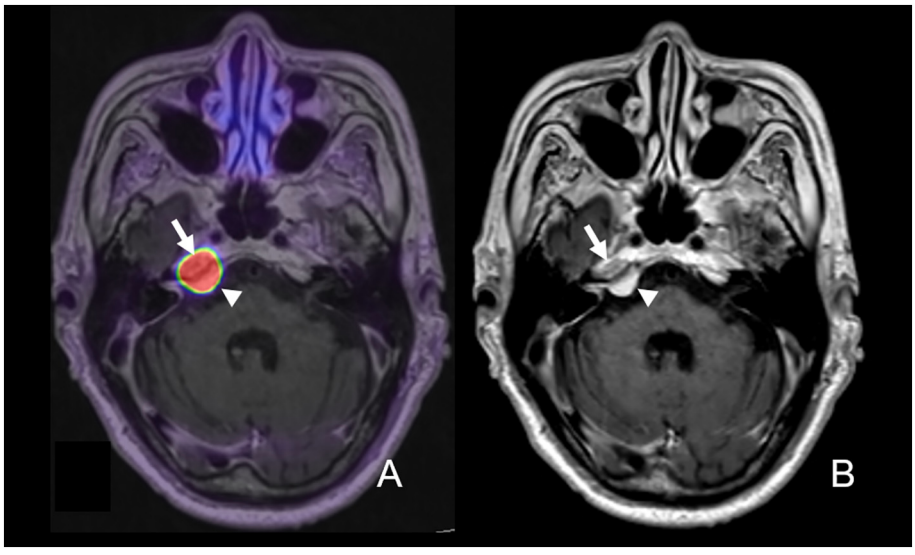

Fig. 8. 86 year-old man with history of recurrent atypical meningioma previously treated with stereotactic radiosurgery. A. fused PET/ T1-postcontrast MRI and corresponding T1-postcontrast MRI alone (B). There is an avidly enhancing lesion with broad-based dural attachment within the right cerebellopontine angle cistern anterior to the auditory canal consistent with a meningioma which demonstrates intense DOTATATE avidity (arrowhead). Osseous invasion including the petrous apex is noted as T1-hypointensity on MRI corresponding to intense DOTATATE avidity (arrow).

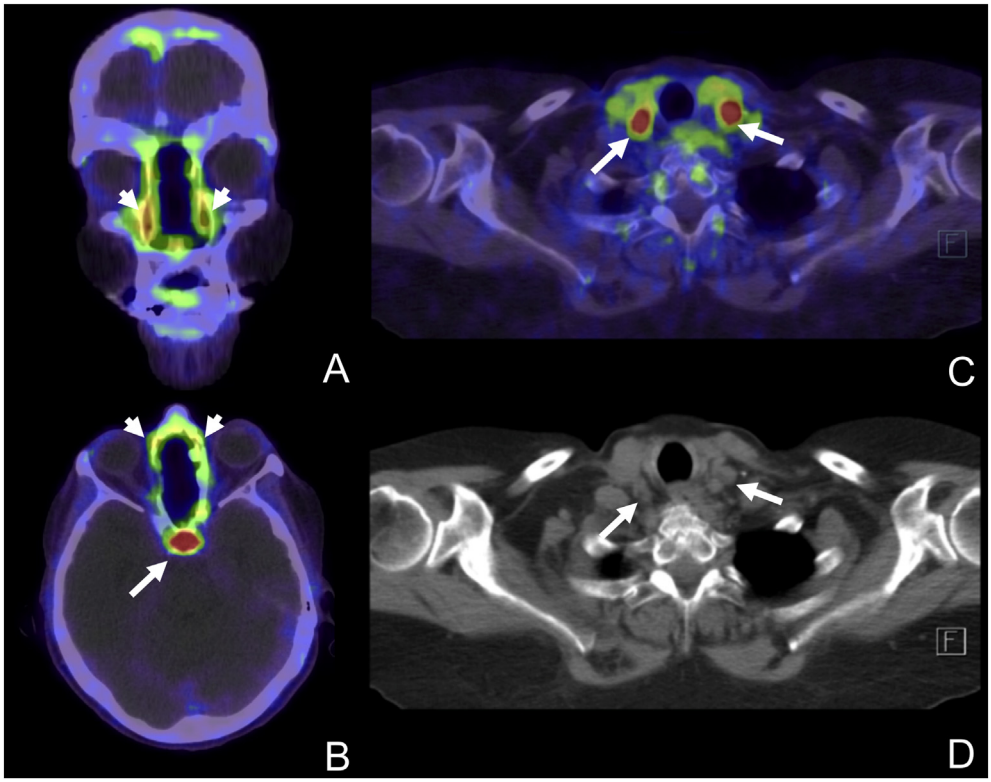

Fig. 9. 72 year-old woman with a history of resected esthesioneuroblastoma underwent ^{68}Ga DOTATATE PET/CT for evaluation of suspicious metastatic nodes. ^{68}Ga DOTATATE PET/CT fused images on axial (A) and coronal (B) planes demonstrate mild DOTATATE activity within the sinonasal canal corresponding to post-resection sinonasal inflammation (short arrows in A and B). Marked DOTATATE avidity noted physiologically within the pituitary gland (long arrow in B). ^{68}Ga DOTATATE PET/CT fused image at the level of lower neck demonstrates intensely DOTATATE avid bilateral foci in level IV of the neck (arrows in C) corresponding to subcentimeter lymph nodes on nonenhanced CT (arrows in D), consistent with cervical node metastatic esthesioneuroblastoma, a diagnosis that was considered uncertain based on CT alone.

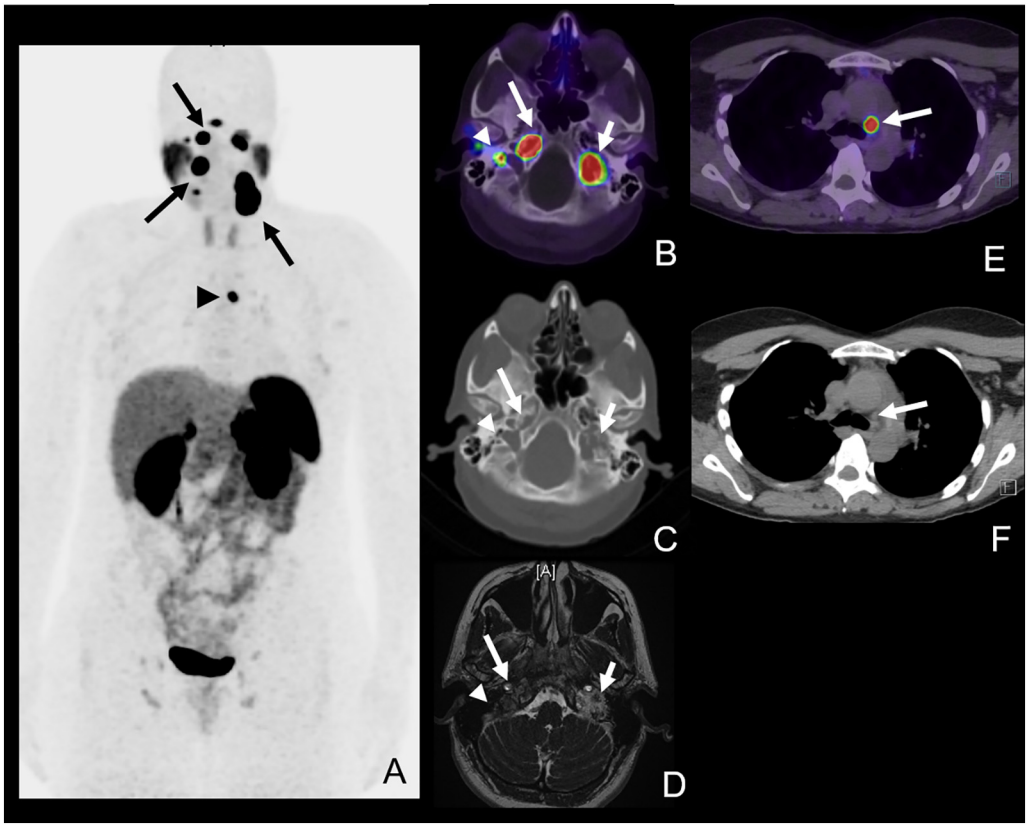

Fig. 10. 52 year-old woman with history of multiple glomus tumors and stereotactic radiosurgery of a left jugulare tumor underwent follow-up evaluation with MRI and ^{68}Ga DOTATATE PET/CT. A. Maximum Intensity Projection Image from a Whole-Body Ga-68-DOTATATE PET/CT demonstrates multiple intensely avid lesions in the skull base and neck (arrows in A) as well as one lesion at the level of the aortic arch (arrowhead in A). Axial fused PET/CT image (B) at the level of the skull base demonstrates intensely avid lesions with corresponding permeative lytic osseous changes in the axial noncontrast CT image with bone window (C) at the site of a known left glomus jugulare (short arrow in B). Additionally, there is a right-sided glomus jugulare (long arrow in B) and a right-sided glomus faciale (arrowhead in B) which were incompletely characterized on MRI alone. Corresponding 3D-T2-weighted FIESTA MRI (D) reveals heterogeneous enhancement and T2-hyperintensity within the left glomus jugulare reflecting high vascularity of the tumor, and suggestion of abnormal enhancement and T2-hyperintensity within the right glomus jugulare. Axial fused PET/CT image (arrow in E) at the level of the aortic arch demonstrates an intensely avid focus in the aortopulmonary groove corresponding to a subcentimeter soft tissue nodule on nonenhanced CT with soft tissue window (arrow in F), consistent with an aortic body paraganglioma.

nodose ganglia of the vagus nerve (glomus vagale paraganglioma), jugular bulb (glomus jugulare paraganglioma), and cochlear promontory (glomus tympanicum paraganglioma). Paragangliomas are associated with multiple clinical syndromes, including VHL, multiple endocrine neoplasia (MEN), neurofibromatosis type 1 (NF-1) and Carney-Stratakis Syndrome [48]. The most common genetic cause of hereditary

paragangliomas, particularly HSNPGLs, is a mutation in the succinate dehydrogenase (SDH) subunit (SDHB, SDHD, SDHA or SDHAF2), with SDHB conferring a higher rate of malignancy [49]. Treatment includes surgical resection or radiotherapy. ^{68}Ga-DOTATATE PET has been shown to demonstrate a significantly superior detection rate of paragangliomas compared to all other functional and anatomical imaging modalities, particularly in the localization of HNPGLs and in the evaluation of SDHB-related metastatic paragangliomas [38,50]. In our institutional experience, ^{68}Ga-DOTATATE PET/CT and PET/MRI improved the detection rate for small paragangliomas (Fig. 10).

2.9. ^{68}G8-DOTATATE PET/CT in the imaging work-up of pituitary adenoma

Pituitary adenomas are primary tumors occurring within the pituitary gland, broadly classified as a pituitary microadenoma, less than 10 mm in size, or pituitary macroadenoma, greater than 10 mm in size. Pituitary adenomas are one of the most common intracranial neoplasms, accounting for approximately 10% of all intracranial neoplasms, with a population prevalence of approximately 0.1% and autopsy prevalence of approximately 15%. Pituitary adenomas may present due to hormonal imbalances or mass effect upon the adjacent structures (macroadenomas), classically the optic chiasm. Treatment of pituitary adenomas depends on their size, symptoms related to mass effect, and cell type, with treatment options including transphenoidal surgery, medical management and SRS. ^{68}Ga-DOTATATE avidity has been reported in a case of Cushing Syndrome [51]. ^{68}Ga-DOTATATE has normally high avidity for the pituitary gland, making it challenging to delineate a pituitary tumor. However, a recent study suggested a dual-tracer approach using both 18F-FDG and ^{68}Ga-DOTATATE for differentiating pituitary adenomas from normal pituitary tissue [52]. Further prospective studies are needed to assess clinical utility.

3. SSTR targeted radionuclide therapy

Radionuclides can also be utilized to target tumors for treatment. Yttrium 90 (^{90}Y) DOTATOC and ^{90}Y-DOTATATE emit β-electrons to destroy malignant cells using direct receptor binding [53]. Studies have demonstrated a favorable therapeutic outcome from using this radionuclide; one report listed radiological partial response in 23% of cases and therapeutic benefit in terms of general condition improvement in 72% [53]. Although considered a relatively safe treatment strategy, ^{90}Y-DOTATATE and ^{90}Y-DOTATOC can cause renal impairment since the kidneys are important sites of somatostatin receptor concentration and receive a considerable amount of radiation.

Lutetium-177 (^{177}Lu) emits β- as well as γ- electrons [54]. It has been chelated to DOTA as well to form the radionuclide ^{177}Lu-DOTATATE for potential treatment of neuroendocrine tumors. The usefulness of ^{177}Lu-DOTATATE as a therapeutic agent was recently investigated in the NETTER-1 trial. In this study, patients with advanced, somatostatin receptor positive neuroendocrine tumors in the small intestine and proximal colon were assigned to either a dose of ^{177}Lu-DOTATATE 7.4 GBq every 8 weeks or octreotide long-acting release 60 mg every 4 weeks [55]. Patients receiving ^{177}Lu-DOTATATE had an estimated rate of progression-free survival at month 20 of 65.2%, while the rate for patients receiving octreotide was 10.8% [54]. More patients in the ^{177}Lu-DOTATATE group also reported better maintenance of overall health status. The response rate was 18% for patients receiving ^{177}Lu-DOTATATE versus 3% in the octreotide group. It is important to note that patients in the ^{177}Lu-DOTATATE group were more likely to develop neutropenia, thrombocytopenia and lymphopenia at rates of 1%, 2% and 9%, respectively; no patients in the octreotide treatment group developed any of these adverse reactions. Overall, treatment with ^{177}Lu-DOTATATE led to a risk of disease progression or death that was lower by 79% than the risk linked to octreotide therapy. ^{177}Lu-DOTATATE has also been associated with very high tumor response rates and increased durations of progression-free survival in patients with advanced, progressive, somatostatin-receptor–positive midgut neuroendocrine tumors which were refractory to first line somatostatin analogue therapy [54].

Since ^{177}Lu-DOTATATE led to a significantly longer progression-free survival period than octreotide in these patients in the NETTER-1 trial, ^{177}Lu-DOTATATE was recently FDA approved in January 2018 as a treatment for patients with advanced GEP-NETs [56].

4. Radioguided surgery using ^{68}Ga-DOTATATE

Surgical intervention in patients with abdominal NETs can be difficult for many reasons including small size of functioning tumors, scarring or anatomic changes from prior surgeries. Two prospective studies have demonstrated the feasibility and reliability of ^{68}Ga-DOTATATE use for intraoperative guidance in surgical candidates [57,58]. However, more studies with larger cohorts and long-term analysis are needed to determine if this surgical approach improves the overall disease-free progression.

5. Conclusion

^{68}Ga-DOTATATE PET has superior sensitivity and specificity compared to ^{111}In-Octreotide scintigraphy, contrast-enhanced CT or MR imaging, and has recently become a necessary clinical tool for management of patients with GEP-NETs. Advantages of ^{68}Ga-DOTATATE include higher specificity in targeting the SSTR2 with resultant improved target-to-background ratio, decreased radiation dose, improved resolution, ability to quantify uptake, lower cost and a more convenient imaging protocol. While ^{68}Ga-DOTATATE PET/CT has become the preferred imaging test for the diagnosis, staging and treatment response assessment of GEP-NETs, further studies are needed to confirm pilot data suggesting its clinical utility in other types of SSTR2-positive tumors, such as meningioma, paraganglioma, and ENB. Furthermore, use of SSTR2-targeted radionuclide therapy is already approved for the treatment of GEP-NETs. The potential role of ^{177}Lu-DOTATATE for the treatment of SSTR-positive neoplasms is vast. Future studies evaluating clinical outcomes in these patient populations are needed both to determine treatment efficacy and response assessment.

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