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SPECIAL ARTICLE

THERAGNOSTICS APPLICATIONS AND CHALLENGES

Theragnostic in neuroendocrine tumors

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ABSTRACT

In the last few decades, the incidence and prevalence of neuroendocrine tumors has been increasing. The theragnostic approach, that allows the diagnosis and treatment of different neoplasms with the same ligand, is a typical nuclear medicine tool. Applied for years, is also pivotal in neuroendocrine tumors (NETs) where it has improved the diagnostic accuracy and the therapeutic efficacy with impact on patient's survival. Theragnostic also allows the identification of important prognostic factors such as tumor location and burden, presence of liver metastases and intensity of somatostatin receptors (SSTR) expression to consider in new and possibly combined studies to ameliorate patient's outcome. Moreover, the possibility to evaluate receptor expression even in non-NET malignancies has *de facto* widened the possible indications for PRRT. We believe that this innovative therapeutic approach will be implemented in next years by radiomics and biological tumors characterization to better address PRRT applications.

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KEY WORDS: Neuroendocrine tumors; Lutetium; Receptors, somatostatin.

Neuroendocrine tumors (NETs) constitute a heterogeneous group of predominantly slow-growing malignancies, arising from the diffuse neuroendocrine cell system, which share the ability of overexpressing somatostatin receptors (SSTRs) on the cells' surface.[1]

Epidemiology

Although NETs are generally considered relatively rare tumors, the incidence rates and the prevalence have been constantly increasing over the last three decades (incidence of 6.98 per 100,000 in the USA),[2] especially those arising from the small intestine and pancreas.[3] This increase in incidence and prevalence reflects the ameliorated sensibility of the imaging modalities, which have greatly improved the ability to detect neuroendocrine neoplasias (NENs) in more early stages, and the effectiveness of the new therapeutic options, respectively.

About 72% of NETs are primarily rising from the gastrointestinal (GI) system and 25% originate in the bronchopulmonary system.[4] Rarely NETs can also arise from other sites where neuroendocrine cells are present[2] such as pheochromocytoma (Pheo) and paraganglioma (Pgl).

Most of this neoplasm occurs sporadically but, in some cases, they can be associated with some hereditary conditions such as type 1 multiple endocrine neoplasia (MEN

1), neurofibromatosis (NF), Von-Hippel-Lindau Syndrome (VHL) and tuberous sclerosis (TS). In these setting NETs are frequently multifocal and the onset is generally more precocious.[5]

Carcinoid syndrome and other symptoms

This heterogeneous group of tumors can be either asymptomatic (non-functional) or symptomatic (functional), considering NETs property of secreting biogenic amines (like serotonin) and hormones (such as glucagon, insulin and gastrin).

In case of functionally active tumor, the patient could show Carcinoid Syndrome, caused by the hypersecretion of serotonin (with symptoms like diarrhea as well as flushing and, in a complex scenario, right heart failure).

Other functioning tumors include insulinomas (which can cause hypoglycemia), gastrinomas (associated with Zollinger-Ellison Syndrome) and VIP-omas (which can induce watery diarrhea, hypokalemia and achlorhydria).

Classification

The 2019 World Health Organization (WHO) Classification[6] categorizes gastroenteropancreatic-NETs (GEP-NETs) into three grades depending on cell proliferation, number of mitosis per high-power fields (HPF) and nuclear antigen Ki-67 expression.

Grade 1 (G1) refers to a Ki-67<3% (and <2% mitoses per 10HPF), grade 2 (G2) refers to Ki-67 of 3-20% (or 2-20 mitoses per 10HPF) and grade 3 (G3) refers to Ki-67>20% (or >20% mitoses per 10HPF).

WHO classification also divides GEP-NENs into well-differentiated NETs (G1-G3) and poorly-differentiated neuroendocrine carcinomas (NECs – always G3) on the basis of the degree of differentiation, reflecting their molecular differences.

The classification once considered only for pancreatic neoplasms (p-NENs), has been recently validated for all gastrointestinal NENs.

Theragnostic strategies

Since the beginning, nuclear medicine had in the theragnostic approach its main *raison d'être*. Starting from the diagnosis, staging, therapy and follow-up of thyroid tumors done with 131I, and 123I, the modality conquered its own space in the diagnosis and treatment of pheo and neuroblastomas with 123/131I- MIBG, of bone metastases with 99mTc-biphosphonates and 153Sm/188Re8 (recently 2233Ra) and of lymphomas.

The ability to use the same molecule with a high affinity for the target, bound to different radionuclides, for diagnostic, prognostic, and therapeutic purposes, enables the capacity of diagnose the presence of the disease, monitoring its evolution, predict and quantify the activity of therapeutic agents that can be conveyed to the target lesions. Nowadays the theragnostic modality has gained new interesting perspectives not only with somatostatin analogues in PRRT but also with radioligand therapy (RLT) in prostate cancer and future promising applications, with the development of fibroblast activating proteins inhibitors (FAPi), in many different malignancies including colon, breast and lung tumors.

Enabling the diagnosis, the evaluation of prognosis, the follow-up, dosimetry and, in some specific settings also allowing to verify the effective delivery of the therapeutic agent to the target sites and the eventual occurrence of new metastatic lesions with post therapy images, the theragnostic approach is of fundamental importance in the process of personalizing the management options.

In GEP-NETs in particular, in order to select the best treatment options for the individual patient, information about anatomic location of primary tumor, grade, stage, local invasion, tumor functionality and SSTR expression are of pivotal importance to decide the therapeutic strategy in metastatic patients. If this aspect is particularly evident in GEP-NETs G1 /2 it does not end its potential with these tumors. The theragnostic approach is in fact highly effective even in high grades NETs (G3), in nonintestinal NETs, such as Pheo and Pgl, and in general in several non-NET tumors, as long as they overexpress SSTR, especially when of low grade as in the case of meningiomas.

Conventional imaging

Computed tomography (CT) is considered the basic radiological imaging modality for NETs staging because it is widely available, well standardized, and reproducible. The sensitivity of CT to detect NETs is 61-93% and the specificity is 71-100%. The sensitivity of CT for bone metastasis is poor, small pathological lymph nodes and small peritoneal metastasis could be difficult to detect. Moreover, the detection rate of CT for liver metastases is 79% (range 73% to 94%) and for extra-abdominal soft tissue metastases the sensitivity is about 70% (60-100%).

Magnetic resonance imaging (MRI) has demonstrated to be superior to CT for the evaluation of liver metastases, for the pancreas, and in the imaging of bone and brain me-

tastases. Quite the opposite, according to the ESMO clinical guidelines,[5] CT is to be preferred for lungs' imaging.

Endoscopic ultrasound is considered as the optimal imaging method for the diagnosis of small p-NETs (also allowing needle aspiration cytology or biopsy for histopathological examination) and contrast-enhanced ultrasounds (CEUS) is considered a very useful tool for the characterization of equivocal liver lesions at MR or CT imaging. Also, intraoperative ultrasounds facilitate localization of lesions in the pancreas and in the liver.

PET/CT imaging

68Ga-DOTA-peptides PET

Five SSTRs subtypes have been identified in NENS cells membrane surface. Each of them is a 7-transmembrane-domain G-protein-coupled molecule with a weight of approximately 80 kDa. SSTR2 is generally overexpressed in G1/2 NETs and is the basic target molecule for radiolabelled somatostatin analogues (SSA).

The first scintigraphic studies to evaluate the SSTR expression have been done using the tracer 111In--DTPA-octreotide (OctreoScan [OCT]) that offered a detailed representation of the disease distribution. Over the years the long time required for testing, the image quality and detection accuracy favored 68Ga dota-peptide PET as demonstrated by the work of Krausz *et al.*[7] In this paper the authors compared ^{111}In-DTPA-octreotide with ^{68}Ga-DOTA-NOC for the detection of NETs. They enrolled 19 patients (8 carcinoid, 9 pancreatic NETs, and 2 NE carcinoma of unknown origin) with a positive OCT scan to undergo ^{68}Ga-DOTA-NOC PET/CT and OCT SPECT imaging. They found out that ^{68}Ga-DOTA-NOC showed more true positive tumor foci and was better tolerated by patients, supporting the replacement of OCT with ^{68}Ga-DOTA-NOC-PET/CT in NETs patients.

^{68}Ga-DOTA-peptides PET imaging provide a total body, non-invasive and accurate evaluation with a pivotal clinical impact on the management of the patients. It is otherwise characterized by a relatively low radiation exposure and a short acquisition time.

SSA are short peptides linked to the 68Ga (a positron-emitter) by a bifunctional chelate, (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid – DOTA).

68Ga-DOTA-peptides bind to the SSTRs over-expressed on NET cells' membrane and the complex is then internalized.

Currently, three different 68Ga-DOTA-peptides are utilized: 68Ga- DOTATOC, 68Ga-DOTANOC, and 68Ga-DOTATATE. These three agents are comparable in terms of sensitivity and specificity.

68Ga-DOTANOC binds SST receptors 2, 3 and 5 with relatively good affinity. 68Ga-DOTATOC shows a good affinity for SSTR2 and also has a good affinity to SST receptor 5 (lower than DOTANOC), and a lower affinity for SSTR3. 68Ga-DOTATATE has a predominant high affinity for SST receptor 2 (it shows a six- to nine-fold higher affinity for SSTR2 than DOTATOC), and low affinity for SSTR5 and SSTR3.[8]

The sensitivity of PET with 68Ga-DOTA-peptides, can vary among different tumor types and tumor grades, depending on the density of SSTR expression on cells' membrane.

The sensitivity to detect NET disease of the 68Ga-DOTA-peptides PET imaging is approximately 92% (range 64-100%) and the specificity 95% (83% to 100%) and this reflects also in the ability to detect disease localizations earlier than conventional morphological imaging modalities.[9]

Indications

- Localization of primary tumors (if unknown) and detection of eventual sites of metastatic disease (staging). In a study by Screiter *et al.*,[10] the study group found that 68Ga-dotatoc PET/CT detected unknown primaries in 45.5% of patients;
- follow-up, in order to detect residual, recurrent or progressive disease (restaging);
- determination of SSTR status can be performed both with visual evaluation as well as with the support of semiquantitative parameters (SUV), in order to select patients with SSTR positive tumors (which are more likely to benefit from therapy with SSA and with peptide receptor radionuclide therapy (PRRT);[11]

In regard to patients' selection for PRRT with SSTR-PET, a "modified" Krenning score was proposed. It is a 5-point scale based on qualitative evaluation of the tracer uptake in lesions compared with blood-pool, hepatic and spleen uptake: 0 no uptake; 1 very low uptake; 2 uptake ≤ liver; 3 uptake ≥ liver; and 4 uptake > spleen. Moreover, in a study by Kratochwil *et al.*[12] the investigators observed that the semiquantitative parameter SUV_{max} at baseline 68Ga-DOTA-Peptides PET scan in liver metastases was predictive of response in patient who underwent PRRT, and they proposed a SUV_{max} cut-off >16.4 to select patients suitable for PRRT.

Consequently, the evaluation of the response to therapy has been proposed as an indication for 68Ga-DOTA-peptides imaging[13] but possible standardization still needs

further investigations because a change in receptor status is not necessarily indicative of therapy response (possible tumors' dedifferentiation with a potential reduction in receptors expression must be taken into account). In these cases, an evaluation with 18F-FDG PET/CT can provide complementary information about tumor metabolism. This information could be an important issue for the multidisciplinary group which coordinates the patient's treatment, to better address the right therapies. The assessment of SSTR expression also enables the capacity to estimate the absorbed dose to the tumor for dosimetric purpose.

Prognostic data

NETs arising from multiples gastrointestinal sites usually differs from one another for biological behaviour and clinical presentation. Patients presenting with small intestine primary tumor generally have a better prognosis compared with patients affected by pancreatic or colorectal NETs.

Proliferation Index relates with the prognosis of the patients, the biological behavior and the clinical evolution of the disease. High-grade tumors, also, often demonstrate a reduced SSTR expression, limiting the imaging sensibility and PRRT efficacy.[14]

The presence of functioning tumor is a negative prognostic factor and patients presenting with clinical syndrome generally have a worst prognosis than those with non-functioning NENs.

A highly positive somatostatin receptor imaging (SRI) is generally considered a favorable prognostic factor and also has an important predictive value. Ambrosini *et al.* reported that patients affected by G1-G2 pancreatic-NETs with a high baseline SUV_{max} at 68Ga-DOTA-peptides scans showed more favorable outcomes.[15]

Regarding the use of 18F-FDG PET, the high number of false negative scans in every grade of NEN tumors has, *de facto*, excluded the possibility of using this examination for the diagnosis of both primary tumor site and metastases. Nevertheless, some evidence in literature[16] have shown a worst prognosis in patients with positive FDG PET, opening the door to the possible use of the metabolic tracer FDG for prognostic purpose. Starting from these findings, in our Centre, we evaluated a group of 52 patients with advanced well-differentiated grade 1/2 NETs and found out that 57% of G1 had a FDG PET positive (+) scan *vs.* 66% of G2. Moreover, we studied the role of FDG PET in predicting response and progression-free survival (PFS) after ^{177}Lu-dotatate peptide receptor radionuclide therapy. The rates of disease control (DCR) in grade 1 and grade 2 patients were 95% and 79%, respectively (P=0.232). In FDG PET negative (−) and PET+ patients, the DCR was 100% and 76% respectively with a PFS of 32 and 20 months. Of the PET+ patients with grade 1 NET, 91% showed disease control, instead, about one in three PET+ patients with grade 2 NET (32%). Furthermore, none of PET− patients showed progression at the first FUP examination.[17] For these reasons the concomitant use of 18F-FDG PET can be considered as complementary predictive option and its utilization may be taken into account in clinical protocols considering that there are still limited evidence supporting its use in the routinary theragnostic work-up of NEN.[18]

Again, many studies have demonstrated that patients with a higher tumor burden have a worst prognosis and, also, patients presenting with diffuse liver metastases demonstrates a reduced survival.[19]

Recently NETest was suggested as a novel diagnostic tool.[20] Introduced by Prof Modlin *et al.*, represents a transcriptomic signature of NETs. The NETest associate the modulation of a panel of transcripts with the Ki67 index and represent an indicator which, evaluated initially in correlation with PRRT,[21] has demonstrated to be effective also in a more diffuse diagnostic use. It is a standardized and reproducible clinical laboratory measurement in GEP-NETs, bronchopulmonary NETs, in PGL and PHEO. The test allows the accurate diagnosis of a NET disease, a real-time monitoring of the disease status (stable/progressive disease), predicts aggressive tumor behavior and correlates with the efficacy of the medical treatment or (PRRT). NETest out-perform standard biomarkers like chromogranin A and it is not influenced by antiacid therapy.

Conventional therapeutic strategies

Nowadays multiple treatment options are available for NETs' patients, with the necessity of choosing the most appropriate, tailored, approach. Treatment of advanced NETs is generally multidisciplinary and should be individualized on the basis of tumor histology, neoplasm site, extent, grade, stage, symptoms and patient performance status.

Surgery

Surgery is the treatment of choice for local and locoregional disease.

Whenever feasible, removal of the primary tumor should be attempt in order to prevent possible local events (such as obstruction, perforation, ischemia or bleeding), to reduce loco-regional invasion and the likelihood of metastatic spread. Surgery should also be considered for palliative purpose.

Moreover, in case of functional NENs, surgery could be indicated in order to reduce the symptomatology.

Surgical resection is generally associated with an improved prognosis and a lower risk of recurrences.[22]

The surgical options include locoregional therapies with primary tumor or metastatic resection with trans-arterial embolization (TAE), trans-arterial chemoembolization (TACE), radiofrequency ablation

(RFA) and selective internal radiation therapy (SIRT). Combined approach could also be considered in selected patients.

Medical therapy

Medical therapy can be undertaken in order to control symptoms and reduce tumor growth. There is a wide range of strategies which could be taken into account, such as the use of bioactive agents (SSA-or interferon alpha), or new targeted drugs (everolimus, sunitinib), as well as conventional chemotherapy. Also, in functional tumors (*e.g.*, gastrinomas or insulinomas), pharmacological treatments directed to the control of symptoms (*e.g.*, proton pump inhibitors or antihypoglycemic agents) are effective.

Long-acting somatostatin analogues

Currently, the use of long-acting somatostatin analogues is the standard first-line therapeutic strategy, especially in functioning NETs.[23]

Octreotide and lanreotide (long-acting somatostatin analogues [SSA]) show high affinity for SSTR2, moderately high affinity for SSTR5, and intermediate affinity for SSTR3. The over expression of SSTR in NETs allows an effective treatment of the symptoms related to the hypersecretion of bioactive peptides/amines.

Long-acting release (LAR) somatostatin analogues are usually well tolerated and an improvement of symptoms (such as diarrhea and flushing) can be archived in 70-80% of the patients.

SSAs also show, in selected patients, some inhibitory effect on primary and metastatic lesions growth but PR on imaging is obtained in a small percentage of cases considering the lack of cytotoxic activity.

Positive SSTR status is generally required but is not predictive of response to Long acting SSA therapy.

Also rescue s.c. injections of octreotide can be considered in cases of intermittingly increasing symptoms.

Interferon alpha

Interferon alpha is also approved for the control of symptomatology in syndromic patients, generally as a second-line treatment in refractory cases and shows a similar efficacy when compared to SSA but has a less favourable tolerability.[24] Interferon alpha (INF-α) can also be considered in patients with SSTR negative status on functional imaging.

Chemo-bio therapy

In recent years, some novel agents such as everolimus, sunitinib, and bevacizumab, with different molecular targets (mTOR, TKI and VEGF respectively) have been introduced for the management of NETs' patients.

Traditional chemotherapeutic agents, generally, has little space in the control of well-differentiated NETs since most of them show an indolent behaviour. Nevertheless, in some specific settings (*e.g.* advanced P-NET and in G3 NENs), the administration of systemic chemotherapy (in ex. a combined use of cisplatin/etoposide or carboplatin/etoposide, capecitabine alone or in combination with temozolomide[25, 26] could be taken into consideration despite the lacking of controlled randomized phase III trials. In case of doubt, a high-grade and extensive FDG PET positivity can lead to a more aggressive therapeutic approach.

PRRT

PRRT has been used as a systemic and effective treatment option in metastatic and/or inoperable patients with SSTR positive GEPs, bronchopulmonary and other NETs for over two decades within specific research protocols, in the absence of an approved radiopharmaceutical. It requires the systemic administration of a radiopharmaceutical composed of a β- emitting radionuclide (usually ^{177}lutethium or ^{90}yttrium), chelated to a specific somatostatin analogue. The radio-pharmaceutical, similarly as demonstrated in 68Ga-Dota-peptides PET, binds with a high-level specificity to the SSTR, widely expressed on NETs cells' surface (primarily SSTR2) and is internalized.

Because of this mechanism, the radiopharmaceutical is concentrated in the tumor cells, where the targets (*e.g.* DNA), are attained. Afterwards the receptor is either recycled on the cell membrane or trapped into lysosomes to be degraded.

PRRT protocols involve a baseline, *in vivo*, assessment of the SSTR density status of the tumor nowadays generally obtained with 68Ga-DOTA- peptides PET/CT. The indication to treat can be assessed with a qualitative evaluation of the SSTR density, modified Krenning Score >3 or with a semiquantitative SUV_{max} evaluation, >16.4.

The effectiveness and the safety of PRRT have been evaluated over the years in multiple therapeutic protocols

which differs for administered activity, cycles number and administration intervals, making it difficult to compare the results.

The two most commonly used radionuclides are Yttrium-^{90} (^{90}Y; E_{max} 2.27 MeV, R_{max} 11 mm, $T_{1/2}$ 64 h, pure β-emitting isotope) and lutetium-^{177} (^{177}Lu; $E_{\beta max}$ 0.49 MeV, $R_{\beta max}$ 2 mm, $T_{1/2}$ 6.7 days, two main gamma emissions: 113 keV and 208 keV, allowing post-treatment imaging).

The multiple therapeutic studies have highlighted that the more favorable combination of radionuclide/DOTA-peptide are ^{90}Y-dotatoc and ^{177}Lu-dotatate. Other different combination resulted either to be less effective or causing more toxicity.[27]

Actually, the recommended administered activities for each cycle range from 1.8 to 2.5 GBq for ^{90}Y-dotatoc (with a time interval of 8-10 weeks) with a median 4 cycles and range from 3.7 to 7.4 for ^{177}Lu-dota-tate (every 6-12 weeks) for median of 4 to 5 cycles.

In general, ^{90}Y-dotatoc takes advantage of the higher β particle emission while ^{177}Lu-dotatate avail of higher SSTR2 affinity, a longer residence time in tumor and of a lower kidney exposure. ^{90}Y-dotatoc is generally preferred for the treatment of larger neoplastic lesions because of its high β emission range (approximately 5-7 mm). ^{177}Lu-dotatate β-rays have a smaller range (less than 2 mm) and are, consequently, considered for smaller lesions.

About ^{90}Y-dotatoc PRRT, we underline a study by Bushnell *et al.*[28] who evaluated the clinical effect of the treatment in symptomatic patients affected by carcinoid tumors. Ninety patients with metastatic carcinoid and with at least one symptom refractory to octreotide and one measurable lesion were enrolled. Patients were treated with 3 cycles of 4.4 GBq of ^{90}Y-dotatoc, with 6 weeks intervals. According to SWOG criteria, 67/90 patients (74%) showed SD or response to therapy. A significant trend in improvement of the 12 different symptoms took into consideration was observed and mean PFS (mPFS) was significantly longer (18.2 months) for the 38 patients who showed improvement of diarrhea than for the 18 patients without symptoms improvement (7.9 months). Most of the adverse events were G1 and reversible; only two cases of G3 and G4 reversible renal toxicity were registered.

Subsequently the longer residence time in neoplastic lesions, the higher SSTR affinity and the lower renal toxicity, favored ^{177}Lu-dotatate that, for its tolerability and effectiveness, became *de facto* the more widely used. ^{177}Lu-dotatate is indicated both for intestinal and other NET histologies. Good tolerability and effective symptomatic response have been reported for pain relief and syndromic symptoms.

Kwekkeboom *et al.*[29] have been one of the first group who studied ^{177}Lu-dotatate analyzing efficacy and safety in 504 patients, treated up to a cumulative activity of 27.8-29.6 GBq, in four cycles, (intervals of 6-10 weeks). Subacute Hematologic toxicity grade 3 or 4 occurred in 3.6% of administrations while myelodysplastic syndrome in 3 patients, and temporary liver toxicity in 2 patients. Complete response (CR) and partial response (PR) were respectively, in 2% and 28% of 310 GEP-NET patients. Minor tumor response was obtained in 16% of cases. mPFS was 40 months and comparison with historical results showed a survival benefit of 40 to 72 months from diagnosis.

In a recent paper[30] our group analyzed in 10 years follow-up the late toxicity and activity in a cohort of 43 progressive GI-NETs patients who underwent ^{177}Lu-dotatate at two different dosages (18.5 GBq and 27.5 GBq, in 5 cycles). With an overall 84% DCR previously evaluated, patients were monitored for a median period of 118 months (range: 12.6-139.6). mPFS in patients receiving 18.5 GBq was 59.8 months as the ones treated with 27.5 GBq. On the other hand, median overall survival (mOS) was 71.0 months in the group who received 18.5 GBq and 97.6 months in the group treated with 27.5 GBq (P=0.22). Higher hepatic involvement and age over 65 years at the time of PRRT were also significant for OS. No late renal or hematological toxicity have been observed, in either group. The long-term follow-up of the study confirmed that ^{177}Lu-dotatate is well tolerated and is effective over the time also in patients with renal and bone marrow risk factors when treated with lower dosages.

PRRT, with either ^{177}Lu-dotatate or ^{90}Y-dotatoc, generally shows a very good tolerability, with in most cases, only minimal toxicity to the target organs specially kidney, and bone marrow.

Acute side effects comprise mild nausea (25%) and rarely vomiting (usually related to the coadministration of renal protective amino acid solutions). These symptoms are easily controlled or prevented with the administration of appropriate antinausea pharmaceuticals. About 10% of patients refers of G2 abdominal pain lasting no more than few days in post treatment phase.

The most frequent subacute effects are G1 and rarely G2 fatigue, mild (G1) alopecia (no more than 10% of patients after ^{177}Lu-dotatate) and hematological toxicity. All these symptoms are mild and transient. Severe (G 3 and 4) toxicity occurs approximately in 10% of patients, more frequently using ^{90}Y-dotatoc, but is usually reversible and only in rare cases requires support.

Chronic and permanent effects, such as loss of renal

functionality and reduction of bone marrow reserve, are rare and generally mild. Secondary myeloproliferative diseases (such as leukemia or myelodysplastic syndrome) are extremely rare.[31]

The likelihood of all these adverse events is significantly reduced if the necessary precautions are undertaken (*e.g.*, renal protection with specific amino acids and dosage tailoring).

In the last years, ^{177}Lu-dotatate has been approved as a therapeutic option for patients with progressive, advanced, SSTR–positive, well-differentiated G1/2 GEP-NETs following the NETTER-1 trial.[32] In this pivotal phase III randomized protocol, 229 patients in disease progression during first line SSA therapy were assigned to receive high dose octreotide LAR alone (60 mg/28 gg) or PRRT with four cycles ^{177}Lu-dotatate 7.4 GB/8 weeks in association with octreotide LAR therapy. In the first interim analysis, the investigators found out a 65.2% mPFS in the PRRT group *vs.* 10.8% in the octreotide group. Moreover, the ^{177}Lu-dotatate group had 18% response *versus* 3% in the control group (P<0.001). The overall survival studied at the time of interim registered 14 deaths in the ^{177}Lu-dotatate group *versus* 26 in the control group (P=0.004). The small number of Grade 3 or 4 neutropenia, thrombocytopenia, and lymphopenia (1%, 2%, and 9%, respectively) *versus* the absent toxicity in the control group, confirmed the good tolerability of the treatment. The preliminary results of the NETTER-1 trial, have clearly shown the superiority of ^{177}Lu-dotatate over high-dose SSAs in midgut NETs, and opened the way to the radiopharmaceutical registration that at the present times gives the possibility to treat GEP-NETs G1/2 patients with an active therapy previously not available.

Future perspectives and promising experiences

The experience gained in a long time of PRRT utilization led to investigate various possible administration modalities and to explore beyond standard boundaries of application. This research is of great interest because demonstrated that different administration or combination protocols, can actually influence the efficacy of PRRT and highlighted the possibility to offer an effective therapy in pathologies with poor therapeutic alternatives.

We report below some interesting, published studies and we expect important results from an ongoing phase III multicenter randomized protocol (NETTER 2) to verify efficacy and safety of lutathera in patients with grade 2 and grade 3 advanced GEP-NET *versus* high dose octreotide long-acting.

Combination protocols with ^{90}Y- and ^{177}Lu-DOTA-peptides

Combination protocols, with alternate ^{90}Y-dotatoc and ^{177}Lu-dotatate, also called "tandem therapy,"[33] have the purpose of making the most of the different physical properties and receptor affinity of each radiopharmaceutical. The first is useful in large lesions using the higher penetration range of the ^{90}Y emissions while the second take advantage of the higher receptor affinity, the longer residence time and the good efficacy in smaller lesions.

In a phase II study Seregni *et al.*[34] evaluated the feasibility of combined tandem PRRT in patients with metastatic NETs refractory to conventional therapy. Twenty-six patients were treated with four therapeutic cycles alternating ^{177}Lu-dotatate 5.55 GBq and ^{90}Y-dotatoc 2.6 GBq. Tandem therapy obtained objective responses in 42.3% of patients with an mPFS longer than 24 months. Moreover, 90% of patients with carcinoid syndrome showed a symptomatic response and/or a reduction in tumor-associated pain.

Different administration modality

Currently, in our Institute, we are mainly involved in a phase II randomized study (EUDRACT N. 2015-004727-31; ClinicalTrials.Gov N. NCT03454763) to compare standard *vs.* intensive radionuclide therapy with ^{177}Lu-dotatate in advanced GEP and pulmonary NETs (Figure 1, 2). We calculated, in a mathematical model, PRRT tumor control probability (TCP) and possible toxicity when

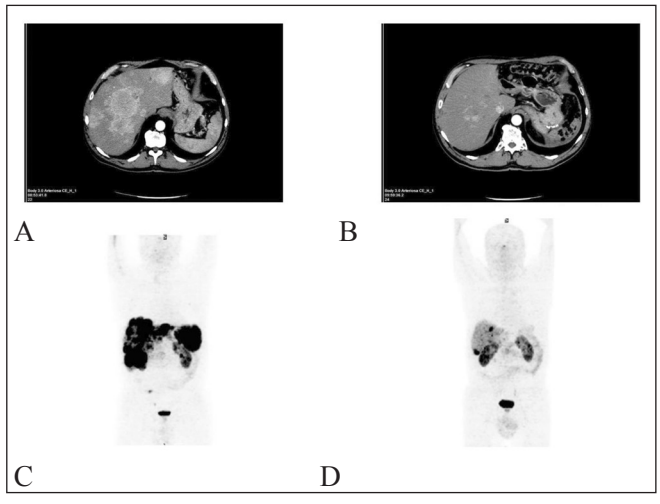

Figure 1—Fifty-six-year-old man, p-NET G2 (ki67 15%) with diffuse liver lesions, Luthree Prot.: 5.5 GBq ^{177}Lu-dotatate every 8 weeks, 5 cycles: A) CT pre-PRRT 2011; B) CT post-PRRT and liver resection 2014; C) 68 Ga-dotatoc PET pre-PRRT 2011; and D) 68Ga-dotatoc post-PRRT and liver resection 2014.

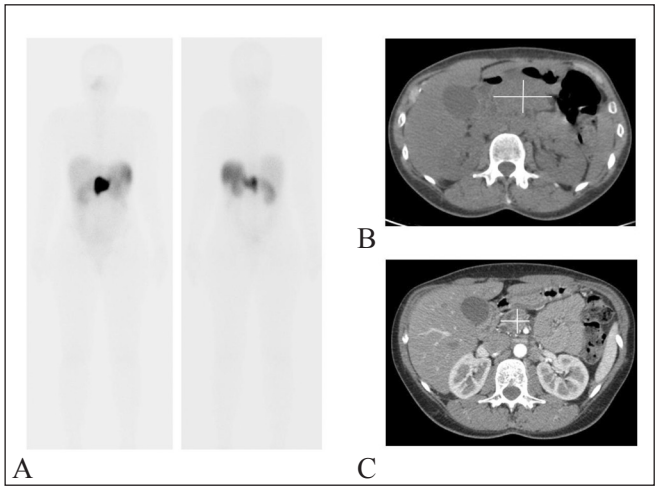

Figure 2.—Forty-two-year-old female, p-NET G2 (ki67 9%), FDG PET positive. Luthree Prot.: 5.5 GBq ^{177}Lu-dotatate every 8 weeks, 5 cycles. A) Post-PRRT images (17/1/2017 1st cycle); B) TC January 2017; and C) TC August 2017.

therapies are performed every 5 weeks *versus* the standard 8 weeks treatment. The obtained results allowed us to compare safety and efficacy of intensive *versus* standard treatment in two cohort of patients treated with high and reduced dosages (5.5 *versus* 3.7GBq) in five cycles. Lower dosages were reserved to patients with renal or bone marrow risk factors. Preliminary data demonstrated an optimal safety without G4 medullary and kidney toxicity and respectively 2.5% and 1% G3 toxicity. We also demonstrated a tendency toward a better overall response rate (ORR) in patients who received the intensive treatment. In our opinion these data suggest that ^{177}Lu-dotatate PRRT has a great possibility to overcome the obtained results with more intensive protocols without generate toxicity issues.

Combined capecitabine and PRRT protocols

In a recent publication, we evaluated in a prospective phase II protocol[35] efficacy and toxicity of PRRT with ^{177}Lu-dotatate in association with metronomic capecitabine as a radio-sensitizing agent, in patients with advanced progressive FDG+GEP-NETs. We enrolled 37 consecutive patients with advanced G1-G3 GEP-NETs (Ki67≤55%) positive in both SSR and FDG PET/CT scans. The patients were treated with a cumulative activity of 27.5 GBq of ^{177}Lu-dotatate in five cycles (5.5 GBq each) every 8 weeks. Metronomic capecitabine (1000-1500 mg daily) was administered orally in the inter-cycle period. All patients were tested for dihydropyrimidine dehydrogenase. 25/37 (68%) patients had pancreatic NETs, 12 (32%) had GI-NETs. Twelve patients (32%) had G1 (Ki67≤2%), 22 (59%) had G2 (3%<Ki67≤20%), and 3 patients (9%) had G3 (Ki67>20%) NETs. Grade 3 (G3) or 4 (G4) hematological toxicity occurred in 16.2% of patients. Other G3-G4 adverse events such as diarrhea and asthenia have been registered in 5% of cases. No renal toxicity was observed. Thirty-three patients were eligible for response. Objective responses (OR) included partial response (PR) in 10 patients (30%) and stable disease (SD) in 18 patients (55%), with a DCR of 85%. The median follow-up period was 38 months (4.6-51.1). The median PFS was 31.4 months (17.6-45.4). Median OS was not reached. Hence, we concluded that the combination of ^{177}Lu-dotatate and metronomic capecitabine is active and well tolerated in patients with aggressive FDG+G1-G3 GEP-NETs.

Also, in a recently published study, Satapathy *et al.*[36] investigated the efficacy and safety of ^{177}Lu-dotatate plus radio-sensitizing capecitabine and octreotide long-acting release (LAR) as first-line systemic therapy in advanced well-differentiated GEP-NETs. They took into consideration 76, treatment-naïve, patients with advanced G1 or 2 GEP-NETs. Thirty-six patients received a median cumulative dose of 27.3 GBq of ^{177}Lu-dotatate (8 to 12 weeks' intervals) in combination with 1.250 mg/m^2 oral capecitabine (days 0-14 of each cycle). Forty patients received 30 mg octreotide LAR i.m. every 4 weeks. The objective response rate (ORR) was 38% in the ^{177}Lu-dotatate arm compared with 15% in the octreotide arm (P=0.025), the DCR were, respectively, 88% and 67%. The median durations of PFS were 54 months and 16 months, respectively. The mOS was not reached in both arms. They did not detect major difference in treatment-related adverse events between the two groups.

In a trial by Claringbold *et al.*[37] a combination of ^{177}Lu-octreotate with capecitabine and temozolomide was investigated in 35 patients with advanced low-grade NETs, aiming to evaluate safety and efficacy. 7.8 GBq of ^{177}Lu-dotatate was administered (8 weeks intervals) combined with 14 days of capecitabine (1500 mg/m^2) and, in successive grouping, with escalating doses of temozolomide (100, 150, and 200 mg/m^2 in the last 5 days of each capecitabine cycle). Treatment was well tolerated in all groups. Adverse events were mild to moderate, and no grade 4 toxicity occurred. Complete response (CR) was observed in 15% of patients, PR in 38%, and SD in 38%. Patients with GEP-NETs tended to have higher Response Rates (RR) than patients with small intestine primaries. mPFS was 31 months, mOS was not reached (90% surviving at 24

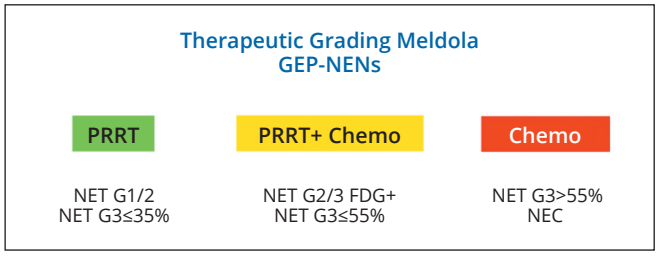

Figure 3.—Hypothesis of application of PRRT alone or in association in different pathological scenario. From Nicolini *et al.*[38]

months). In addition to an earlier use of PRRT, the data presented propose its possible use in GEP-NENs beyond the registered drug indications. In Figure 3[38] we present a hypothesis of application of PRRT alone or in association in different pathological scenarios. The proposal is open for discussion.

Retreatment

In G1 and 2 GEP-NETs a median PFS after PRRT of more than 20-30 months is generally observed, however, the majority of patients relapse after 2-3 years. In this setting the hypothesis of a PRRT retreatment is extremely interesting also in presence of many therapeutic options. The indication to treat always needs a 68Ga DOTA-peptides PET positivity and a history of good PRRT response, which support the possible treatment efficacy.

In a phase II study conducted in our Centre,[39] we investigated the use of low dosage re-treatment with ^{177}Lu-dotatate in patients with GEP-NETs who relapsed after PRRT with ^{90}Y-dotatoc. We consecutively enrolled 26 patients in PD after ^{90}Y-dotatoc (PFS of at least 12 months) to receive a re-treatment with ^{177}Lu-dotatate. All patients received 14.8-18.5 GBq of ^{177}Lu-DOTATATE in 4 or 5 cycles (median total activity 16.5 GBq in five cycles). The DCR was 84.6%, mPFS was 22 months compared to 28 months after ^{90}Y-dotatoc. Toxicity was mild after ^{177}Lu-dotatate re-treatment in majority of the patients. Only two patients had G2 and one had G3 bone marrow toxicity also, only one patient had G2 and one had G3 renal toxicity. Therefore, low-dosage ^{177}Lu-dotatate resulted to be safe, and DCR and PFS rates were comparable with those observed when ^{90}Y-dotatoc was used as primary treatment, also considering the worse clinical condition and the advanced stage that these patients present.

PRRT beyond GEP-NETs

Pheo and Pgl are NEN pathologies that in the metastatic phase currently have only limited treatment options. These rare tumors generally overexpress somatostatin receptors and therefore are susceptible to be treated with PRRT.

In a study conducted in our Centre by Severi *et al.*,[40] recently published, we analyzed 46 progressive Pheo and Pgl patients, consecutively enrolled, to receive ^{90}Y-dotatoc or ^{177}Lu-dotatate, during over a decade. All patients showed positivity to SRI. Twelve patients were treated with ^{90}Y-dotatoc (cumulative dosages ranging from 7.4 to 11 GBq), 34 patients received ^{177}Lu-dotatate (cumulative dosages 18.5 or 27.5GBq). Both ^{90}Y-dotatoc and ^{177}Lu-dotatate were well tolerated. No significant renal or bone marrow toxicity was observed. The median FUP was 73 months (5-146 months). The overall DCR was 80%. ^{177}Lu-dotatate patients showed a longer median OS than those treated with ^{90}Y-Dotatoc and a better DCR was observed in those receiving higher dosages. Syndromic patients had a poorer mOS. In this group of progressive Pheo/Pgl, SDHx mutations did not correlate with treatment efficacy. Hence, we concluded that PRRT is safe and effective in patients with progressive Pheo/Pgl, especially at higher dosages.

There are also non-NENs pathologies over-expressing SSTR receptors. We tested the possibility to treat with PRRT in some of this histotypes and realized that Meningiomas are those that generally better performs. Meningiomas are generally benign neoplasms and usually surgery is effective and curative but in case of high-grade histotypes or in cases in which tumors cannot be completely resected, recurrence is possible and quite common. Somatostatin receptors are commonly highly expressed on meningioma cell surfaces allowing the treatment of these kind of neoplasm (advanced or recurrent) with PRRT.

Several studies, like the work by Bartolomei *et al.*,[41] investigated the role of PRRT in treatment of recurrent meningiomas, demonstrating that the treatment is well tolerated and can interfere with tumor growth. Also, a study by Kreissl *et al.*[42] investigated the role of PRRT in association with external beam radiation therapy (EBRT) in patient with recurring or progressive symptomatic meningiomas, with encouraging results, showing that the combination of PRRT and EBRT is well tolerated and can represents an attractive treatment option that deserves further investigations.

Conclusions

Nowadays theragnostic represent an absolutely useful approach in NETs patients' management allowing to diagnose the tumor, giving the indication to treat and predicting in advance the efficacy of the therapy with a pivotal

possibility of treatment tailoring. We must certainly underline that the usefulness of this approach has made possible re-treatments with PRRT, utilize PRRT for some high grade GEP-NETs, non GEP NETs such as Pheo and Pgl and also other non-NET tumors expressing SSTR2. On the other hand, there are no doubts that modern oncology cannot overlook the future innovative development represented by radiomics and biological phenotypization. We think that the theragnostic approach combined with this deep biological characterization, will give the opportunity to further improve PRRT activity and efficacy.

References

1. Reubi JC. Peptide receptors as molecular targets for cancer diagnosis and therapy. Endocr Rev 2003;24:389–427.

2. Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, *et al.* Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. JAMA Oncol 2017;3:1335–42.

3. Modlin IM, Oberg K, Chung DC, Jensen RT, de Herder WW, Thakker RV, *et al.* Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol 2008;9:61–72.

4. Bodei L, Mueller-Brand J, Baum RP, Pavel ME, Hörsch D, O'Dorisio MS, *et al.* The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2013;40:800–16.

5. Pavel M, Öberg K, Falconi M, Krenning EP, Sundin A, Perren A, *et al.*; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2020;31:844–60.

6. Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, *et al.*; WHO Classification of Tumours Editorial Board. The 2019 WHO classification of tumours of the digestive system. Histopathology 2020;76:182–8.

7. Krausz Y, Freedman N, Rubinstein R, Lavie E, Orevi M, Tshori S, *et al.* 68Ga-DOTA-NOC PET/CT imaging of neuroendocrine tumors: comparison with 111In-DTPA-octreotide (OctreoScan®). Mol Imaging Biol 2011;13:583–93.

8. Reubi JC, Schär JC, Waser B, Wenger S, Heppeler A, Schmitt JS, *et al.* Affinity profiles for human somatostatin receptor subtypes SST1-SST5 of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use. Eur J Nucl Med 2000;27:273–82.

9. Geijer H, Breimer LH. Somatostatin receptor PET/CT in neuroendocrine tumours: update on systematic review and meta-analysis. Eur J Nucl Med Mol Imaging 2013;40:1770–80.

10. Schreiter NF, Bartels AM, Froeling V, Steffen I, Pape UF, Beck A, *et al.* Searching for primaries in patients with neuroendocrine tumors (NET) of unknown primary and clinically suspected NET: evaluation of Ga-68 DOTATOC PET/CT and In-111 DTPA octreotide SPECT/CT. Radiol Oncol 2014;48:339–47.

11. Virgolini I, Ambrosini V, Bomanji JB, Baum RP, Fanti S, Gabriel M, *et al.* Procedure guidelines for PET/CT tumour imaging with 68Ga-DOTA-conjugated peptides: 68Ga-DOTA-TOC, 68Ga-DOTA-NOC, 68Ga-DOTA-TATE. Eur J Nucl Med Mol Imaging 2010;37:2004–10.

12. Kratochwil C, Stefanova M, Mavriopoulou E, Holland-Letz T, Dimitrakopoulou-Strauss A, Afshar-Oromieh A, *et al.* SUV of [68Ga]DOTA-TOC-PET/CT Predicts Response Probability of PRRT in Neuroendocrine Tumors. Mol Imaging Biol 2015;17:313–8.

13. Gabriel M, Oberauer A, Dobrozemsky G, Decristoforo C, Putzer D, Kendler D, *et al.* 68Ga-DOTA-Tyr3-octreotide PET for assessing response to somatostatin-receptor-mediated radionuclide therapy. J Nucl Med 2009;50:1427–34.

14. Strosberg J, Nasir A, Coppola D, Wick M, Kvols L. Correlation between grade and prognosis in metastatic gastroenteropancreatic neuroendocrine tumors. Hum Pathol 2009;40:1262–8.

15. Ambrosini V, Campana D, Polverari G, Peterle C, Diodato S, Ricci C, *et al.* Prognostic Value of 68Ga-DOTANOC PET/CT SUVmax in Patients with Neuroendocrine Tumors of the Pancreas. J Nucl Med 2015;56:1843–8.

16. Binderup T, Knigge U, Loft A, Federspiel B, Kjaer A. 18F-fluorodeoxyglucose positron emission tomography predicts survival of patients with neuroendocrine tumors. Clin Cancer Res 2010;16:978–85.

17. Severi S, Nanni O, Bodei L, Sansovini M, Ianniello A, Nicoletti S, *et al.* Role of 18FDG PET/CT in patients treated with 177Lu-DOTATATE for advanced differentiated neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2013;40:881–8.

18. Muffatti F, Partelli S, Cirocchi R. Combined 68Ga-DOTA-peptides and 18F-FDG PET in the diagnostic work-up of neuroendocrine neoplasms (NEN). Clin Transl Imaging 2019;7:181–8.

19. Strosberg J, Kunz PL, Hendifar A, Yao J, Bushnell D, Kulke MH, *et al.*; NETTER-1 study group. Impact of liver tumour burden, alkaline phosphatase elevation, and target lesion size on treatment outcomes with 177Lu-Dotatate: an analysis of the NETTER-1 study. Eur J Nucl Med Mol Imaging 2020;47:2372–82.

20. Modlin IM, Kidd M, Malczewska A, Drozdov I, Bodei L, Matar S, *et al.* The NETest: The Clinical Utility of Multigene Blood Analysis in the Diagnosis and Management of Neuroendocrine Tumors. Endocrinol Metab Clin North Am 2018;47:485–504.

21. Bodei L, Kidd MS, Singh A, van der Zwan WA, Severi S, Drozdov IA, *et al.* PRRT neuroendocrine tumor response monitored using circulating transcript analysis: the NETest. Eur J Nucl Med Mol Imaging 2020;47:895–906.

22. Norlén O, Stålberg P, Öberg K, Eriksson J, Hedberg J, Hessman O, *et al.* Long-term results of surgery for small intestinal neuroendocrine tumors at a tertiary referral center. World J Surg 2012;36:1419–31.

23. Modlin IM, Pavel M, Kidd M, Gustafsson BI. Review article: somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine (carcinoid) tumours. Aliment Pharmacol Ther 2010;31:169–88.

24. Oberg K. Interferon in the management of neuroendocrine GEP-tumors: a review. Digestion 2000;62(Suppl 1):92–7.

25. Bongiovanni A, Riva N, Ricci M, Liverani C, La Manna F, De Vita A, *et al.* First-line chemotherapy in patients with metastatic gastroenteropancreatic neuroendocrine carcinoma. OncoTargets Ther 2015;8:3613–9.

26. Bongiovanni A, Liverani C, Foca F, Fausti V, Di Menna G, Mercatali L, *et al.* Temozolomide Alone or Combined with Capecitabine for the Treatment of Metastatic Neuroendocrine Neoplasia: A "Real-World" Data Analysis. Neuroendocrinology 2021;111:895–906.

27. Esser JP, Krenning EP, Teunissen JJ, Kooij PP, van Gameren AL, Bakker WH, *et al.* Comparison of [(177)Lu-DOTA(0),Tyr(3)]octreotate and [(177)Lu-DOTA(0),Tyr(3)]octreotide: which peptide is preferable for PRRT? Eur J Nucl Med Mol Imaging 2006;33:1346–51.

28. Bushnell DL Jr, O'Dorisio TM, O'Dorisio MS, Menda Y, Hicks RJ, Van Cutsem E, *et al.* 90Y-edotreotide for metastatic carcinoid refractory to octreotide. J Clin Oncol 2010;28:1652–9.

29. Kwekkeboom DJ, de Herder WW, Kam BL, van Eijck CH, van Essen M, Kooij PP, *et al.* Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. J Clin Oncol 2008;26:2124–30.

30. Paganelli G, Sansovini M, Nicolini S, Grassi I, Ibrahim T, Amadori E, *et al.* 177Lu-PRRT in advanced gastrointestinal neuroendocrine tumors: 10-year follow-up of the IRST phase II prospective study. Eur J Nucl Med Mol Imaging 2021;48:152–60.

31. Bodei L, Modlin IM, Luster M, Forrer F, Cremonesi M, Hicks RJ, *et al.* Myeloid neoplasms after chemotherapy and PRRT: myth and reality. Endocr Relat Cancer 2016;23:C1–7.

32. Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, *et al.*; NETTER-1 Trial Investigators. Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors. N Engl J Med 2017;376:125–35.

33. Kunikowska J, Pawlak D, Bąk MI, Kos-Kudła B, Mikołajczak R, Królicki L. Long-term results and tolerability of tandem peptide receptor radionuclide therapy with 90Y/177Lu-DOTATATE in neuroendocrine tumors with respect to the primary location: a 10-year study. Ann Nucl Med 2017;31:347–56.

34. Seregni E, Maccauro M, Chiesa C, Mariani L, Pascali C, Mazzaferro V, *et al.* Treatment with tandem [90Y]DOTA-TATE and [177Lu]DOTA-TATE of neuroendocrine tumours refractory to conventional therapy. Eur J Nucl Med Mol Imaging 2014;41:223–30.

35. Nicolini S, Bodei L, Bongiovanni A, Sansovini M, Grassi I, Ibrahim T, *et al.* Combined use of 177Lu-DOTATATE and metronomic capecitabine (Lu-X) in FDG-positive gastro-entero-pancreatic neuroendocrine tumors. Eur J Nucl Med Mol Imaging 2021;48:3260–7.

36. Satapathy S, Mittal BR, Sood A, Sood A, Kapoor R, Gupta R, *et al.* 177Lu-DOTATATE Plus Radiosensitizing Capecitabine Versus Octreotide Long-Acting Release as First-Line Systemic Therapy in Advanced Grade 1 or 2 Gastroenteropancreatic Neuroendocrine Tumors: A Single-Institution Experience. JCO Glob Oncol 2021;7:1167–75.

37. Claringbold PG, Price RA, Turner JH. Phase I-II study of radiopeptide 177Lu-octreotate in combination with capecitabine and temozolomide in advanced low-grade neuroendocrine tumors. Cancer Biother Radiopharm 2012;27:561–9.

38. Nicolini S, Severi S, Ianniello A, Sansovini M, Ambrosetti A, Bongiovanni A, *et al.* Investigation of receptor radionuclide therapy with 177Lu-DOTATATE in patients with GEP-NEN and a high Ki-67 proliferation index. Eur J Nucl Med Mol Imaging 2018;45:923–30.

39. Severi S, Sansovini M, Ianniello A, Bodei L, Nicolini S, Ibrahim T, *et al.* Feasibility and utility of re-treatment with (177)Lu-DOTATATE in GEP-NENs relapsed after treatment with (90)Y-DOTATOC. Eur J Nucl Med Mol Imaging 2015;42:1955–63.

40. Severi S, Bongiovanni A, Ferrara M, Nicolini S, Di Mauro F, Sansovini M, *et al.* Peptide receptor radionuclide therapy in patients with metastatic progressive pheochromocytoma and paraganglioma: long-term toxicity, efficacy and prognostic biomarker data of phase II clinical trials. ESMO Open 2021;6:100171.

41. Bartolomei M, Bodei L, De Cicco C, Grana CM, Cremonesi M, Botteri E, *et al.* Peptide receptor radionuclide therapy with (90)Y-DOTATOC in recurrent meningioma. Eur J Nucl Med Mol Imaging 2009;36:1407–16.

42. Kreissl MC, Hänscheid H, Löhr M, Verburg FA, Schiller M, Lassmann M, *et al.* Combination of peptide receptor radionuclide therapy with fractionated external beam radiotherapy for treatment of advanced symptomatic meningioma. Radiat Oncol 2012;7:99.

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