



May the Nuclear Medicine be with you! Neuroendocrine tumours and the return of nuclear medicine

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Introduction

In the Star Wars series, Jedi knights bring balance to the galaxy, improving life for the many people in the Galactic Republic. Metaphorically, multiple established and novel radioligands may act like modern-day midi-chlorians, the medians of the Force for Jedi knights, that leverage the potential to target and illuminate neuroendocrine tumours (NETs). An increasing number of radioligands are bringing new insights to diagnosing and treating neuroendocrine tumours (NETs). The new era is precision medicine and targeted therapy in disease management.

The Star Wars series is an apt metaphor for these advancements in nuclear medicine. Somatostatin receptor (SSTR) imaging with SPECT and PET/CT imaging, and peptide receptor radionuclide therapy (PRRT) have become established in a central position with level 1b evidence in therapy practice from NETTER-1 clinical trial and further progressing with the NETTER-2 trial [1, 2]. The initial results of NETTER-2 trial, which is the first randomized clinical study

of radioligand therapy (RLT) in first-line setting, showed that [¹⁷⁷Lu]Lu-DOTATATE plus octreotide LAR significantly improved progression-free survival (PFS) and the objective response rate (ORR) compared to high-dose octreotide LAR alone in patients with newly diagnosed advanced G2 and G3 GEP-NETs. There is increasing prospective evidence that [¹⁷⁷Lu]Lu-DOTA-Octreotate is more effective compared to other treatments including sunitinib (OCCLURANDOM) [3] and comparative trials in progress include COMPETE (NCT03049189) and COMPOSE (NCT04919226) studies. Whilst [¹⁷⁷Lu]Lu-DOTA-Octreotate is likely superior to other treatments, the NETTER-1 trial [1] showed that only 18% of patients achieved an objective response rate, with the majority having stabilisation of disease. Hence, new strategies are needed to increase the efficacy of PRRT and to overcome therapy resistance, especially with different radioligands and combination therapies. Consequently, these methods will shape the future patient-specific treatment methods in NETS.

This editorial discusses our overview of recent advancements in nuclear medicine, with the results of the clinical studies and the ongoing clinical trials with promising results expected, for the future of personalized and patient-specific treatments in NETs, and remark on the potential of new radioligands to further improve the imaging and diagnosis. While current guidelines must recommend routine methods for imaging and PRRT, recently published data with new theragnostic agents have brought about exciting potential additions and combinations. The new radiopharmaceuticals and radioisotopes are expected to improve therapy options and patient outcomes. Can Jedi Knights through the Force help clinical teams to improve the care of patients with NETs?

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Advancements in NET imaging

Current NET imaging relies heavily on the availability of radioligands and nuclear medicine practices. Most well-differentiated GEP-NETs express SSTR, making SSTR imaging part of gold standard care, particularly in grade 1 and 2 tumours. Multiple international and national guidelines from NANETS, ENETS, ESMO, and NCCN recommend the use of SSTR agonist PET in the initial staging algorithm for patients newly diagnosed with GEP-NETs [4–7]. [^{68}Ga]Ga-DOTA-TATE, [^{68}Ga]Ga-DOTA-TOC and [^{68}Ga]Ga-DOTA-NOC are routinely used for the assessment of patient suitability for PRRT.

The use of SSTR agonists labelled with other radioisotopes has been investigated by various international groups. Comparative studies of DOTA peptides labelled with Cu^{64} and Zr^{89} , rather than Ga^{68} , have shown various advantages in imaging GEP-NETs. Some groups demonstrated that [^{64}Cu]Cu-DOTATATE provides higher quality imaging with improved tumour uptake over Ga^{68} , allowing for clearer visualization of GEP-NETs and recently received FDA approval [8]. In a small study, [^{64}Cu]Cu-SARTATE was shown to be a safe PET radioligand with excellent imaging qualities. The image quality and lesion-to-liver ratio of [^{64}Cu]Cu-SARTATE imaging showed a potential advantage for therapeutics and suitability for prospective dosimetry for [^{67}Cu]Cu-SARTATE PRRT [9].

[^{18}F]F DOPA is particularly effective for imaging certain types of NET-related tumours, such as pheochromocytomas and paragangliomas, due to its involvement in catecholamine metabolism [10]. The commonest ^{18}F agent is, nevertheless, Fluro-deoxyglucose (FDG), with uptake more commonly associated with high-grade NETs, and can be useful in indicating de-differentiation and tumour aggressiveness. High-grade tumours may still exhibit SSTR positivity and preliminary data on newer ^{18}F -labelled SSTR agonists, specifically [^{18}F]AIF-NOTA-octreotide and [^{18}F]SiFALin-TATE, show promising results in large trials, offering logistical and biodistribution advantages due to their longer half-life [11, 12]. We will see how these new agents interact with the more common [^{68}Ga]Ga-DOTA peptides and bring the advantage of ^{18}F imaging to SSTR PET imaging.

SSTR antagonists, rather than the more common DOTA peptide agonists have shown superior imaging quality due to more binding sites on SSTR. [^{68}Ga]Ga-OPS202 (NODAGA-JR11) PET has demonstrated high receptor affinity and low background activity in a small group of GEP-NET patients [13]. According to Lin et al., SSTR antagonists offer better sensitivity and image quality with higher target-to-background ratios than agonists. These

higher detection rates may impact clinical management for certain patient subgroups [14].

Imaging insulinomas remains challenging since only about 50% express SSTR 2, although this may be underestimated. Targeting glucagon-like peptide-1 receptors (GLP-1R) with the specific ligand Exendin-4 has proven to be a superior method for imaging benign insulinomas compared to conventional techniques. The higher tumour-to-pancreas ratio and strong binding affinity for GLP-1R provide a significant advantage for localizing even small tumours, important in this challenging rare condition [15, 16].

Last but not least, Fibroblast activation protein inhibitor (FAPI) is one of the most promising agents in PET oncology imaging with FAP expression, Cancer-associated fibroblasts (CAFs) and FAPI binding related to clinical outcomes in multiple tumour types with potential for “pan-tumour imaging”. Early findings from FAPI studies show intermediate to high ^{68}Ga -FAPI uptake with favourable biodistribution in GEP-NETs [17, 18]. Variable FAPI uptake is seen in multiple tumour types but appears generally favourable with currently limited evidence for GEP-NETs. Can this “mid-chlorian” find a place in modern GEP-NET imaging or therapy? Further clinical studies are needed to determine its potential value in the clinical management of GEP-NETs.

Recent developments in NET management

NETs have often reached an advanced stage by the time of diagnosis, with metastasis spread across various organs. Disease spread diminishes the efficacy of curative surgery and elevates the role of medical therapies in managing these tumours. SSA is known to control hormone secretion and tumour growth [19, 20]. Leading health authorities, including the European Neuroendocrine Tumour Society, North American Neuroendocrine Society, and National Comprehensive Cancer Network, advocate for initiating SSA therapy in patients with inoperable, symptomless, well-differentiated NETs with substantial tumour load. This recommendation is supported by evidence from the PROMID [21] and CLARINET [20] trials.

However, when patients do not respond to SSAs, other options including molecular targeted therapies, PRRT, and chemotherapy are considered. The mTOR inhibitor everolimus, endorsed for G1/G2 pancreas NET treatment by the European Society of Medical Oncology, showed efficacy in the RADIANT-4 trial [22]. Combination therapy with everolimus and SSAs has shown added benefits over monotherapy in advanced, metastatic pancreas NETs (pan-NETs). Nevertheless, chemotherapy is an option for patients with high-volume disease. Chemotherapy (e.g. capecitabine and temozolomide, CAPTEM) is recommended for patients

with G1-G2 higher volume pancreatic-NETs. Also, CAPTEM [23] or sunitinib [24] may be offered to SSTR-negative patients with G1-G2 pan-NETs. Carbozantinib led to delay in disease progression in patients with progressive NET in the CABINET trial [25]. Looking ahead, a better understanding geno- and phenotypes of NETs is paving the way for personalized treatment options. PD-1 expression and abundance of tumour-infiltrating lymphocytes hint at the potential efficacy of immunotherapies, especially PD-1 inhibitors, in combination with anti-vascular endothelial growth factor (bevacizumab) in managing these tumours. Carbozantinib in combination with atezolizumab was associated with high disease control rates in patients with lung NET and G1-3 GEP-NET in the CABATEN basket trial [26].

PRRT stands out as a promising option for metastatic G1-G2 NETs, with the NETTER-1 trial showing a notable PFS improvement in patients treated with [^{177}Lu]Lu-DOTATATE and SSA over SSA alone. This evolving treatment landscape underscores the importance of ongoing research and clinical trials in advancing the management of pan-NETs, offering hope for more effective and tailored therapeutic strategies. Radiolabeled somatostatin receptor antagonists like [^{177}Lu]Lu-DOTA-LM3 with higher tumour uptake and tumour-to-background ratio have demonstrated a safe and potential alternative to agonists in patients with less SSTR agonist binding [27, 28]. Furthermore, alpha-labelled SSTR-based analogues recently gained more clinical interest with higher energy and less penetration range. This demonstrated a great advantage for the tumours especially resistant to standard methods of PRRT with beta particles. [^{225}Ac]Ac-labeled somatostatin receptor analogues like [^{225}Ac]Ac-DOTATATE or [^{161}Tb]Tb-labeled SSTR antagonist LM3 combined with [^{177}Lu]Lu-DOTATOC and the new SSTR ligand [^{211}Pb]Pb-DOTAMATE are still under investigation with clinical trials [29–31].

The heterogeneity of the NETs and resistance to RLT underlines the need for other complex strategies like combination therapies that are mostly still investigated with ongoing clinical trials. Regarding this, several retrospective studies have used concomitant chemotherapy including infusional 5FU, oral capecitabine (32–33), or capecitabine + temozolomide (CAPTEM) [34] with favourable responses for patients with metastatic NEN of G1-2 or unclassified grade NET. These chemotherapeutic agents have both single-agent efficacy in NET and radiosensitizing characteristics, making them logical choices for combination use, particularly in the context of disease heterogeneity. The long-term outcome data of 104 patients treated in four separate phase 2 clinical trials with [^{177}Lu]Lu-based PRRT mostly in combination with chemotherapy, reported durable responses with median PFS 37 months, overall survival

(OS) 71 months, and PFS at 10 years of 21% [35]. A 'sandwich' chemo-PRRT approach has also shown encouraging results for selected patients with SSTR and FDG-avid disease, where a study of 38 patients who received CAPTEM between 2 cycles of [^{177}Lu]Lu-DOTA-Octreotate showed ORR in 45%, disease control rate (DCR) of 84%, and PFS 72.5% and OS of 80.4% at 36 months [36].

There have only been two reported randomised controlled trials (RCTs) evaluating the use of chemotherapy concurrent with PRRT [37, 38]. The first study with [^{177}Lu]Lu-DOTA-Octreotate and capecitabine appears to be safe and is associated with a trend toward longer PFS [37]. The next reported Phase II RCT (CONTROL NETS, NCT02358356) evaluated CAPTEM combined with [^{177}Lu]Lu-DOTA-Octreotate relative to control in patients with midgut NETs (PRRT control) and pancreatic NETs (CAPTEM control) [38]. PRRT + CAPTEM combined appears to be safe and associated with a higher response rate than PRRT alone in midgut NET, and CAPTEM alone for pancreatic NET (pNET) which has the greatest benefit. However, a larger comparative Phase III RCT in pNET and longer-term follow-up will be essential to determine the overall benefit and any delayed toxicities.

Another novel technique is considered for a combination approach with a DNA-repair modifying agent that could further enhance radiation efficacy. Pre-clinical data supports that PARP inhibitor (PARPi) combined with PRRT significantly enhances NET cell death and prolonged animal survival compared to [^{177}Lu]Lu-DOTA-Octreotate alone [39, 40]. This combination reduces the efficacy of single-strand DNA-break repair and thereby enhance tumour control [39, 40]. An Australian Phase 1 study is evaluating [^{177}Lu]Lu-DOTA-Octreotate with talazoparib for patients with metastatic Grade 2 GEP NET (NCT05053854). Two current Phase I prospective trials are evaluating [^{177}Lu]Lu-PRRT with olaparib (NCT04086485, NCT05870423).

There is preclinical evidence using epigenetic modifiers to induce SSTR2 upregulation and targeting [41], including the inhibitor of DNA methyltransferase decitabine as well as the inhibitors of histone deacetylase tacedinaline and romidepsin [42]. Valproic acid, a histone deacetylase (HDAC) inhibitor may suppress proliferation and was observed to stimulate the expression of SSTR2 [43, 44]. These interesting combination approaches may improve PRRT efficacy, particularly relevant for NET with low SSTR expression. However, a prospective evaluation of efficacy and safety is needed. A prospective Phase 1 study is in progress to evaluate the epigenetic modification of SSTR-2 using ASTX727 (cedazuridine + decitabine) to improve therapeutic outcomes with Lutathera in patients with metastatic NET Ki67 < 55% with no or mild uptake on [^{68}Ga]Ga-DOTA-TATE imaging (NCT05178693).

As it is well known, sunitinib malate is a kinase inhibitor targeted therapy that blocks the action of VEGFRs that signal tumour cells to multiply. A Phase I study is in progress to evaluate the combination of sunitinib malate with [^{177}Lu]Lu-DOTA-Octreotate in metastatic progressive unresectable pancreatic NET (NCT05687123). Furthermore, an ongoing Phase II trial is testing the effectiveness of an anti-cancer drug Triapine (a ribonucleotide reductase inhibitor) combined with [^{177}Lu]Lu-DOTA-Octreotate, compared to [^{177}Lu]Lu-DOTA-Octreotate alone (NCT05724108) for patients with progressive metastatic NET.

In addition to all these promising recent developments, the possibility of increasing immune recognition of NET through cellular radiation damage and subsequent neo-antigen presentation provides an attractive rationale for combining PRRT with immune checkpoint therapy. This is especially relevant for patients with high-grade disease and heterogeneous imaging phenotype. A proof-of-concept study using PRRT with immunotherapy (avelumab) is being performed in Merkel cell carcinoma (NCT04261855). Another study in Merkel cell carcinoma is evaluating the combination of pembrolizumab and PRRT (NCT05583708). For patients with Grade 3 well-differentiated NET or poorly differentiated neuroendocrine carcinomas (NEC), a Phase II combination study is underway using [^{177}Lu]Lu-DOTA-Octreotate and nivolumab (NCT04525638).

The future in NET management is bright if we choose the right imaging technique and suitable treatment for each patient. Whilst more novel and combination strategies are expected to be discovered and developed in the pre-clinical setting, advancing these into the clinical setting would necessitate careful evaluation in clinical trials to assess feasibility, safety, dosimetry and efficacy. Given the complexity of clinical decision-making and treatment sequencing, patients with advanced NETs should be analyzed and decision-making regarding treatment should be personalized. This should leverage a multidisciplinary team approach, to devise and periodically reassess the treatment strategy based on the progression or control of the disease. The Force in Nuclear Medicine and the formulation of this treatment strategy ought to consider factors specific to the disease and the individual patient, including comorbid conditions and personal treatment preferences.

Conclusion

As once told by a well-known Jedi master “Detect and treat, you must.” Similar to the prospect and innovation in the Star Wars epic, the advancements in nuclear medicine bring a new perspective to NET management. The development of advanced radioligands, akin to the evolution of the

Jedi, marks a significant leap in diagnosing and treatment. This progress improved diagnostic accuracy, better patient stratification, and integrated therapeutic options, leading to more effective and personalized care. Further research and clinical trials will continuously validate the efficacy of these novel radioligands, promising further improvements in the diagnosis and treatment of NETs, aiming for a future with better outcomes and an improved quality of life for all patients. May the Force be with us all!

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Declarations

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