



REVIEW

# Optimising Radioligand Therapy for Patients with Gastro-Entero-Pancreatic Neuroendocrine Tumours: Expert Opinion from an Italian Multidisciplinary Group

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## ABSTRACT

Radioligand therapy (RLT) with lutetium ( $^{177}\text{Lu}$ ) oxodotreotide is an approved therapy in combination with somatostatin analogues (SSAs) for

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patients with advanced, well-differentiated G1–G2, gastro-entero-pancreatic neuroendocrine tumours (GEP-NETs) that progress on SSAs. We conducted a series of round table meetings throughout Italy to identify issues related to RLT delivery to patients with GEP-NETs. Four key issues were identified: (1) the proper definition of tumour progression prior to RLT initiation; (2) the impact of RLT in

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patients with bone metastases and/or high hepatic tumour burden; (3) the optimal follow-up protocol after RLT; and (4) organisational issues related to RLT use and managerial implications. This article reviews the literature relating to the aforementioned issues and makes recommendations based on available evidence and Italian NET experts' opinions. In particular, the group recommends the development of a diagnostic–therapeutic care pathway (DTCP) for patients undergoing RLT which provides systematic guidance but can still be individualised for each patient's clinical and psychosocial needs. A DTCP may clarify the diagnostic, therapeutic and post-treatment monitoring process, and improve communication and the coordination of care between hub and spoke centres. The DTCP may also contribute to

changes in the care process related to the 2013/59/EURATOM Directive and to the definition of costs when planning for future or updated reimbursement of RLT in Italy.

**Keywords:** Diagnostic–therapeutic care pathway; Expert opinion; Gastro-enteropancreatic neuroendocrine tumours; Italy; Lutetium ( $^{177}\text{Lu}$ ) oxodotreotide; Organizational implications, radioligand therapy

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## Key Summary Points

Radioligand therapy [RLT; e.g. lutetium ( $^{177}\text{Lu}$ ) oxodotreotide (Lutathera<sup>®</sup>)] is an established treatment option for progressive, well-differentiated, grade 1–2 gastro-entero-pancreatic neuroendocrine tumours (GEP-NETs).

In clinical practice, however, RLT is underutilised, and the optimal sequence of treatment is undefined; successful treatment of GEP-NETs requires clear practical guidance on managing the patient therapeutic journey and optimisation of RLT.

In this article, we analyse four key areas where (in the opinion of Italian experts) practical clarification of RLT guidelines is needed, including: (1) defining tumour progression prior to RLT; (2) RLT impact on bone metastases and/or high hepatic tumour burden; (3) optimal protocols for monitoring tumour response; and (4) organisational issues related to RLT use.

The development of a diagnostic-therapeutic care pathway (DTCP) is recommended in order to provide systematic guidance being personalised according to clinical and psychosocial needs of each patient.

A DTCP may clarify the diagnostic, therapeutic and post-treatment monitoring process and improve the coordination of care in patients with GEP-NETs.

## INTRODUCTION

Radioligand therapy (RLT), also known as peptide radionuclide receptor therapy (PRRT), is now an established treatment option for progressive, well-differentiated, grade 1–2 (G1–G2) gastro-entero-pancreatic neuroendocrine tumours (GEP-NETs) [1]. RLT use is also gradually increasing as a second-line treatment for patients with GEP-NETs progressing on or after

treatment with somatostatin analogues (SSAs) [2]. Lutetium ( $^{177}\text{Lu}$ ) oxodotreotide (Lutathera<sup>®</sup>) is the first authorised radiopharmaceutical for RLT in the treatment of GEP-NETs that entered the market, representing an important step forward in the management of patients with these types of tumours. In 2017, this radiopharmaceutical was designated as an orphan medicine and indicated for the treatment of unresectable locally advanced or metastatic, progressive, well-differentiated (G1–G2), somatostatin receptor (SSTR)-positive GEP-NETs in adults [3]. This indication is predominantly based on data from the phase III NETTER-1 clinical trial, in which lutetium ( $^{177}\text{Lu}$ ) oxodotreotide (also referred to as  $^{177}\text{Lu}$ -DOTA<sup>0</sup>-Tyr<sup>3</sup>-octreotate) plus label-dose long-acting repeatable (LAR) octreotide were compared with high-dose octreotide LAR [60 mg every 4 weeks (q4w)] in 229 patients with advanced, SSTR-positive midgut NETs who had progressed on octreotide LAR 20–30 mg every 3–4 weeks within a time frame of up to 3 years [4]. The estimated rate of progression-free survival (PFS) at month 20 was 65.2% [95% confidence interval (CI), 50.0–76.8] with lutetium ( $^{177}\text{Lu}$ ) oxodotreotide and 10.8% (95% CI 3.5–23.0) with high-dose octreotide LAR [4]. The risk of disease progression or death was 79.0% lower in the group receiving lutetium ( $^{177}\text{Lu}$ ) oxodotreotide plus octreotide LAR at standard dose compared with the control group receiving high-dose octreotide LAR [4]. The extension to treat all GEP-NETs was also based on data from a previously published patient series [5–7].

While these results indicate a clinically relevant improvement of PFS with lutetium ( $^{177}\text{Lu}$ ) oxodotreotide compared with high-dose octreotide LAR, RLT is underutilised in clinical practice [6]. In addition, several therapeutic options are available for patients with GEP-NET and the optimal sequence of these treatments has yet to be clearly defined [8]. In this setting, several factors need to be taken into account for decision-making, including the treatment goal, tumour characteristics (i.e. SSTR status, functioning/non-functioning tumour, primary site, tumour morphology and grading), patient profile (i.e. performance status, comorbidities and

quality of life) and treatment characteristics (i.e. safety profile and schedule) [1, 8].

These issues make adopting this promising therapy into clinical practice a major challenge that requires extensive coordination of different specialists within a NET-dedicated multidisciplinary team (MDT). The challenge is compounded by the fact that clinical outcomes depend on an appropriately designed and adequately managed patient therapeutic journey, including accurate disease characterisation, identification of the best treatment candidates, and appropriate therapy administration and monitoring. Therefore, physicians wishing to optimise RLT need practical guidance on implementing this treatment in clinical practice.

This article aims to critically analyse four key areas where (in the opinion of Italian experts) practical interpretation and clarification of guideline recommendations related to RLT are needed. These four areas are: (1) the definition of tumour progression prior to RLT initiation; (2) the impact of RLT in patients with bone metastases and/or high hepatic tumour burden; (3) the optimal follow-up protocol to monitor tumour response to RLT; and (4) organisational issues related to RLT use and managerial implications.

## MATERIALS AND METHODS

To identify the most relevant issues related to RLT in Italy and formulate recommendations, the authors (Scientific Committee) met and convened a series of 24 local round table meetings with other oncology practitioners throughout Italy between 12 May 2021 and 22 February 2022 (see 'Round table discussion' in Electronic Supplementary Material).

Before carrying out these round table meetings, the Scientific Committee conducted various systematic literature searches [9] using the topics and keywords identified by working groups at a primary meeting (see below). Relevant publications identified via searches were presented at a second meeting to guide scientific discussions. Moreover, in May 2021, an initial survey on the multidisciplinary

management of patients with GEP-NETs in Italy was administered to 90 physicians who treat such patients (see 'Survey Results' and 'Supplementary Fig. 1' in Electronic Supplementary Material).

Literature search results were presented using a narrative approach to discuss the available evidence and report the authors' viewpoints. Arguments and topics of interest for the discussion were defined using PICO, i.e. patient/population (e.g. patients with progressing GEP-NETs, bone metastases and/or high hepatic tumour burden), intervention (RLT), comparators (SSAs), and outcomes (efficacy, safety, optimal follow-up procedures, economic burden, organisational issues and managerial implications) [10].

The literature search was conducted in April 2021 on PubMed and Scopus using keywords generated from collegial discussions and brainstorming processes [11], during the first round table meeting. Titles and/or abstracts containing the following keywords were included in the search: GEP-net patient treatment, GEP-net tumour progression, GEP-net bone metastases, high hepatic tumour burden, RLT, RLT initiation, RLT use, SSA initiation, SSA use, efficacy outcome, safety outcome, GEP-net follow-up protocols, RLT economic aspect, RLT organisational issue, GEP-net organisational issue.

The article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

## DEFINITION OF BASELINE TUMOUR PROGRESSION

According to the United States Food and Drug Administration and European Medicine Agency guidelines, tumour *progression* must be identified before initiating lutetium ( $^{177}\text{Lu}$ ) oxodotreotide treatment [3]. However, these guidelines do not provide a specific definition of tumour progression; it is still unclear if progression should be based on imaging and/or clinical behaviour and/or an increase in circulating biomarkers. Notably, recommendations on imaging in patients with NETs failed to reach

**Table 1** Criteria for definition of tumour progression used in phase III clinical trials with gastro-entero-pancreatic neuroendocrine tumour treatments

Study/ treatment	Criteria	Definition
PROMID [15]	RECIST 1.0	Increase of $\geq 20\%$ in the sum of the longest diameter of target lesions, taking as a reference the smallest sum on longest diameter recorded since the treatment started
Octreotide long-acting	[16]	The appearance of $\geq 1$ new lesion(s)
CLARINET [17]	WHO [14]	Increase of $\geq 25\%$ in the size of one or more measurable lesions
Lanreotide Autogel		The appears of new lesions
NETTER-1 [4]	RECIST 1.1	Increase of $\geq 20\%$ in the sum of diameters of target lesions, taking as a reference the smallest sum on study (including the baseline sum if that is the smallest on study)
$^{177}\text{Lu}$ - octreotate	[13]	The increase must also demonstrate an absolute increase of $\geq 5$ mm
		The appearance of $\geq 1$ new lesion(s)

RECIST response evaluation criteria in solid tumours,  
WHO World Health Organization

a consensus on the type of imaging to be used to monitor tumour response [12].

In the NETTER-1 study [4], tumour progression was defined according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria [13], using either computed tomography (CT) or magnetic resonance imaging (MRI) for monitoring treatment response (Table 1). Other major phase III studies of

various SSAs used the World Health Organization (WHO) criteria [14] (e.g. the PROMID study with octreotide LAR [15]) or RECIST version 1.0 criteria [16] (e.g. CLARINET study with lanreotide autogel [17]) to assess tumour progression during treatment (Table 1). Despite the well-established role of RECIST in clinical research, these criteria have drawbacks that limit their application in clinical practice. For example, they do not guide the choice of target lesions or imaging technique and identifying reliable extrahepatic target lesions in GEP-NETs can be difficult [18]. In addition, the usually low proliferation rate in GEP-NETs means that the magnitude of change defined by RECIST criteria may not reflect clinically meaningful changes in tumour size or density [19, 20].

In daily clinical practice, progressive disease (PD) may follow different criteria than those utilised for pivotal clinical trials. Specifically, PD can be determined by evidence of tumour progression via imaging, even when the classical WHO/RECIST criteria are not met. Moreover, tumour progression can be considered a composite concept that includes hybrid imaging-based characterisation and clinical assessment; some patients may have radiologically stable tumours, yet simultaneously show clinical/biochemical signs of PD. Such non-radiological signs of progression can include worsening of a clinical/biochemical syndrome and increases in the levels of a circulating biomarker (e.g. chromogranin A [CgA]).

In the case of GEP-NETs, the recommended functional imaging modality is  $^{68}\text{Ga}$  gallium ( $^{68}\text{Ga}$ )-DOTA-SSA-positron emission tomography (PET) [12]. However, with respect to functional imaging, there are no clear criteria defining PD [21], and there is no standardisation in the interpretation of, for example, the appearance of new lesions or an increase in maximum standardised uptake value ( $\text{SUV}_{\text{max}}$ ). The increase in lesion uptake from  $^{68}\text{Ga}$ -DOTA-SSA-PET indicates an increase in SSTR expression and lesion uptake should be higher than the background liver uptake [21]. However, there is no evidence that an increase in  $\text{SUV}_{\text{max}}$  with  $^{68}\text{Ga}$ -DOTA-SSA-PET is a sign of PD, since there is a lack of standardised imaging protocols, and, therefore, this parameter should not

be interpreted as PD. On the other hand, functional imaging assessed with  $^{18}\text{F}$ fluorodeoxyglucose ( $^{18}\text{F}$ FDG)-PET provides different information, since the presence of a 'new lesion' on PET imaging in patients with radiographically stable disease and without clinical/biochemical signs of PD might be sufficient to consider that the disease is progressing.

The lack of strict criteria for defining PD allows physicians the flexibility to determine patient eligibility for RLT using a broad clinical context. We recommend that a NET-dedicated MDT determines the identification of PD prior to RLT. The MDT should consider the presentation on complete morphological imaging (i.e. CT or MRI), the patient's clinical and biochemical profile, and/or functional imaging results. MDTs play a key role in adjudicating ambiguous evidence of PD in, for example, patients with 'slow' radiological PD, who may benefit from closer monitoring and adjustment of their SSA treatment schedule rather than initiating RLT.

If the patient is a potential candidate for RLT, blood tests, including haematology and renal and hepatic function, should be conducted at least once 2–4 weeks prior to initiating RLT (Table 2) [21], as well as shortly before administration [3]. The results of these tests should be

**Table 2** Blood tests recommended 2–4 weeks prior to treatment with radioligand therapy

Blood urea nitrogen
Serum creatinine and creatinine clearance for calculation of glomerular filtration rate
Albumin
Alkaline phosphatase
Aspartate aminotransferase
Alanine aminotransferase
Total bilirubin
White blood cell count with differential
Haemoglobin
Platelet count

used to guide decisions about eligibility and eventually to adjust the administered doses.

## RLT IN PATIENTS WITH HIGH BONE AND/OR HEPATIC TUMOUR BURDEN

Currently, there is a lack of clarity regarding the role and value of RLT in patients with high bone and/or hepatic tumour burden. Therefore, clinical criteria are needed to define which of these patients may benefit from RLT.

### Bone Metastases

GEP-NETs are much less likely to metastasise to bone than to liver [22]. Nevertheless, patients with bone metastases have worse clinical outcomes and shorter PFS and overall survival (OS) compared with patients without bone metastases [23]. Regarding RLT, bone metastases raise concerns about radioligand penetration into bone and the risk of treatment-related myelosuppression caused by the accumulation of radioactivity in skeletal segments rich in bone marrow.

In clinical practice, the superior sensitivity and specificity of  $^{68}\text{Ga}$ -DOTA-SSA-PET/CT compared with conventional imaging and radiological evaluation enable earlier identification of bone metastases [24]. Some MRI techniques can be considered in addition to  $^{68}\text{Ga}$ -DOTA-SSA-PET/CT.

From the discussions at the round table meetings, two major concerns, related to RLT use in patients with bone metastases, were apparent: (1) the effective ability of the radioligand to penetrate bone and reach metastatic sites; and (2) the potential increased risks of myelotoxicity and haematological adverse events, after RLT administration, in patients with significant skeletal metastasis. Generally, RLT appears effective in patients with bone metastases, and treated patients typically show a good prognosis and a low probability of experiencing skeletal events [25, 26]. Researchers from Germany reported a median OS of 51.0 months in patients treated with RLT with

GEP-NETs and bone metastases, and a median OS of 56.0 months in those with a measurable bone response [25, 26]. Factors associated with a significantly worse prognosis were neuron-specific enolase (NSE) > 15.0 ng/mL, Ki67 index > 10.0% at baseline and blood CgA > 600.0 ng/mL. In contrast, age, performance status and the number of lesions were not significant predictors [25, 26]. Many patients with bone metastases or bone marrow involvement experienced symptomatic improvement after RLT, including complete or partial bone pain relief, performance status improvement and better self-reported quality of life [25, 26]. Overall, preliminary data indicate that RLT can be effective even in patients with diffuse bone metastases [27]. The incidence of significant haematological toxicity is generally low (10.2% in the study described above [25]) and reversible, possibly because of the low expression of SSTRs in bone marrow [28]. Among six patients with GEP-NETs and bone marrow involvement who received RLT, the only haematological adverse event was grade 1 anaemia in one patient [29]. The myelotoxicity of RLT seems related to the relative extent of irradiation received by red bone marrow from adjacent organs largely involved by NETs rather than to the presence of bone metastases [30, 31]

In patients with NETs, there is no evidence of RLT-related toxicity in healthy bone tissue. Lutetium ( $^{177}\text{Lu}$ ) oxodotreotide has a beta emission [3], with a mean range penetration in the bone of 0.16 mm, which is lower than most other beta emitters currently used for therapeutic purposes [32, 33]. Regarding a possible effect of RLT on osteoblasts, one expert mentioned that there is no evidence that RLT affects healthy bone (endosteum) but is focused on the bone marrow. Dosimetry does not lead to precise doses to the endosteum, but the dose of  $^{177}\text{Lu}$  released to healthy bone is much lower than the dose given by external beam radiotherapy.

Bone metastases are not common in NETs, affecting 4.0–12.0% of patients [24], although their prevalence may be underestimated [23].

However, they represent a negative prognostic factor, usually because they are a marker of more extensive metastatic spread [34]. Based on the abovementioned clinical results in patients with metastatic GEP-NETs [25, 26, 29], RLT is an effective treatment for those with bone metastases. Although some patients may experience haematological toxicity, it is generally manageable through dose interruption or supportive measures [27]. Because of potential issues in accurately imaging bone metastases, we recommend assessing the response to RLT using a combination of clinical, functional and radiological parameters.

### **Patients with High Hepatic Tumour Burden**

The liver is the most common metastatic site in patients with GEP-NETs [22]. Patients with high hepatic tumour burden are likely to benefit from RLT, similarly to patients with low hepatic tumour burden. A post hoc analysis of data from the NETTER-1 study showed that PFS after RLT was similar in patients with a high hepatic tumour burden (i.e. > 50.0% of liver involvement on CT or MRI) as in those with moderate (25.0–50.0%) or low (< 25.0%) hepatic tumour burden; the same pattern was seen in patients with elevated or normal alkaline phosphatase levels at baseline [35]. The rates of grade 3–4 hepatic toxicities were low in all groups in the NETTER-1 post hoc analysis, so no statistical comparison was undertaken; there was, however, no evidence of increased risk of liver enzyme abnormalities in those with greater versus smaller hepatic involvement [35]. A Polish study of 42 patients receiving RLT [39 (93.0%) with liver metastases] reported small but statistically significant reductions in albumin and alanine aminotransferase levels and an increase in bilirubin in the 2 days after each treatment. However, all hepatic parameters stayed within the normal range [36].

## OPTIMAL FOLLOW-UP PROTOCOL AFTER RLT

While it is important to define the optimal approach to follow-up during and after RLT (in relation to the type and timing of tests), follow-up should also be tailored to each patient's circumstances because "one size does not fit all". We believe current guidelines do not offer sufficient guidance for a standardised approach to patient follow-up after RLT.

In the NETTER-1 study, patients were monitored every 2–4 weeks during RLT with tests for haematology, biochemistry and renal function [4]. We recommend defining the strategy for monitoring tumour response to RLT based on the morphological and functional characteristics of the tumour, degree of malignancy and the capabilities of the clinical centre (e.g. availability of imaging modalities and MDTs). Patients undergoing RLT provide blood samples regularly for the detection of adverse reactions [3], so other tests (e.g. urinary 5-hydroxyindoleacetic acid in patients with carcinoid syndrome-associated GEP-NETs) can be undertaken at the same time. Imaging assessment should not be performed during RLT treatment unless PD is suspected. CgA may be a useful adjunct

assessment but should not be considered a surrogate marker for defining response.

When developing a strategy for tumour monitoring, it is important to balance the need for early detection of PD against the risks (radiation exposure and use of contrast media) and the costs of monitoring stable patients [19]. Imaging patients with NETs can be extremely complex because of high tumour heterogeneity. Table 3 summarises our recommendations for using CT, MRI and ultrasound in the follow-up of patients with GEP-NETs, based on current recommendations and evidence [37–40]. PET plays only a marginal role during prolonged follow-up because of the cost. On the other hand, liver ultrasound has an important role, because of its long-term safety during repeated use.

In addition to the type of imaging modality, the timing of imaging assessments must also be considered. In the NETTER-1 study, patients were followed up every 12 weeks after completing the last treatment cycle, starting 2 months after the fourth cycle using CT or MRI [4]. No specific follow-up intervals after RLT are described in the European Society for Medical Oncology guidelines. However, these guidelines do recommend imaging assessments every

**Table 3** Expert opinion on the role of different imaging modalities in the diagnosis and follow-up of patients with gastroentero-pancreatic neuroendocrine tumours

CT	MRI	US
Mandatory for diagnosis [39], including recurrences, so use if recurrence suspected	During diagnosis, use DWI and liver-specific contrast media for better study of the liver [37, 38]	Can be used at any stage. The use of US contrast medium does not carry any risks, so can be used repeatedly during long-term follow-up [40]
Dynamic CT scanning should be used after contrast medium injection; quadruphase acquisition should be used for imaging the liver	During prolonged follow-up, MRI may be used in order to reduce the use of CT and risks associated with ionising radiation and the use of contrast agents	
During follow-up, can be progressively replaced by other techniques without ionising radiation (MRI, US)		

CT computed tomography, DWI diffusion-weighted imaging, MRI magnetic resonance imaging, US ultrasound



**Table 4** Follow-up protocol after completion of radioligand therapy recommended in the NANETS/SNMMI guidelines [21]

Time after treatment <sup>a</sup>	Clinical evaluation	Laboratory tests <sup>b</sup>	Tumour markers <sup>c</sup>	Diagnostic imaging
2–4 weeks	✓	✓		✓ <sup>d</sup>
2 months		✓		
3 months	✓	✓	Per team	
6 months	✓	✓	Per team	✓
12 months	✓	✓	Per team	✓
Long term	Per team	Per team	Per team	Per team

*ALP* alkaline phosphatase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *GFR* glomerular filtration rate, *NANETS* North American neuroendocrine tumor society, *RLT* radioligand therapy, *SNMMI* society of nuclear medicine and molecular imaging

<sup>a</sup>Increase monitoring as needed based on patient's clinical presentation, symptoms, concern about progressive disease, or post-treatment sequelae

<sup>b</sup>Complete blood count with differential, ALP, ALT, AST, total bilirubin, and serum creatinine/GFR

<sup>c</sup>Monitoring of markers should be based on clinical indication/presentation

<sup>d</sup>Imaging is recommended once between 1 and 3 months after RLT

3 months for patients with G2 NETs and Ki67 > 5.0% (i.e. candidates for RLT), extending to every 1–2 years over time [1]. Similarly, the Spanish consensus recommendations suggest assessments every 3 months for 2 years when following up patients with metastatic G1–G2 GEP-NETs, then every 6 months if patients are stable [19]. Once PD is detected, these guidelines recommend restarting assessments every 3 months [19]. The European Neuroendocrine Tumour Society (ENETS) recommendations specify different follow-up intervals based on tumour site, size and type (e.g. type 1, 2 and 3 stomach NEC/NETs, gastrinoma or insulinoma); however, in most G1–G2 GEP-NETs, the recommended interval is 3–6 months [41].

Among the existing guidelines, only those by the North American Neuroendocrine Tumor Society (NANETS) and Society of Nuclear Medicine and Molecular Imaging (SNMMI) provide guidance on follow-up after RLT completion (Table 4) [21]. These guidelines recommend laboratory assessments, clinical evaluations, and imaging at specific intervals; however, tumour marker assays should be determined by the patient's cancer team. Similarly, they note that the follow-up protocol should be modified

according to the patient's clinical presentation, symptoms, or sequelae [21], consistent with our recommendation for tailoring the follow-up schedule according to the patient's characteristics and the unit's facilities.

Survival after a diagnosis of well-differentiated GEP-NETs in Italy is high, with 5-year survival rates of 75.0–85.0% for well-differentiated functional or non-functional tumours [42], so follow-up will be lifelong in most patients. We recommend follow-up every 3–6 months for the first 2–3 years and annually thereafter. This follow-up should include clinical assessment, blood tests, imaging (using ultrasound, MRI, and triple-phase CT with contrast for an accurate study of the liver) and endoscopy as indicated. When recurrence or PD is suspected, functional imaging using <sup>68</sup>Ga-DOTA-SSA- or <sup>18</sup>F-FDG-PET/CT should be integrated with morphological imaging. Prolonged follow-up has a significant economic impact, with the costs of diagnostic tests, such as PET/CT, making a substantial contribution. Follow-up should be tailored to the individual patient according to the aggressiveness of the patient's NET, the stage at diagnosis, the site(s) of the tumour and all available prognostic parameters and

modified as needed according to any changes in their clinical or personal circumstances.

While survival is the major goal of cancer treatment, it brings its own challenges, including long-term physical and functional treatment effects (which may be particularly relevant in patients who have received radiation), worse quality of life, fatigue, psychological impacts (e.g. anxiety, fear of recurrence, post-traumatic stress disorder and depression), effects on sleep and impact on the patient's ability to return to work [43–46]. Since not all centres have sophisticated imaging modalities, some patients must travel to a tertiary centre for assessment, contributing to the economic burden and potentially to their distress. Therefore, follow-up of patients with GEP-NETs must be multifactorial and include not only assessment for recurrence. Some patients appear particularly vulnerable to psychological distress, including elderly patients and those who do not have a spousal partner [43, 47]. Survivorship is not a “one size fits all” experience, with each patient having a different physical and psychological reaction to cancer treatment [48]. This highlights the importance of developing a systematic and comprehensive approach to the follow-up of patients with GEP-NETs after RLT that encompasses all the patient's needs (i.e. clinical, psychosocial and financial) and ensures effective communication between all stakeholders, including the patient's primary care team and their family/support network [43, 44]. If possible, the follow-up protocol for each patient should be developed by an MDT.

## ORGANISATIONAL ISSUES

The complexity of the diagnostic–therapeutic care pathway (DTCP), particularly that related to RLT treatment, requires standardised management of each phase, which can optimise both patient access to the treatment and clinical outcomes, as well as maximising the efficiency and potential benefits of overall DTCP management. Multiple biological tests are required to monitor the patient's condition and adapt the therapeutic protocol as required, including the dose, infusion interval or the number of

infusions [3]. Our round table meetings identified several issues related to the organisation and delivery of RLT services, including difficulties in accessing the services needed to define PD at smaller centres (e.g. advanced imaging techniques or NET-dedicated MDTs). Other issues included difficulties in coordinating treatment between different centres, poor recognition of the value of RLT due to a lack of training in peripheral centres, and difficulties in referring patients from smaller centres to RLT centres. We have identified several actions that will help to organise the DTCP better and optimise RLT from a hospital perspective, as well as improve the patient journey and experience.

### Organisational Model

RLT delivery in Italy should be based on a “hub-and-spoke” model, where patients are referred from smaller centres (spokes) and receive treatment at high-volume expert centres (hubs). Hubs need to receive feedback on waiting times and their ability to provide services to investigate how closely real-world practice aligns with forecasts made at a regional level. Ideally, there should be an ongoing monitoring process to identify the difficulties in providing services within defined deadlines. Feedback should inform how care can be better delivered and identify performance indicators that can be used to highlight specific needs and barriers.

To optimise the DTCP, training needs to be developed around a core curriculum of skills to address knowledge gaps. While the core curriculum should define key learnings for both hub and spoke centres, the training itself should be tailored to each type of centre to ensure that personnel receive the information that is most relevant for them, specifically based on their knowledge gaps (e.g. referral criteria and post-treatment monitoring at spoke centres versus RLT procedures in hub centres).

There is also a need to define the entire DTCP more comprehensively for patients with GEP-NET who are candidates for RLT. The DTCP should explicitly define the timing and sequence of tasks involved and the clinical team/discipline responsible for each task [49].

This can be performed through specific management tools, such as the Responsible, Accountable, Consulted and Informed (RACI) matrix [50], defining responsibilities in patient management at all stages of the RLT process. The RACI matrix should be aligned with performance indicators identified during the research and monitoring phases and include care quality indicators. These indicators should cover a range of outcomes: clinical (e.g. response and recurrence), organisational (e.g. follow-up visits), managerial (e.g. costs) and patient-related (e.g. quality of life, satisfaction, and perceptions of the treatment experience). Because of disease and patient heterogeneity, a single DTCP is unlikely to be suitable for all patients with GEP-NET, who will need to be stratified and specific pathways developed based on patients' health and social needs and characteristics. These DTCPs would help clarify the process within a single centre and aid in the organisation/coordination of care between hub and spoke centres. Moreover, they can potentially improve efficiency and optimise the overall clinical pathway from the hospital and the patient's perspectives.

Furthermore, the proper development of a DTCP for RLT could support the identification of a specific reimbursement tariff devoted to RLT administration. This is important in Italy, where the public healthcare system provides reimbursement based on a single healthcare service, which complicates reimbursement for complex treatment protocols, such as RLT. To achieve this, scientific societies and clinical communities should collaborate to show the policymakers that a DTCP could provide an economic advantage by avoiding the unnecessary repetition of examinations and assessments. Another advantage of a DTCP is to foster a network mindset among healthcare personnel for managing patients with GEP-NETs and develop a more collaborative framework to streamline processes and reduce the risk of repetition and errors arising from poor communication.

### ***Impact of new EURATOM Regulations***

The Council Directive 2013/59/EURATOM defined basic safety standards for ionising

radiation exposure in a medical setting and was implemented in Italian law in 2020 as statute 101/2020 [51], although several issues around radioprotection, optimisation and the dosimetric approach are yet to be addressed [52].

Under this legislation, lutetium ( $^{177}\text{Lu}$ )-based treatments could be administered in a day-hospital setting if the necessary safety protocols are in place, whereas, previously, all RLT had to be administered in an inpatient setting. Day-hospital treatment has pros and cons from a clinical and organisational perspective. Although day-hospital administration may not suit all eligible patients, this organisational model could potentially reduce hospital costs and increase the number of centres that can offer RLT, thus improving overall patient access to care. Alternatively, day-hospital administration of lutetium ( $^{177}\text{Lu}$ )-based treatments could be risky for patients with a high tumour burden or highly functional tumours. In addition, it will be difficult to manage adverse events occurring after discharge, since a 'radioactive' patient cannot simply access emergency services or provide samples for assessment without protections being implemented. Therefore, proper characterisation and stratification of patients, as part of the DTCP described above, could help identify those who are potential candidates for day-hospital RLT administration.

We strongly recommend DTCPs, operative procedures and continuous training for day-hospitals to limit the exposure to and risk of radiation contamination of hospital staff (i.e. involved in post-discharge roles and treatment optimisation) and caregivers (i.e. at-home contamination). A personalised, dosimetry-based approach is advisable.

### ***Innovative Medicine Funding and Drug Reporting***

In Italy, the fund for innovative oncological drugs (FIO) provided coverage for RLT as a new cancer treatment for the first 36 months after it became available; however, the period for FIO funding of lutetium ( $^{177}\text{Lu}$ ) oxodotreotide ended in March 2022.

In the short term, properly evaluating the number of patients who access RLT each year is mandatory to define budgetary needs.

**Table 5** Summary of expert recommendations on optimising radioligand therapy in Italy

Definition of tumour progression prior to initiation of RLT

Identification of progression prior to RLT should be based on a broad (holistic) clinical assessment

RLT in patients with bone metastases and/or high hepatic tumour burden

Bone metastases of GEP origin are effectively controlled by RLT and multifocality should not represent an obstacle to the indication for this therapy

The fear of using RLT in patients with well-differentiated GEP-NETs and bone metastases does not seem justified, both in terms of disease control and symptom control

RLT is effective in patients with hepatic disease, regardless of the baseline liver disease burden, and treatment does not have effects on liver function parameters

It is important to assess the degree of initial liver involvement since adverse events can be related to disease progression in compromised patients

The optimal follow-up protocol after RLT

The strategy to monitor response to RLT should be defined based on the morphological and functional characteristics of the tumour, its degree of malignancy, and the patient's general clinical profile

In the absence of any clinical indication, CgA evaluation and imaging are unnecessary during RLT

Follow-up for each patient should be defined by the MDT and tailored to the patient's disease characteristics and therapeutic goals (e.g. survival or quality of life)

Follow-up timing, modulated based on prognostic parameters, could be proposed in the persistent disease setting

Follow-up protocols should take into account the psychological impact of monitoring on patients, as well as the financial impact on the health system

**Table 5** continued

The timing should involve closer assessments early after RLT, becoming less frequent over time

Assessments involving ionising radiation (e.g. CT) should be used less often over time and replaced with safer modalities (e.g. US)

Organisational issues related to RLT use and managerial implications

Hub centres need to obtain feedback on waiting times, needs, and difficulties associated with service access (e.g. patient travel time) and provision in order to effectively provide RLT services

Training on RLT is needed in both hub and spoke centres, with curriculum tailored to the specific needs of each

A DTCP for RLT is needed to meet patients' needs and facilitate MDT interactions, as well as to codify the service parameters for reimbursement

DTCP development should involve an expert panel with the contribution of Scientific Societies

Patient associations should be involved to reflect patient experiences and perceptions, as well as to suggest areas for improvement from a patient perspective

Performance indicators should be defined for the ongoing assessment of services

Efforts should be made to promote collaborations between small local centres and reference centres to optimise diagnosis and access to treatment, as well as to define standards in work organisation and patient management

*CgA* chromogranin A, *CT* computed tomography, *DTCP* diagnostic-therapeutic care pathway, *GEP* gastro-entero-pancreatic, *GEP-NETs* gastro-entero-pancreatic neuroendocrine tumours, *MDT* multidisciplinary team, *RLT* radioligand therapy, *US* ultrasound

Pharmacists need to be involved in this process to guarantee adequate resources and ensure that this therapy, supported by strong evidence of efficacy and safety, is administered to all patients who can benefit from it. A forecast analysis can be developed from this information, along with accurate budget estimates.

The funding of hospital treatments in Italy is based on diagnosis-related groups (DRGs). Currently, RLT services are coded as DRG409, which is arguably inappropriate for the range of diagnostic, monitoring and treatment modalities involved in this form of therapy, particularly if RLT may be administered in the day-hospital setting.

We recommend that Scientific Societies collaborate for the development of cost mapping and cost-absorption analyses, as well as for the formulation of appropriate DRG codes for RLT at Italian centres.

## DISCUSSION AND CONCLUSIONS

RLT is an effective and well-tolerated treatment option for patients with SSTR-positive progressive G1–G2 GEP-NETs. However, it requires expertise to monitor patients before each administration, during treatment and in the subsequent months or years. We have shared several recommendations based on our experience and expertise as Italian clinicians across various disciplines and have critically reviewed the literature (Table 5). These recommendations do not consider off-label applications of RLT (i.e. using RLT as first-line treatment, retreatment in patients with relapsing GEP-NETs, etc.) because they are not approved by European and Italian agencies and are classified as “investigational” when used in clinical practice.

These recommendations highlight the mandatory role of MDTs in patient selection for RLT. Educating MDTs on RLT is also important and educational initiatives must be appropriate for the whole care team, especially when it is expected that other radioligands will be approved and the use of RLT will rapidly increase. There is a general trend in Europe, supported by ENETS and the European Reference Network on Rare Adult Solid Cancers

(EURACAN), that the role of expert centres is to treat patients with rare diseases exclusively. Among the centres conducting RLT in this survey in Italy, six centres are monitored and certified by ENETS, with few exceptions that are hub-and-spoke linked. Their MDTs generally act independently to decide on patient eligibility and diagnostic and therapeutic pathways of patients admitted to RLT. This includes handling of side effects, choice of drugs, protocols before administration in symptomatic patients, use of SSAs during the RLT cycles, use of corticosteroids and/or mannitol in patients with CNS lesions, and eventual imaging modalities and/or other tests.

Conversely, the following options are decided by the nuclear medicine physician: imaging post-RLT for dosimetry, the use of doses lower than the scheduled 740 GBq of  $^{177}\text{Lu}$  Lutathera to provide clinical evidence (i.e. renal impairment, haematological toxicity, etc.), as well as the administration of corticosteroids and amino acids before radioligand administration to minimise possible side effects (nausea, vomiting, etc.) and to reduce the delivered dose to the kidneys.

Patients with high bone and/or hepatic tumour burden should not immediately be considered ineligible for RLT but should be carefully assessed within the NET-dedicated MDT focusing on the extent of the disease, the previous therapies and the presence of metastases negative for the expression of SSTR (mismatch results among PET/CT with  $^{68}\text{Ga}$ -DOTA-SSA, CT with contrast enhancement or  $^{18}\text{F}$ FDG-PET/CT).

In Italy, the clinical utilisation of RLT and its funding will benefit from developing a DTCP that can clarify the diagnostic, therapeutic and post-treatment monitoring process and improve care coordination between hub and spoke centres. RLT delivery can also be improved by comprehensive training at both hub and spoke centres. The availability of RLT as an outpatient therapy (i.e. through day-hospitals) is now possible due to the recent 2013/59/EURATOM Directive, which is likely to continue improving access to treatment. However, RLT as outpatient therapy must be carefully planned for patients with risk factors (e.g.

comorbidities, high tumour burden and functioning NETs). Another urgent need in the Italian setting is the development of a proper reimbursement tariff devoted to RLT, since funding through the FIO is no longer available. We recommend that Scientific Societies collaborate with policymakers on cost-mapping and reimbursement procedures (e.g. choice of DRG) to ensure that RLT is available for all Italian patients with GEP-NETs who may benefit from this treatment.

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**Ethical Approval.** This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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