



Radioligand Therapy and Sequencing in Gastroenteropancreatic Neuroendocrine Tumors: A Patient Perspective Review

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ABSTRACT

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are the most frequent subtype of NETs and their incidence has steadily increased over the past few decades. Patients with GEP-NETs often experience a large symptom burden and decrease in quality of life. Delays in diagnosis and high incidence of metastatic disease are the consequences of a lack of awareness or a lack of understanding of how to manage GEP-NETs among health care professionals. Although surgical resection is the only curative approach for GEP-NETs, many patients are not candidates for surgery. For these patients, new therapies have emerged recently, including radiolabeled therapeutic peptides used to target cancer cells and inhibit tumor growth. Radiolabeled somatostatin analogs, such as [¹⁷⁷Lu]Lu-DOTA-TATE (¹⁷⁷Lu-DOTATATE), are often used in radioligand therapy (RLT). ¹⁷⁷Lu-DOTATATE has been approved for the treatment of advanced GEP-NETs and has demonstrated efficacy and safety in clinical trials as well as in real-world studies. With the emergence of RLT for the management of GEP-NETs, treatment sequencing is of increasing importance. Considering the perspectives of patients with GEP-NETs on using RLT in their treatment journey is not only key to understanding and allaying their concerns regarding the safety of RLT but is also important in helping to identify patient priorities of treatment attributes. This review aims to identify the factors influencing patients considering RLT, their perceptions regarding treatment sequence options, the barriers in RLT access, and the disparities (eg, racial, geographical) among patients with GEP-NETs in accessing care.

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INTRODUCTION

Neuroendocrine tumors (NETs) are rare neoplasms arising from neuroendocrine cells and occurring primarily in the digestive tract, pancreas, or lungs.¹ Gastroenteropancreatic NETs (GEP-NETs), comprising NETs of the GI tract and pancreas, are the most frequent subtype of NETs, reported in about two thirds of these patients.¹⁻³ The incidence of GEP-NETs is approximately 5.5/100,000 per year and increased by more than five-fold between 1975 and 2015, probably because of improvement in imaging and recognition of neuroendocrine histology.²⁻⁴ GEP-NETs can be graded as grade 1 (low grade), grade 2 (intermediate grade), or grade 3 (high grade, classified as either well-differentiated NETs or poorly differentiated neuroendocrine carcinomas) on the basis of their proliferation.^{3,5,6} Patients with functional GEP-NETs present clinical symptoms attributable to hormonal secretion contrary to patients with nonfunctional GEP-NETs.⁷ Patients with advanced or metastatic GEP-NETs experience daily symptom burden of various intensities for many years, thus affecting their quality of life (QoL).⁸

This review aims to understand the perspectives of patients with well-differentiated GEP-NETs on considering radioligand therapy (RLT) in their treatment journey, highlighting their concerns regarding safety and treatment sequencing, and the potential barriers to RLT access.

MANAGEMENT OF GEP-NETs WITH SOMATOSTATIN RECEPTOR-TARGETED AGENTS

Surgical resection is a common treatment approach for GEP-NETs; however, many patients are not candidates for surgery because of their advanced or metastatic stage at diagnosis; for these patients, systemic treatments are recommended.⁹ Somatostatin receptors (SSTRs) are G-protein-coupled receptors that can regulate hormone secretion.³ SSTRs are expressed in the majority of GEP-NETs, making it an important target for treatment development.^{10,11}

RLT involves the administration of radiolabeled therapeutic peptides to target cancer cells.^{10,12} Radiolabeled somatostatin analogs (SSAs), such as [¹⁷⁷Lu]Lu-DOTA-TATE (¹⁷⁷Lu-DOTATATE), are used in RLT as they can be internalized via

endocytosis and retained by tumor cells.¹⁰ Once internalized, beta particles released by radionuclides mainly cause DNA single-strand breaks, leading to the death of the internalizing cells.^{13–15} ¹⁷⁷Lu-DOTATATE mechanism of action has been previously described by Hennrich and Kopka.¹⁶ In patients with SSTR-positive GEP-NETs, RLT has demonstrated shrinkage of tumor or inhibition of tumor growth thereby significantly delaying disease progression.¹⁷

¹⁷⁷Lu-DOTATATE is a RLT combining ¹⁷⁷Lu with the SSA DOTA-TATE.¹⁶ The NETTER-1 trial reported the comparative efficacy and safety of ¹⁷⁷Lu-DOTATATE in combination with best supportive care (¹⁷⁷Lu-DOTATATE + BSC), consisting of octreotide long-acting repeatable at 30 mg once every 4 weeks versus high-dose BSC alone (octreotide long-acting repeatable at 60 mg once every 4 weeks) in patients with midgut grade 1 to 2 NETs who had progressive disease after treatment. The study demonstrated that patients who received ¹⁷⁷Lu-DOTATATE + BSC had longer progression-free survival (PFS) and a significantly higher response rate than those who received high-dose BSC alone.¹⁸ ¹⁷⁷Lu-DOTATATE treatment showed no significant improvement in the secondary end point of overall survival (OS); however, the authors suggested that crossover to RLT might have affected the OS results in the high-dose BSC alone group.¹⁹ Results from NETTER-1 led to the US Food and Drug Administration (FDA) and European Medicines Agency approval of ¹⁷⁷Lu-DOTATATE for the treatment of SSTR-positive GEP-NETs in adults.¹⁶ More recently, ¹⁷⁷Lu-DOTATATE has been the first RLT approved by the FDA in pediatric patients age 12 years and older with SSTR-positive GEP-NETs. Primary analysis of the phase II NETTER-P study evaluating ¹⁷⁷Lu-DOTATATE in adolescents (age 13–17 years) with advanced, SSTR-positive, well-differentiated, grade 1 to 2 GEP-NET or pheochromocytoma/paraganglioma reported no new safety signals attributable to ¹⁷⁷Lu-DOTATATE in this population compared with adults with GEP-NET.²⁰ Furthermore, the NETTER-2 trial enrolled patients with newly diagnosed, higher grade 2 (Ki-67 $\geq 10\%$ and $\leq 20\%$) and grade 3 (Ki-67 $> 20\%$ and $\leq 55\%$), SSTR-positive GEP-NETs who received ¹⁷⁷Lu-DOTATATE + BSC. ¹⁷⁷Lu-DOTATATE + BSC significantly prolonged PFS and increased response rates versus high-dose BSC in this population.²¹

PATIENT PERCEPTIONS ON AVAILABLE TREATMENTS

Diagnosis and Treatment Initiation Timing in Patients With GEP-NETs

Delays in diagnosis often occur because of a lack of awareness or a lack of understanding of the appropriate management of GEP-NETs, with symptoms reported an average of 4–5 years in patients with NETs before their diagnosis (Table 1).^{22–24,27,28} Consequently, these delays are associated with a high incidence of metastatic disease, with over 50% of patients presenting with advanced or metastatic GEP-NETs at diagnosis.^{22–24,29} It is common for patients to be examined by several health care professionals

(HCPs) before receiving a diagnosis, with a mean of 6.2 HCPs involved from symptom onset until NET diagnosis.^{23,27} Further information regarding delays in diagnosis and treatment can be found in Table 1.

Patient Experiences of Symptom Burden and QoL With GEP-NET Treatments

Functional GEP-NETs are associated with overproduction and secretion of hormones, including, but not limited to, serotonin, histamine, bradykinins, and prostaglandins, resulting in clinical symptoms.^{30,31} On the other hand, nonfunctional GEP-NETs are characterized by a slow tumor growth and nonspecific symptoms related to tumor mass.^{9,30} However, not all patients experience symptoms from their disease. Symptom burden and QoL have been investigated in patients with NETs using electronic patient-reported outcome instruments.³² Patients reported a large symptom burden, with the most common symptoms being fatigue (76.7% of patients), diarrhea (62.5% of patients), abdominal discomfort (64.1% of patients), and trouble sleeping (57.5% of patients), with great variation in intensity from day to day.^{30,32,33}

When it comes to treatments, patients are often concerned about the adverse events (AEs) they will experience and how it will affect their QoL. SSAs are used to ease symptom burden and control disease progression in these patients.^{30,33} Some AEs (eg, GI, diarrhea, abdominal pain, and pain at injection site) have been reported with SSAs. Treatments such as telotristat ethyl in combination with SSAs have been approved for the treatment of carcinoid syndrome diarrhea while on SSAs alone.^{34,35}

¹⁷⁷Lu-DOTATATE + BSC provides significant QoL benefits for patients with midgut NETs compared with high-dose BSC.³⁶ In a post hoc analysis of the NETTER-1 trial, time to QoL deterioration on the basis of the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core 30 and the QLQ-G.I.NET21 was significantly longer in patients treated with ¹⁷⁷Lu-DOTATATE + BSC compared with those treated with high-dose BSC for the following domains: global health status (hazard ratio [HR], 0.41 [95% CI, 0.24 to 0.69]), physical functioning (HR, 0.52 [95% CI, 0.30 to 0.89]), role functioning (HR, 0.58 [95% CI, 0.35 to 0.96]), fatigue (HR, 0.62 [95% CI, 0.40 to 0.96]), pain (HR, 0.57 [95% CI, 0.34 to 0.94]), diarrhea (HR, 0.47 [95% CI, 0.26 to 0.85]), disease-related worries (HR, 0.57 [95% CI, 0.36 to 0.91]), and body image (HR, 0.43 [95% CI, 0.23 to 0.80]).³⁶ Symptom diaries kept by patients with midgut NETs showed that patients treated with ¹⁷⁷Lu-DOTATATE + BSC experienced significantly fewer days with symptoms such as abdominal pain, diarrhea, and flushing, compared with those treated with high-dose BSC.³⁷ Overall, these results were consistent with the data presented in a systematic literature review of health-related QoL benefits in patients with GEP-NETs who received ¹⁷⁷Lu-DOTATATE.³⁸ More recently, in the NETTER-2 trial, ¹⁷⁷Lu-DOTATATE + BSC showed no QoL deterioration in newly diagnosed patients

TABLE 1. Delays in Patients' Journey

Study	Studies Based in the United States				Studies From Outside the United States			
	Study Design	Patient Population	No.	Delay, Mean	Study Design	Patient Population	No.	Delay, Mean, Years
Time from first symptoms to diagnosis								
Wolin et al ²²	Subanalysis of the first global survey focusing on patients from the United States and conducted between February and May 2014	Patients diagnosed with NETs	758	59 months				
Singh et al ²³					First global survey between February and May 2014	Patients diagnosed with NETs	1,928	4.3
Dureja et al ²⁴					Global survey between September and November 2019	Patients diagnosed with NETs, their family/caregivers, and HCPs	2,359 patients and 436 HCPs	4.8 for misdiagnosed patients
Time from diagnosis to 1L SSA								
Lesén et al ²⁵					Population-based register-linkage study between 2005 and 2013 in Sweden	Patients diagnosed with GEP-NETs	811	0.25
Time from diagnosis to first RLT								
Almeamar et al ²⁶					Retrospective analysis between January 2008 and November 2020 in Ireland	Patients diagnosed with inoperable, well-differentiated NETs	45	Median: 87 days (waiting time to first RLT as at least 2L therapy)

Abbreviations: 1L/2L, first-/second-line; GEP-NET, gastroenteropancreatic neuroendocrine tumor; HCP, health care professional; NET, neuroendocrine tumor; RLT, radioligand therapy; SSA, somatostatin analog.

with advanced, higher grade 2 and grade 3 GEP-NETs.²¹ Reported AEs and tolerability of ¹⁷⁷Lu-DOTATATE are covered in the next section.

PATIENT PERCEPTIONS OF SAFETY WHEN USING ¹⁷⁷Lu-DOTATATE

Summary of ¹⁷⁷Lu-DOTATATE Safety Data

The kidneys and bone marrow are the dose-limiting organs for ¹⁷⁷Lu-DOTATATE, with low physiologic uptake by other nontumorous tissues and organs.³⁹⁻⁴¹ However, coinjection of amino acids with ¹⁷⁷Lu-DOTATATE administration reduces kidney radiation exposure by approximately 47%.⁴²

Safety in the Second and Further Lines ($\geq 2L$) Setting

In the NETTER-1 trial of patients with unresectable, metastasized, or locally advanced midgut NETs, there was no evidence of renal toxic effects with ¹⁷⁷Lu-DOTATATE + BSC therapy over long-term follow-up (median: 76.3 months; range, 0.4-95.0).^{18,19} Only low rates of transient grade 3 to 4 neutropenia (1%; 1/111 patients) and thrombocytopenia

(2%; 2/111 patients) were reported with ¹⁷⁷Lu-DOTATATE + BSC.¹⁸ Secondary hematologic malignancies were low (2%; 2/111 patients had myelodysplastic syndrome, no AML reported) and no new safety signals were observed in the long-term follow-up of ¹⁷⁷Lu-DOTATATE + BSC.¹⁹ Treatment-related adverse events (TRAEs) were more common with ¹⁷⁷Lu-DOTATATE + BSC (86%; 95/111 patients) compared with high-dose BSC (31%; 34/110 patients).¹⁸ The most commonly reported AEs of any grade were nausea (59%, 65/111 patients in the ¹⁷⁷Lu-DOTATATE + BSC v 12%, 13/110 patients in the high-dose BSC group) and vomiting (47%, 52/111 patients in the ¹⁷⁷Lu-DOTATATE + BSC v 10%, 11/110 patients in the high-dose BSC group; [Table 2](#)). The most common grade ≥ 3 AEs were lymphopenia (9%, 10/111 patients in the ¹⁷⁷Lu-DOTATATE + BSC v none of the patients in the high-dose BSC group) and vomiting (7%, 8/111 patients in the ¹⁷⁷Lu-DOTATATE + BSC v 1%, 1/110 patients in the high-dose BSC group). Many of the nausea and vomiting cases were attributable to amino acid infusion and were resolved after infusion was completed.¹⁸ The administration of arginine and lysine amino acids concurrently with ¹⁷⁷Lu-DOTATATE can minimize the

TABLE 2. Most Commonly Reported AEs

AE	NETTER-1 ¹⁸		NETTER-2 ²¹	
	¹⁷⁷ Lu-DOTATATE + BSC (n = 111)	High-Dose BSC (n = 110)	¹⁷⁷ Lu-DOTATATE + BSC (n = 147)	High-Dose BSC (n = 75)
Most common AEs of any grade ^a (≥20% in the ¹⁷⁷ Lu-DOTATATE + BSC arm of either study), No. (%)				
Nausea	65 (59)	13 (12)	40 (27.2)	13 (17.8)
Vomiting	52 (47)	11 (10)	21 (14.3)	6 (8.2)
Fatigue/asthenia	44 (40)	28 (25)	29 (19.7)	13 (17.8)
Diarrhea	32 (29)	21 (19)	38 (25.9)	25 (34.2)
Musculoskeletal pain	32 (29)	22 (20)	NR	NR
Abdominal pain	29 (26)	29 (26)	26 (17.7)	20 (27.4)
Thrombocytopenia	28 (25)	1 (1)	NR	NR
Most common grade ≥3 AEs ^a (≥3% in the ¹⁷⁷ Lu-DOTATATE + BSC arm of either study), No. (%)				
Lymphopenia/lymphocyte count decreased	10 (9)	0	8 (5.4)	0
Vomiting	8 (7)	1 (1)	1 (0.7)	1 (1.4)
Gamma-glutamyltransferase	NR	NR	7 (4.8)	2 (2.7)
Nausea	4 (4)	2 (2)	1 (0.7)	0
Abdominal pain	3 (3)	6 (5)	4 (2.7)	3 (4.1)
Diarrhea	3 (3)	2 (2)	2 (1.4)	1 (1.4)

Abbreviations: AE, adverse event; BSC, best supportive care; NR, not reported.

^aOn the basis of the group receiving ¹⁷⁷Lu-DOTATATE.

nausea and vomiting compared with using commercial amino-acid formulations.^{43,44}

Safety in the First-Line (1L) Setting

In the NETTER-2 phase III trial of patients with SSTR-positive GEP-NETs who received either 1L ¹⁷⁷Lu-DOTATATE + BSC or high-dose BSC, low incidence of grade 3 to 4 nephrotoxicities (2% [3/147]) was reported in patients who received ¹⁷⁷Lu-DOTATATE + BSC.²¹ Similar to NETTER-1, rates of thrombocytopenia were also low in the ¹⁷⁷Lu-DOTATATE + BSC group (2%; 3/147 patients) and one case of myelodysplastic syndrome was reported in the ¹⁷⁷Lu-DOTATATE + BSC group.²¹ TRAEs of any grade were reported in 69% of patients (101/147) in the ¹⁷⁷Lu-DOTATATE + BSC group versus 59% of patients (43/73) in the high-dose BSC group.²¹ Most AEs were mild to moderate in severity. The most commonly reported AEs of any grade were nausea (27% [40/147] and 18% [13/73] of patients in the ¹⁷⁷Lu-DOTATATE + BSC group and high-dose BSC group, respectively) and diarrhea (26% [38/147] and 34% [25/73] of patients, respectively; **Table 2**).²¹ The most common grade ≥3 AEs were lymphocyte count decreased (5% of patients [8/147] v none in the ¹⁷⁷Lu-DOTATATE + BSC group and high-dose BSC group, respectively) and gamma-glutamyltransferase (5% [7/147] and 3% [2/73] of patients in the ¹⁷⁷Lu-DOTATATE + BSC group and high-dose BSC group, respectively). In the ¹⁷⁷Lu-DOTATATE + BSC group, AEs led to discontinuation of ¹⁷⁷Lu-DOTATATE in 2%

(3/147) of patients and of BSC in 3% (5/147) of patients. Similarly, in the high-dose BSC arm, AEs led to BSC discontinuation in 3% (2/73) of patients.²¹

Safety Results From Real-World Settings

Results from NETTER trials are supported by real-world (RW) outcomes of patients with GEP-NETs treated with ¹⁷⁷Lu-DOTATATE.^{45,46}

In the retrospective RW data NETTER-R study of patients with advanced pancreatic NETs (median follow-up from first treatment cycle: 24.5 months; range, 2.0-123.4 months), ¹⁷⁷Lu-DOTATATE demonstrated a safety profile consistent with NETTER-1 and NETTER-2.⁴⁷ Grade 3 anemia, lymphopenia, and thrombocytopenia were reported in 1%, 5%, and 1% of patients, respectively; no myelodysplastic syndrome or acute leukemia were reported in the NETTER-R study.⁴⁷ Treatment-emergent AEs (TEAEs) occurred in 72% (79/110) of patients, most of which were grade 1 or grade 2, and required treatment modification in 9% (10/110) of patients. None of the TEAEs led to discontinuation.

In another RW study, the safety profile of heavily pretreated patients with NETs (40% [42/104] of patients had three or more previous lines of therapy) was also largely consistent with the NETTER-1 trial, but with some differences.^{19,46} Grade ≥3 AEs were reported in 39% (40/104) of patients.⁴⁶ Increases in liver transaminases and bilirubin after RL

treatment were common in RW settings, but were generally of mild severity. Slightly more patients discontinued RLT due to intolerance or AEs compared with the NETTER-1 trial (10% v 6% of patients, respectively).^{19,46} Among patients with peritoneal/mesenteric involvement at baseline, 21% (7/33) of patients developed bowel-related toxicity (bowel ischemia, gastric outlet obstruction, bowel rupture, and small bowel obstruction), which may mean that patient selection is important for intrahepatic versus extrahepatic disease burden. Six patients developed rapid tumor progression and terminal liver failure leading to treatment discontinuation within 1 year after RLT initiation; liver failure was not reported in the NETTER trials.⁴⁶ Overall, the authors from the RW study recommended further investigations regarding minimal-change nephrotic syndrome and liver failure.⁴⁶

A retrospective study of ¹⁷⁷Lu-DOTATATE efficacy in patients with SSTR-positive GEP-NETs from the Kansas Medical Center showed an even higher number of patients achieved a partial response with ¹⁷⁷Lu-DOTATATE treatment when compared with results of the initial clinical trials, further supporting the use of RLT.⁴⁵ Subgroup analysis also demonstrated significant response rate improvement in patients with nonfunctional GEP-NETs compared with those with functional GEP-NETs.⁴⁵ Overall, these results validated the efficacy of ¹⁷⁷Lu-DOTATATE and superior response rate compared with early clinical trials.⁴⁵

Finally, various RW studies from Spain, Brazil, and India analyzing the efficacy and safety of ¹⁷⁷Lu-DOTATATE in patients with GEP-NETs confirmed that ¹⁷⁷Lu-DOTATATE was well tolerated and effective, with improved survival in patients with metastatic and SSTR-positive GEP-NETs.⁴⁸⁻⁵⁰

Altogether, the safety and tolerability profiles for ¹⁷⁷Lu-DOTATATE were similar in the NETTER-1 and NETTER-2 trials and were consistent with RW and retrospective study data for ¹⁷⁷Lu-DOTATATE.

Factors Influencing Patient Considerations for Using RLT

Living with NET has a considerable impact on patients' personal and professional life. In a global self-reported survey conducted by the International Neuroendocrine Cancer Alliance (INCA), patients reported experiencing various NET-related symptoms, including general fatigue and muscle fatigue or weakness (56% of patients), diarrhea (48% of patients), and abdominal pain or cramping (41% of patients).²³ Many patients also reported that living with NETs substantially affected (a moderate amount/a lot) their emotional health (60% of patients), the emotional health of their family and/or friends (48% of patients), their relationship with their family (34% of patients), and with their friends (34% of patients).²³ Furthermore, in a cross-sectional survey study, patients tend to value more QoL factors, such as

maintaining their independence (46.7% of patients) and their thinking ability (85.0% of patients), rather than survival (30.0%).⁵¹ The majority of patients (66.7%) surveyed felt that they would rather live a shorter life than lose the ability to care for themselves.⁵¹ However, overall and ideally, patients would love to be able to maintain their QoL, doing activities that bring them joy while living longer.

Access to treatment and care remain an unmet need in the context of NET management. According to a global survey conducted by the INCA, most patients interviewed wished to have better availability of a wider range of NET treatment options (60%) and access to NET experts and NET specialist centers (56%).²³ In addition, many patients believed that NET could be improved with more knowledgeable NET medical providers (47%) and with a better coordinated/aligned NET medical team (45%).²³

There is a high level of medical mistrust among patients with NETs. A literature landscape search on trust in oncology has been conducted, then discussed with the Northern California NET patient support group, which concluded that medical mistrust is associated with poorer cancer screening compliance, reduced adherence to treatment recommendations, and decreased QoL.⁵² The rarity of NETs and the lack of clinician expertise in community settings play a major role in impairing patients' communication with and trust in their HCPs.⁵² Efforts to improve patient-physician communication, as well as considering values and goals of patients with NETs, are still needed to optimize patients' care.^{51,52}

Finally, patients' fear of the imagined effects of radiation could also influence their decision regarding whether or when to use RLT.

PATIENT PERCEPTIONS OF TREATMENT SEQUENCE OPTIONS

Patient Understanding Regarding Availability and Outcome of Subsequent Treatment Options if RLT Used in 1L

Patients undergo two or more different treatment modalities, depending on stage and tumor grade; surgery is the most common therapy (67% of patients) followed by SSAs (30% of patients) and RLT (22% of patients).²⁹ There is currently a lack of consensus for the sequence of approved therapies in GEP-NETs.⁵³ RLT is an umbrella term that can encompass many therapeutic isotopes. It remains to be seen, both in the wake of NETTER-2 and emerging data, where ¹⁷⁷Lu-DOTATATE should be sequenced in the longitudinal care of patients with NETs and also where retreatment would fit after the possible approval of alpha-emitters for radiotherapy; a retreatment with ¹⁷⁷Lu-DOTATATE trial is currently ongoing (NET RETREAT).⁵⁴ Furthermore, RLT might have potential benefits when used as neoadjuvant therapy; however, further investigations are needed.^{55,56} Finally,

there is a need for better access to diagnosis and treatments, including RLT, although RLTs, such as lutetium (^{177}Lu) vipivotide tetraxetan in the treatment of the more prevalent prostate cancer, are becoming more accessible.^{57,58}

Patient Priorities of Treatment Attributes

Treatment goals vary from patient to patient and can include control of symptoms, maintaining or improving QoL, and extending survival.⁸ However, according to a recent survey, patients with NETs tend to value their independence over survival.⁵¹ There are currently evidence gaps to translating QoL data to clinical decision making, and only a few clinical trials provide information on treatment effect on patients' QoL.^{8,21,36,59,60} In a recent survey, almost half of patients with NETs reported believing that their physician's treatment goals were not aligned with their own.^{8,51} In a further survey, a third of the 175 respondents with cancers reported communication approaches that negatively correlated with discussion outcomes when sharing patient-identified information with their HCPs.⁶¹ Providers who avoided the conversation due to limited time, discouraged future information searches, or made judgmental comments were perceived as dismissive.⁶¹ Effective patient-physician communication remains challenging and the gap could possibly be alleviated by implementing shared decision making and strengthening patient's trust for their physician.^{51,52}

Role of Patient Education in Treatment Decision Making

Neuroendocrine cancer awareness websites, NET-carcinoid support groups, including social media, and general cancer websites were the most useful resources according to patients. Patient advocacy organizations play a key role in supporting patients with NETs, including through social media sites, by providing education to patients and HCPs and engaging both parties to participate in constructive dialogues.⁶² For example, the NET VITALS is a patient-centered self-assessment tool developed by patient advocates from the Learn Advocate Connect Neuroendocrine Tumor Society (now Neuroendocrine Cancer Foundation) in collaboration with NET physicians from City of Hope, which helps to improve communication between patients and their HCPs.⁶³ NET VITALS gives patients a sense of autonomy and control of their journey with NET disease.⁶³ Moreover, patients would like enhanced access to easy-to-understand patient information about the cause of the disease, the progression and prognosis, and to receive psychological support regarding their physical and/or emotional difficulties.⁶⁴ When asked whether patients felt that they are a true partner in decision making alongside HCPs, advocates and patients (41% and 23%, respectively) felt more often than HCPs (18%) that their needs were not fully met.⁵⁷ Patient treatment goals should be discussed with physicians as shared decision making is a part of the patient-centered therapy management in oncology.⁸ For many patients, QoL is more important than survival, thus therapy that maintains or improves QoL while achieving efficacy should be offered to

the patient.^{8,38,51} Results from a survey regarding patient diagnostic experiences reported that the most commonly desired improvements were getting information on the long-term impact of NETs, increasing access to NET specialists, getting better direction on where to find useful information related to NETs, and spreading awareness of NETs among HCPs.²²

BARRIERS TO ASSESSING RLT AND DISPARITIES IN PATIENT ACCESS TO CARE

Minority races have been associated with poor OS and worse cancer outcomes.⁶⁵ Disparities in patient access to care have been summarized in [Table 3](#). In the United States, Black patients with NETs have worse OS and worse pancreatic NET-specific survival compared with White/others patients.⁶⁶ Black patients often have a more advanced tumor stage at diagnosis compared with non-Black patients.⁶⁶ Although the reasons are unclear, various factors related to genetic, diagnosis, or socioeconomic status (SES) could be responsible for racial disparities among patients with NETs. Several genes and pathways associated with metastatic pancreatic NETs are significantly enriched in Black patients compared with White patients, suggesting that transcriptome influences racial disparities in this population.⁷⁵ Furthermore, there is little representation of racial minorities in genomic studies of GEP-NETs, which highlight the necessity to include these populations in clinical studies to improve therapy.^{76,77} Black patients also reported less trust in their physicians compared with White patients, likely because of the history of research abuse and restriction in accessing clinical services.^{78,79} Black people are generally significantly less likely to receive care at high-volume hospitals for complex surgery, and instead cluster in low-quality hospitals.^{66,68,80} This was also observed among Asian and Hispanic patients, who were more likely to receive care at low-volume hospitals.⁶⁸ However, in another study of patients with nonmetastatic pancreatic NETs, race did not directly affect treatment choice or survival, but might indirectly affect these parameters as a result of disadvantaged SES on the basis of race.⁷⁰ In this study, insurance type and SES were associated with treatment choice, and sex, insurance type, and income affected survival.⁷⁰

Lack of insurance can be a barrier to accessing RLT. Patients with GEP-NETs who do not have health insurance in the United States are less likely to receive postoperative SSAs and have a significantly lower OS than those with insurance.⁶⁹ Many uninsured patients with GEP-NETs have difficulties accessing the health care system and it is highly likely that these patients never had access to primary resection.⁸¹

Geographic disparities have also been underlined in patients with pancreatic NETs.⁷¹ Almost 60 million (approximately 20%) of the US population living in rural areas are affected by these diseases. Patients with resected tumors who are living in rural areas have a significantly shorter OS compared with

TABLE 3. Disparities in Accessing Care in Patients With NETs

Study	Design	Patient Population	No.	Main Findings
Disparities on the basis of races				
DePalo et al ⁶⁵	Retrospective analysis on the basis of the US Neuroendocrine Study Group (patients who underwent resection for a NET between 2000 and 2016)	Patients diagnosed with GEP-NETs	1,143	Black patients with GEP-NETs had more adverse characteristics and higher positive lymph nodes compared with White patients However, Black patients have improved 5-year recurrence-free survival compared with White patients, suggesting that the quality of surgery is similar between both races
Zhou et al ⁶⁶	Retrospective study from SEER program (between 2004 and 2013)	Patients diagnosed with pancreatic NETs	3,850	Access to surgery was more limited for Black patients compared with non-Black patients Black patients were diagnosed with a more advanced tumor stage compared with non-Black patients Black patients had worse OS and pancreatic NET-specific survival compared with non-Black patients
Wong et al ⁶⁷	Retrospective study from SEER program (between 1992 and 2000)	Patients with a primary or subsequent cancer occurring between 1992 and 2000	2,711,710 White patients 291,126 African American patients	When modeling survival after diagnosis, differences in cancer stage had a smaller impact on the racial gap in life expectancy compared to the impact of cancer incidence
Liu et al ⁶⁸	Retrospective study on the basis of the California's Office of Statewide Health Planning and Development patients discharge database (between 2000 and 2004)	Patients who received at least one of the following operations: elective abdominal aortic aneurysm repair, coronary artery bypass grafting, carotid endarterectomy, esophageal cancer resection, hip fracture repair, lung cancer resection, cardiac valve replacement, coronary angioplasty, pancreatic cancer resection, and total knee replacement	719,608	Black patients were significantly less likely to receive care at high-volume hospitals for six of the operations compared with White patients
Disparities on the basis of insurance type and SES				
Marincola Smith et al ⁶⁹	Retrospective analysis on the basis of the US Neuroendocrine Study Group (between 2000 and 2016)	Patients with resected GEP-NETs	1,425	Uninsured patients were more likely to undergo emergent surgery and less likely to receive postoperative SSA therapy compared with patients with insurance
St Julien et al ⁷⁰	Retrospective study on the basis of the National Cancer Database (between 2004 and 2013)	Patients with nonmetastatic pancreatic NETs	4,579	Insurance type and SES were associated with treatment choice Sex, insurance type, and income affected survival
Liu et al ⁶⁸	Retrospective study on the basis of the California's Office of Statewide Health Planning and Development patients discharge database (between 2000 and 2004)	Patients who received at least one of the following operations: elective abdominal aortic aneurysm repair, coronary artery bypass grafting, carotid endarterectomy, esophageal cancer resection, hip fracture repair, lung cancer resection, cardiac valve replacement, coronary angioplasty, pancreatic cancer resection, and total knee replacement	719,608	Medicaid patients were significantly less likely than Medicare patients to receive care at high-volume hospitals for seven of the operations Uninsured patients were less likely to be treated at high-volume hospitals for nine of the operations
Disparities on the basis of geographic location				
Mirza et al ⁷¹	Retrospective analysis on the basis of the US Neuroendocrine Study Group (between 2000 and 2016)	Patients diagnosed with pancreatic NETs	1,126	Patients living in rural areas had significantly shorter OS after resection compared with patients living in urban areas

(continued on following page)

TABLE 3. Disparities in Accessing Care in Patients With NETs (continued)

Study	Design	Patient Population	No.	Main Findings
Levit et al ⁷²	Review on the basis of the Closing the Rural Cancer Care Gap hosted by ASCO in 2019	Oncologists, advocates, and rural health experts from the United States	NR	<p>Patients living in rural areas might have risk factors contributing to poorer outcomes, such as being older, have poorer general health, higher rates of obesity, disability, and smoking/drug use, and have lower access to screening and prevention services</p> <p>Disparities between rural and urban areas can be attributed to uneven geographic distribution of health care infrastructure and shortage of HCPs in rural areas</p> <p>Travel distance and costs are also associated with negative clinical outcomes for rural patients</p>
Gosain et al ⁷³	Retrospective study from SEER database (between 1973 and 2015)	Patients diagnosed with NETs	53,522	<p>NET incidence was higher in rural areas than urban areas, which could be associated to environmental or lifestyle factors, such as exposure to pesticides</p> <p>Patients in the rural areas were diagnosed at a more advanced stage than patients from the urban areas</p> <p>Rural residence was associated with poor OS</p>
Hallet et al ⁷⁴	Retrospective study on the basis of a valid Ontario Health Insurance Plan database (between 1994 and 2011)	Patients diagnosed with NETs	6,271	<p>NET incidence was higher in rural areas but was not diagnosed at more advanced stages compared with urban areas</p> <p>Patients living in rural areas have worse cancer recurrence and OS than those living in urban areas</p>

Abbreviations: GEP-NET, gastroenteropancreatic neuroendocrine tumor; HCP, health care professional; NET, neuroendocrine tumor; NR, not reported; OS, overall survival; SES, socioeconomic status; SSA, somatostatin analog.

patients living in urban areas.^{71,73} Several contributing factors have been reported such as lower income and restricted access to local HCPs, and pancreatic NET management has been shown to be a financial burden for these patients.⁸² Medical equipment or tests may not be as well-resourced as those in urban areas, contributing to the delayed or unspecific diagnosis of patients with NETs. Significantly more patients in rural areas were diagnosed with NETs than those living in urban areas.^{73,74} Stage at diagnosis of patients living in rural areas varies between studies; a study from Canada reported that patients from rural and urban areas were diagnosed at similar stage, while another study on the basis of the US SEER program showed that patients from rural areas presented at more advanced stages than those living in urban areas.^{73,74} Additionally, because of the lack of specialists/knowledgeable HCPs in rare diseases such as NETs, patients reported extended distance for appointment with NET specialists, with a mean distance of 126 miles (range, 1-9,942) or 182 km (range, 1-9,656).²³ Access to specialists can also be affected by the weather (eg, snow in winter), with appointments postponed because of problematic weather. Patients in rural areas may have limited knowledge of the health care system and be reluctant to seek medical help. Increasing communication

between NET specialists and local HCPs could alleviate the geographic disparity.

Finally, the level of trust is key in communication and treatment access. Perspectives from the Northern California NET patient support group affirm that mistrust and lack of medical community awareness of NETs are the major barriers to communicating with patients' physicians about symptoms recognition and shared decision making.⁵² This mistrust is associated with worse measures of cancer surveillance, treatment adherence, and QoL.⁵²

In conclusion, under the chronic illness paradigm, only few patients will be cured of NETs by systemic therapy. However, with an increasing array of treatment options, the real challenge will become the proper sequencing of multiple therapeutic interventions over time and ensuring that risk/benefit does not skew toward iatrogenic harm. As the dominant paradigm shifts from HCP-driven decision making to shared decision making, it is important to incorporate patient preferences and select patients who will achieve the greatest benefit from treatment in collaboration with a multidisciplinary team when making and sequencing decisions about noncurative therapies.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Radioligand Therapy and Sequencing in Gastroenteropancreatic Neuroendocrine Tumors: A Patient Perspective Review

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