Title

Best Practices for the Coordinated Care of Patients With Neuroendocrine Tumors Undergoing Peptide Receptor Radionuclide Therapy

Journal

Pancreas, 51(3)

ISSN

0885-3177

Authors

Hendifar, Andrew E
Mehr, Samuel H
McHaffie, Derek R

Publication Date

2022-03-01

DOI

10.1097/mpa.0000000000002002

Peer reviewed

OPEN

Best Practices for the Coordinated Care of Patients With Neuroendocrine Tumors Undergoing Peptide Receptor Radionuclide Therapy

Andrew E. Hendifar, MD, Samuel H. Mehr, MD,† and Derek R. McHaffie, MD‡*

Abstract: Neuroendocrine tumors (NETs) are rare, diverse malignancies; approximately two thirds originate in the gastrointestinal tract and pancreas and are known as gastroenteropancreatic NET. Most cases are diagnosed in the advanced or metastatic setting and overexpress somatostatin receptors. Recommended first-line treatment is somatostatin analogs; however, disease progression is common. [^{177}Lu]Lu-DOTA-TATE is a radiolabeled peptide receptor radionuclide therapy (PRRT) indicated for the treatment of adult patients with somatostatin receptor-positive foregut, midgut, and hindgut gastroenteropancreatic NETs and progression on first-line somatostatin analogs. Many primary oncology practices may lack the staff, expertise, and infrastructure to treat patients with PRRT and primary oncologists may therefore refer their patients to a NET specialist at a tertiary center for treatment. Given the amount of organization required, PRRT treatment may seem to be complex; however, this process will be managed by a care coordinator who acts as a consistent point of contact for primary physicians regarding the care of their patients and ensures blood tests and scans are scheduled. In this article, we share our opinions, procedures, workflow, best practice, and roles and responsibilities when caring for patients receiving [^{177}Lu]Lu-DOTA-TATE and focus on the role of the primary oncologist before, during, and after PRRT treatment.

Key Words: [^{177}Lu]Lu-DOTA-TATE, neuroendocrine tumors, neuroendocrine neoplasms, gastroenteropancreatic, somatostatin receptor-positive, primary oncologist

(*Pancreas* 2022;51: 213–218)

Neuroendocrine tumors (NETs) are a group of rare, heterogeneous malignancies.[1] In the United States in 2012, the annual age-adjusted incidence of NETs was 6.98 cases per 100,000 people[2]; however, the overall incidence of NETs is increasing, and this is thought to be driven by increased awareness and improvements in diagnosis.[2–4]

The largest proportion of NETs are sporadic (approximately 90%) with poorly understood risk factors; the minority of cases arise from rare, genetically inherited conditions.[4,5] Neuroendocrine tumors can be subdivided into nonfunctioning and functioning tumors based on their symptoms. Patients with functional tumors may present with syndromes associated with hypersecretion of hormones, such as carcinoid syndrome and insulinoma.[6] However, most patients present with nonfunctional tumors and may have nonspecific symptoms, such as abdominal discomfort, which can delay making a formal NET diagnosis.[1,6] Delays in diagnosis may lead to patients presenting with more advanced disease, which is more commonly associated with hormone hypersecretion.[4]

Treatment with curative intent for NETs is surgery; however, most cases are diagnosed in the advanced or metastatic setting, which is not amendable to surgical resection.[7,8] For patients in whom surgery with curative intent is not an option, the goals of treatment are symptom control and palliative care.[4] Most NETs with hormone hypersecretion overexpress somatostatin receptors (SSTRs) and first-line treatment with somatostatin analogs (SSAs), such as octreotide or lanreotide, are used to control symptoms.[4] Approximately two thirds of NETs originate in the gastrointestinal tract and pancreas (known as gastroenteropancreatic [GEP] NET) and a smaller proportion (1.49 cases per 100,000 people) originating in the lungs or thymus.[2,4] Gastroenteropancreatic NETs frequently overexpress SSTRs, and the National Comprehensive Cancer Network (NCCN) and North American Neuroendocrine Tumor Society and the Society of Nuclear Medicine and Molecular Imaging guidelines recommend SSA as first-line treatment for SSTR-positive grades 1 and 2 (G1 and G2) GEP NETs. However, treatment resistance frequently occurs.[4,9,10] For patients with GEP NETs who progress on first-line SSA, treatment options include [^{177}Lu]Lu-DOTA-TATE, everolimus, chemotherapy, liver-directed therapy (for liver-predominant disease), and palliative radiotherapy for patients with symptomatic bone metastases.[11] Sunitinib and temozolomide plus capecitabine are also options for patients with pancreatic NETs.[4]

[^{177}Lu]Lu-DOTA-TATE is a radiolabeled peptide receptor radionuclide therapy (PRRT) indicated for the treatment of adult patients with SSTR-positive GEP NET, including foregut, midgut, and hindgut NETs, and was approved by the US Food and Drug Administration in January 2018.[12,13] The NCCN Guidelines recommend [^{177}Lu]Lu-DOTA-TATE as a treatment option for patients whose tumors are SSTR-positive and who have progressed on octreotide or lanreotide.[4] The US approval of [^{177}Lu]Lu-DOTA-TATE was based on the results of the phase 3, open-label NETTER-1 study (NCT01578239), which demonstrated longer median progression-free survival (not reached for [^{177}Lu]Lu-DOTA-TATE plus octreotide LAR 30 mg vs 8.4 months for the octreotide LAR 60 mg alone; hazard ratio for disease progression or death 0.21 [95% confidence interval, 0.13–0.33]; $P < 0.001$) and higher response rates (18% vs 3% for [^{177}Lu]Lu-DOTA-TATE and control, respectively) in patients treated with [^{177}Lu]Lu-DOTA-TATE 7.4 GBq every 8 weeks (4 intravenous infusions, plus best supportive care consisting of octreotide LAR administered intramuscularly at a dose of 30 mg) versus octreotide LAR alone (administered intramuscularly at a dose of 60 mg every 4 weeks).[14] The final overall survival data (median follow-up of 6.3 years)

From the *Department of Medicine, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA; †Nuclear Oncology, Molecular Imaging, Systemic Radiation Therapy and Theranostics, Nebraska Cancer Specialists, Omaha, NE; and ‡Radiation Oncology, Levine Cancer Institute @ Atrium Health; Southeast Radiation Oncology Group. Charlotte, NC.

Received for publication July 9, 2021; accepted February 16, 2022.

Address correspondence to: Andrew E. Hendifar, MD, Department of Medicine, Samuel Oschin Comprehensive Cancer Institute, 127 S San Vicente Blvd, 7th Floor, Cedars-Sinai Medical Center, Los Angeles, CA, 90048 (e-mail: Andrew.Hendifar@cshs.org).

A.E.H. has consultancy or advisory role in Ipsen, Novartis. The other authors declare no conflict of interest.

DOI: 10.1097/MPA.0000000000002002

were presented at the American Society for Clinical Oncology 2021 annual meeting, median overall survival 48.0 months in the [^{177}Lu]Lu-DOTA-TATE arm versus 36.3 months in the control arm.[15]

Management of patients with GEP NET is recommended to be done via a multidisciplinary team (MDT), so as to improve patient prognosis and survival.[16] Team members include a specialist with expertise in the management of NETs and a nuclear medicine physician or radiation oncologist.[9] However, many community practices may lack the necessary expertise, team members, radiation safety infrastructure, or specialized facilities to treat patients with PRRT. Furthermore, access to these facilities and/or the complexities of coordinating care with multiple specialists involved can represent barriers to therapy for many patients. Given these considerations, many primary oncologists may need to refer their patients to a NET specialty team, who act as part of tertiary or academic medical centers, for treatment. Primary oncologists may refer to a NET oncologist who will manage PRRT treatment. However, if there is no NET oncologist in their local area, they may choose to refer to either a nuclear medicine specialist or radiation oncologist with PRRT capabilities who works alongside an MDT.

For primary oncologists to understand how to best care for their patients, we share our opinions, procedures, workflow, and best practice regarding roles and responsibilities for managing care for patients undergoing PRRT treatment with [^{177}Lu]Lu-DOTA-TATE, with a key focus on the role of primary oncologist before, during, and after PRRT. Roles and responsibilities for the primary oncologist are not defined.

THE NET PATIENT JOURNEY: ROLES AND RESPONSIBILITIES OF THE MDT DIAGNOSIS, GRADING, AND STAGING

In patients with a suspected NET, primary oncologists play an integral role in the evaluation and initial management of suspected disease. Given the heterogeneity of GEP NETs, coordination of endoscopy or surgery to obtain a biopsy is recommended to allow complete histopathological assessment and characterization of disease.[6] Histological diagnosis of GEP NET assesses cell morphology and expression of markers, including chromogranin, synaptophysin, and Ki-67.[4] Tumors are graded G1–G3 dependent on cell morphology, mitotic rate, and level of Ki-67 expression; Tumor Node Metastasis staging will also be considered to classify neuroendocrine neoplasms of the gastrointestinal tract and hepatopancreatobiliary organs[4]:

- G1: well-differentiated NET with <2 mitoses per 2 mm^2 and <3% Ki-67 index
- G2: well-differentiated NET with 2–20 mitoses per 2 mm^2 or 3%–20% Ki-67 index
- G3: well-differentiated NET with >20 mitoses per 2 mm^2 or >20% Ki-67 index
- Poorly differentiated neuroendocrine carcinoma with >20 mitoses per 2 mm^2 or >20% Ki-67 index

The NCCN recommends that tumor differentiation, mitotic rate, and Ki-67 rate be included in the pathology report and that the specific classification and grading scheme be noted to avoid any confusion.[4] Overall, histological grade should be considered as secondary to clinical judgment in making clinical decisions, particularly where histology results are not concordant.[4]

ASSESSING PATIENT FOR [^{177}LU]LU-DOTA-TATE TREATMENT

Patients with GEP NET must be assessed for suitability for treatment with [^{177}Lu]Lu-DOTA-TATE. Patients will undergo an SSTR positron emission tomography (PET) scan or SSTR scintigraphy to confirm adequate SSTR expression.[17] It is recommended that somatostatin receptor avidity be demonstrated within 6 months of treatment to establish the appropriateness of PRRT. The use of [^{68}Ga]Ga-DOTA-TATE PET scan has improved sensitivity and specificity for the detection of metastatic disease compared with Indium In-111-pentetreotide scans. In addition, it offers improved accuracy in assessing eligibility for PRRT.[18,19] The [^{68}Ga]Ga-DOTA-TATE scan can be done by the primary oncologist at their respective center; specialists may request an SSTR or [^{68}Ga]Ga-DOTA-TATE PET scan if this has not been done previously or a new scan if the prior scan is several months old.

Patients who are best suited for [^{177}Lu]Lu-DOTA-TATE have low-grade (G1 or G2) metastatic GEP NET with SSTR-positive tumor expression and disease progression with SSA therapy (including progression or persistent clinical symptoms [main criteria]), increased tumor burden by computed tomography or magnetic resonance imaging on first-line SSA therapy, or deterioration of organ function (eg, liver or kidneys) with first-line SSA therapy (Table 1). Other considerations involved in determining suitability for first-line SSA are liver tumor burden, whether there is an option for resection or debulking, or whether the disease is symptomatic or extrahepatic. Certain patients should not receive [^{177}Lu]Lu-DOTA-TATE: patients with inadequate bone marrow, renal or hepatic reserves, or poor performance status. Higher-grade tumors may be considered on a case-by-case basis when there is somatostatin receptor avidity, provided that other eligibility criteria are met. For complex cases, such as patients with organ dysfunction (eg, liver, kidneys), there may be more than one potential treatment approach and a NET specialist can discuss which approach may be optimal with the primary oncologist.

REFERRAL TO A NET SPECIALTY TEAM

Although the patterns of referral and relationships between the specialty center and primary oncologists are unique to each

TABLE 1. Summary of the Patient Characteristics for Eligibility for [^{177}Lu]Lu-DOTA-TATE

Patients Who Can Receive [^{177}Lu]Lu-DOTA-TATE Treatment	Patients Unsuitable for [^{177}Lu]Lu-DOTA-TATE Treatment
• SSTR-positive tumor expression[4,12] • Low-grade (G1 or G2) metastatic GEP NET[4] • Disease progression with first-line SSA therapy; including progression or persistent clinical symptoms[4] • Increased tumor burden by computed tomography or magnetic resonance imaging on first-line SSA therapy, or deterioration of organ function (eg, liver or kidneys) with first-line SSA therapy	• Patients with extensive metastatic disease (liver, bone) • Patients with inadequate bone marrow, renal or hepatic reserves, or poor performance status

GET NET indicates gastroenteropancreatic neuroendocrine tumors.

NET center, patient management may require referral by a primary oncologist from within their own institution or to an outside specialist. If the primary oncologist refers the patient to a NET surgeon, they may subsequently refer the patient to a NET oncologist, nuclear medicine specialist, or a radiation oncologist, who is part of the MDT, who will schedule treatment with [^{177}Lu]Lu-DOTA-TATE. As it is often misperceived that patients will be required to stay in the specialist's care after referral, it is important to note that because of the frequent need for travel to a center with PRRT availability and the inherent logistical barriers to treatment, delivering care closer to home when possible is in the patient's best interests. Therefore, regardless of the type of center, patients should be referred back to the primary physician after [^{177}Lu]Lu-DOTA-TATE treatment. Given NET is a rare disease that is best treated by a dedicated team, primary oncologists are encouraged to reach out to a specialist for early collaboration to establish candidacy before requesting an initial patient consultation.

TREATMENT WITH [^{177}LU]LU-DOTA-TATE PRRT

Before [^{177}Lu]Lu-DOTA-TATE treatment, it is suggested that patients discontinue long-acting SSA for at least 4 weeks and short-acting SSA for at least 24 hours. Patients receiving [^{177}Lu]Lu-DOTA-TATE treatment will have up to 4 intravenous infusions, given 8 weeks apart with administration of octreotide LAR 30 mg intramuscularly between 4 and 24 hours after each [^{177}Lu]Lu-DOTA-TATE dose (Fig. 1). Short-acting octreotide may be given for symptomatic management during [^{177}Lu]Lu-DOTA-TATE treatment but must be withheld for at least 24 hours before each [^{177}Lu]Lu-DOTA-TATE dose. Intravenous amino acid solution, containing L-lysine and L-arginine, should be administered 30 minutes before [^{177}Lu]-Lu-DOTA-TATE; this is required to decrease reabsorption of [^{177}Lu]Lu-DOTATATE via the proximal renal tubules and thereby decrease the radiation dose to the kidneys. [^{177}Lu]Lu-DOTA-TATE infusions are given as an outpatient procedure, and patients will stay in the treatment center for approximately half a day. It is required that each infusion is given in a facility with dedicated resources and qualifications to treat patients with radioactive agents. Staff are licensed and trained in radiation handling, safety, and disposal of nuclear medicine, such as PRRT.

It is our opinion that best practice includes the designation of a care coordinator, often with a nurse navigator or physician assistant, who conveys scheduling of treatment and follow-up to patients and primary oncologists. The care coordinator can also serve an educational role for patients, their families, and other healthcare workers who may have questions regarding radiation safety precautions or associated risks with exposure to the patient; information and safety precautions will usually be given to the patients in writing. After each infusion, the patient must take certain precautions to limit radiation exposure to caregivers and family. Instructions are provided by the treating physician (Table 2).

Patients must have regular blood tests (complete blood count with differential, complete metabolic panel) during [^{177}Lu]Lu-DOTA-TATE treatment to proactively assess for the potential need to delay, adjust dosing, or stop therapy. If there are no signs of toxicity, the primary oncologist is encouraged to perform laboratory tests; these should include blood urea nitrogen, creatinine, albumin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, white blood cell with differential, hemoglobin, and platelet counts. The specialist (NET oncologist, nuclear medicine specialist, or radiation oncologist) may request laboratory blood assessments; communicating this to the primary oncologist is an essential part of effectively managing any treatment-related adverse events, in collaboration with the NET specialist. Monthly SSA injections are the responsibility of the primary oncologist or can be done at the NET specialist center. This can be discussed and agreed upon during discussions with the NET oncologist, nuclear medicine specialist, or radiation oncologist.

Treatment may be delayed in patients with reduced kidney function or reduced white blood cell counts until normal function/blood counts are observed; dose reductions can be considered for patients with toxicity (Table 3). Primary oncologists are obliged to communicate any adverse events to the specialist, who is scheduling PRRT, and discuss whether dose reductions or treatment delays are required. Sharing laboratory results with the PRRT specialist will also allow them to determine whether the patient can tolerate the next treatment or if reduction or delay would be appropriate. Prolonged organ or bone marrow dysfunction necessitates stopping therapy.

COORDINATION OF NET PATIENT CARE: THE ROLE OF THE CARE COORDINATOR

While specialist centers may have slight differences in practices and processes, [^{177}Lu]Lu-DOTA-TATE treatment will benefit from being organized and managed by care coordinators (or nurse navigators; Fig. 2). The care coordinator serves as an advisor and

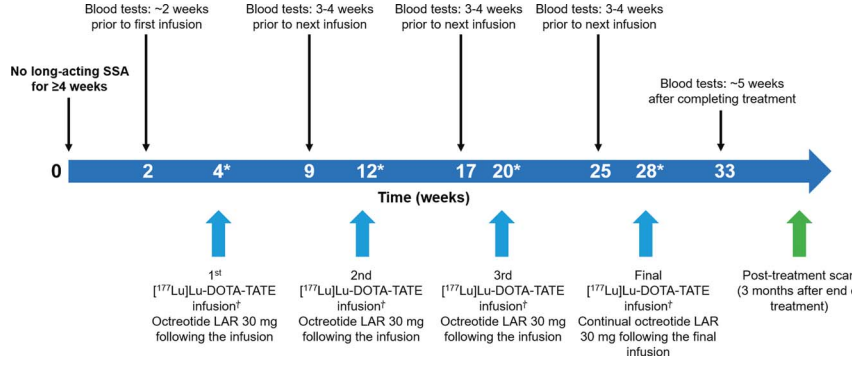

FIGURE 1. [^{177}Lu]Lu-DOTA-TATE treatment workflow.[12] *During [^{177}Lu]Lu-DOTA-TATE treatment, administer octreotide LAR 30 mg every 8 weeks intramuscularly between 4 and 24 hours after each [^{177}Lu]Lu-DOTA-TATE dose. Short-acting octreotide may be given for symptomatic management during [^{177}Lu]Lu-DOTA-TATE treatment but must be withheld for at least 24 hours before each [^{177}Lu]Lu-DOTA-TATE dose. After completion of 4 doses of [^{177}Lu]Lu-DOTA-TATE treatment, octreotide LAR 30 mg is given every 4 weeks until disease progression or for up to 18 months after treatment initiation. †Before each infusion, patients must receive antiemetics and amino acids. Antiemetics are given before intravenous amino acids. Intravenous amino acids are given 30 minutes before [^{177}Lu]Lu-DOTA-TATE and continue during [^{177}Lu]Lu-DOTA-TATE treatment and for approximately 3 hours after treatment.[12] Note: Many centers may repeat blood tests on the day before or on the day of treatment to ensure [^{177}Lu]Lu-DOTA-TATE infusion should proceed.

TABLE 2. Radiation Safety Precautions for the Patients Treated With [^{177}Lu]Lu-DOTA-TATE

Patients should follow the instructions for 7 d after each [^{177}Lu]Lu-DOTA-TATE infusion:
- Sleep in a separate bed
- Maintain approximately 6 ft of space between you and other people as much as possible
- Consider sitting in the backseat of cars and across the table from others
- Limit contact with small children and pregnant women
- Wash hands for one full minute with soap and water after using the toilet
- Flush the toilet 2 times after each use
- No one should touch your bodily fluids or secretions
- Do not have sexual intercourse
- Quickly isolate and remove spilled bodily fluids. Wear gloves while cleaning.
- Throw away any items that become dirty with bodily fluids. The material may be flushed down the toilet or placed in a plastic bag in the household trashcan
- Clothing, sheets, and towels should be washed separately from anyone else's living in the same home
- Shower daily
- Do not have blood drawn for routine evaluations

educational figure for the patient. To the physician(s), this person is a key facilitator in helping to synchronize all aspects of the [^{177}Lu]Lu-DOTA-TATE PRRT treatment workflow, including:

- Ensuring patient scans are current
- New scans are carried out (as required)
- Confirming all routine blood tests are carried out on schedule
- Educating patients regarding radiation safety or ensuring education is done by another member of the team
- Ensuring octreotide injections are carried out at the correct times

Given the amount of organization required, the task of delineating responsibility is critical. As these tasks may change on a case-by-case basis, depending on the physicians involved and patient needs, this is handled by the care coordinator. Care coordinators also provide a consistent point of contact for primary physicians regarding the care of their patients, helping ensure the primary oncologist schedules any blood tests and scans that are required. Overall, the role of the care coordinator is crucial in ensuring the organization of the MDT at the specialist center, patient care is managed efficiently, and that the referring physician has a point of contact for any queries.

POSTTREATMENT CARE

Posttreatment laboratory tests and monthly SSA injections can be coordinated with the referring oncologist to improve patient

TABLE 3. Recommended Dose Modifications During [^{177}Lu]Lu-DOTA-TATE Treatment[12]

Adverse Event	Pause Treatment	Dose Reductions	Discontinue Treatment
Grade 2, 3, or 4 thrombocytopenia	• Withhold treatment until complete or partial resolution (grades 0–1)	• Resume treatment at 3.7 GBq in patients with complete or partial resolution • If dose reduction does not result in grades 2–4 thrombocytopenia, dose can be increased to 7.4 GBq at the next dose	• Grades ≥2 requiring a treatment delay of ≥16 wk or longer • Recurrent grade 2, 3, or 4
Grade 3 or 4 anemia or neutropenia	• Withhold treatment until complete or partial resolution (grade 0, 1, or 2)	• Resume treatment at 3.7 GBq in patients with complete or partial resolution • If dose reduction does not result in grades 3–4 anemia or neutropenia, dose can be increased to 7.4 GBq at the next dose	• Grades ≥3 requiring a treatment delay of ≥16 wk or longer • Recurrent grade 3 or 4
Renal toxicity, defined as: • Creatinine clearance <40 mL/min; calculated using Cockcroft-Gault with actual body weight, or • 40% ncrease in baseline serum creatinine, or • 40% decrease in baseline creatinine clearance; calculated using Cockcroft-Gault with actual body weight	• Withhold treatment until complete resolution or return to baseline	• Resume treatment at 3.7 GBq in patients with complete resolution • If dose reduction does not result in renal toxicity, dose can be increased to 7.4 GBq at the next dose	• Renal toxicity requiring a treatment delay of ≥16 wk or longer • Recurrent renal toxicity
Hepatotoxicity, defined as: • Bilirubinemia >3 times the upper limit of normal (grade 3 or 4), or • Hypoalbuminemia <30 g/L with a decreased prothrombin ratio <70%	• Withhold dose until complete resolution or return to baseline	• Resume treatment at 3.7 GBq in patients with complete resolution • If dose reduction does not result in hepatotoxicity, dose can be increased to 7.4 GBq at the next dose	• Hepatotoxicity requiring a treatment delay of ≥16 wk or longer • Recurrent hepatotoxicity
Grade 3 or 4 nonhematological toxicity	• Withhold treatment until complete or partial resolution (grades 0–2)	• Resume treatment at 3.7 GBq in patients with complete or partial resolution • If dose reduction does not result in grades 3–4 toxicity, dose can be increased to 7.4 GBq at the next dose	• Grades 3–4 toxicity requiring a treatment delay of ≥16 wk or longer • Recurrent grade 3 or 4

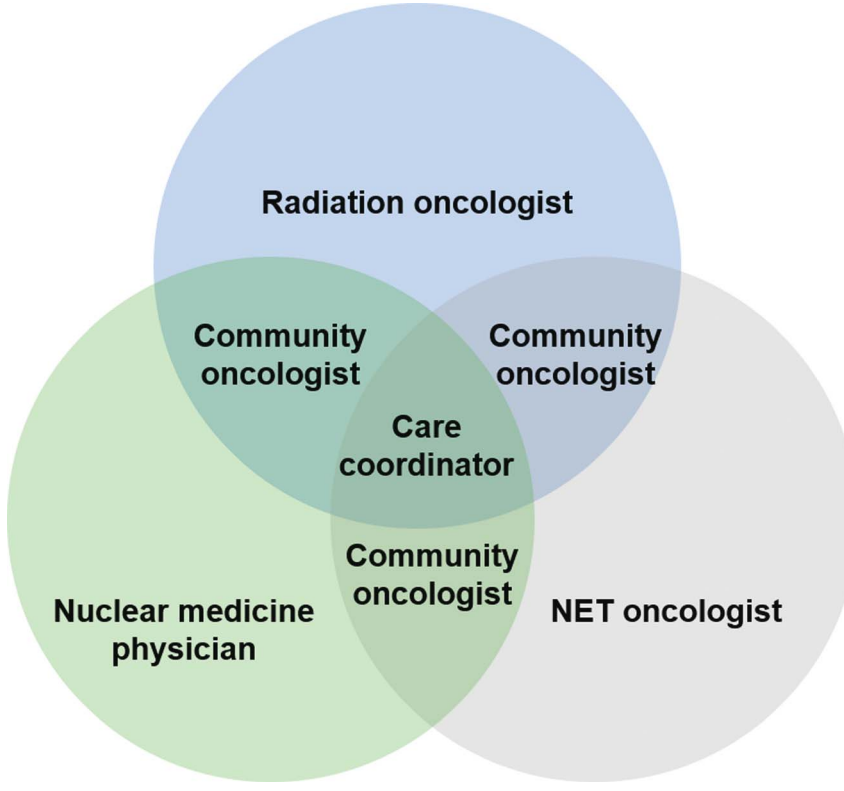

FIGURE 2. Care coordinators are central to the management of care for patients undergoing treatment with [^{177}Lu]Lu-DOTA-TATE.

convenience, by reducing patient travel time. This also allows patients to remain in the care of the referring physician. The management of adverse events may require close follow-up with a PRRT specialist. Neuroendocrine tumor specialists will send a recommendation for the timing of ordering follow-up scans to the referring physician. Laboratory tests are recommended 5 weeks after completing treatment, and the results should be shared with the NET specialist.

There is currently no consensus on the timing and frequency of imaging during a course of [177Lu]Lu-DOTA-TATE. We recommend that computed tomography or magnetic resonance imaging for tumor assessment be continued every 3 months, which would include midcourse imaging.

It is important that physicians be aware that scans performed during or immediately after treatment may demonstrate treatment-related tumor swelling, pseudoprogression, which can be misinterpreted as disease progression. Until the role of pseudoprogression in post–[^{177}Lu]Lu-DOTA-TATE response assessment is fully understood, it is our recommendation not to define clinical progression based solely on the results of the first posttreatment imaging, whether functional or conventional. The precise role of posttreatment [^{68}Ga]Ga-DOTA-TATE PET scans in the assessment of response to therapy has not yet been fully elucidated. It is our recommendation that they be considered no sooner than 3 months after treatment is completed; imaging may be done during PRRT as clinically indicated.

Treatment is generally well tolerated, although the referring physician should be aware that the potential for treatment-related myelodysplastic syndromes exists. However, the incidence of myelodysplastic syndrome is rare and was reported to be 1.8% of patients in the NETTER-1 trial (at a median follow-up of 6.3 years, no new cases of MDS or acute leukemia were observed) and 1.5% in a long-term safety analysis of 610 patients with gastroenteropancreatic and bronchial NETs.[14,15,20] Patients who manifest profound cytopenias or limited recovery need to be monitored more closely long term.

TABLE 4. Barriers to Treatment and Critical Success Factors

Barriers	Critical Success Factors
• Lack of management guidelines • Absence of frameworks for diagnosis or referral • Belief that NET specialists may assume the management of the primary oncologist's patient • Lack of educational and networking resources (blogs, telemedicine network, webpage resources, online physician groups) • Time, as treatment requires coordination	• Working together collaboratively • NET specialists cultivating professional respect through quality of care • Ensuring patients are referred back to the primary oncologist • All parties being supportive of [^{177}Lu]Lu-DOTA-TATE treatment and follow-up • Care coordinator

SUMMARY AND BEST PRACTICES

- Contact NET specialists before referral to discuss your patient
- Ensure scans and blood tests are current or be aware that NET specialists will request these are done
- Establish who will be responsible for SSA injections during treatment and what tests are required after treatment
- Ascertain how the laboratory tests and scans are transferred from primary to NET specialist or treating physicians
- Many barriers to [^{177}Lu]Lu-DOTA-TATE treatment may exist (Table 4); however, working collaboratively with the care coordinator and the NET specialist will ensure that you maintain management of your patient

ACKNOWLEDGMENTS

The authors thank ClinicalThinking for providing editorial support funded by Novartis Pharmaceuticals Corporation. Neither Novartis Pharmaceuticals Corporation nor ClinicalThinking influenced the content of this manuscript, nor did the authors receive financial compensation for authorship.

REFERENCES

1. Oronsky B, Ma PC, Morgensztern D, et al. Nothing but NET: a review of neuroendocrine tumors and carcinomas. *Neoplasia*. 2017;19:991–1002.
2. Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol*. 2017;3:1335–1342.
3. Neuroendocrine Tumors. Available at: https://www.cancer.net/cancer-types/neuroendocrine-tumors. Accessed November 3, 2021.
4. NCCN guidelines for neuroendocrine and adrenal tumors. Version 3. Available at: https://www.nccn.org/. Accessed November 3, 2021.
5. O'Shea T, Druce M. When should genetic testing be performed in patients with neuroendocrine tumours? *Rev Endocr Metab Disord*. 2017;18:499–515.
6. Hofland J, Kaltsas G, de Herder WW. Advances in the diagnosis and management of well-differentiated neuroendocrine neoplasms. *Endocr Rev*. 2020;41:371–403.
7. Uri I, Grozinsky-Glasberg S. Current treatment strategies for patients with advanced gastroenteropancreatic neuroendocrine tumors (GEP-NETs). *Clin Diabetes Endocrinol*. 2018;4:16.
8. Tamburrino D, Spoletini G, Partelli S, et al. Surgical management of neuroendocrine tumors. *Best Pract Res Clin Endocrinol Metab*. 2016;30:93–102.
9. Hope TA, Bodei L, Chan JA, et al. NANETS/SNMMI consensus statement on patient selection and appropriate use of ^{177}Lu-DOTATATE peptide receptor radionuclide therapy. *J Nucl Med*. 2020;61:222–227.
10. Herrera-Martinez AD, Hofland J, Hofland LJ, et al. Targeted systemic treatment of neuroendocrine tumors: current options and future perspectives. *Drugs*. 2019;79:21–42.
11. Guan M, He I, Luu M, et al. Palliative radiation therapy for bone metastases in neuroendocrine neoplasms. *Adv Radiat Oncol*. 2019;4:513–519.
12. Lutathera prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208700s000lbl.pdf. Accessed November 3, 2021.
13. FDA Lutathera approval. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-certain-digestive-tract-cancers#:~:text=The%20U.S.%20Food%20and%20Drug,tumors%20(GEP%2DNETs. Accessed November 3, 2021.
14. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of ^{177}Lu-Dotatate for midgut neuroendocrine tumors. *N Engl J Med*. 2017;376:125–135.
15. Strosberg JR, Caplin ME, Kunz PL, et al. Final overall survival in the phase 3 NETTER-1 study of lutetium-177-DOTATATE in patients with midgut neuroendocrine tumors. *J Clin Oncol*. 2021;39(15 suppl):abstract 4112.
16. Pavel M, O'Toole D, Costa F, et al. ENETS Consensus Guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. *Neuroendocrinology*. 2016;103:172–185.
17. Hope TA, Abbott A, Colucci K, et al. NANETS/SNMMI procedure standard for somatostatin receptor-based peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE. *J Nucl Med*. 2019;60:937–943.
18. Deppen SA, Liu E, Blume JD, et al. Safety and efficacy of 68Ga-DOTATATE PET/CT for diagnosis, staging, and treatment management of neuroendocrine tumors. *J Nucl Med*. 2016;57:708–714.
19. Urbanowski ML, Stauffer GV. Genetic and biochemical analysis of the MetR activator-binding site in the metE metR control region of *Salmonella typhimurium*. *J Bacteriol*. 1989;171:5620–5629.
20. Brabander T, van der Zwan WA, Teunissen JJM, et al. Long-term efficacy, survival, and safety of [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate in patients with gastroenteropancreatic and bronchial neuroendocrine tumors. *Clin Cancer Res*. 2017;23:4617–4624.