North American Neuroendocrine Tumor Society Guide for Neuroendocrine Tumor Patient Health Care Providers During COVID-19.

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During the ongoing COVID-19 pandemic, health care providers have had to make changes to the way they care for patients with neuroendocrine tumors (NETs) and neuroendocrine carcinomas (NECs). Patients coming into clinics or hospitals are at risk of being exposed to the virus, and many may be immunocompromised due to therapy. Health care providers will also be exposed to patients carrying the virus and are at risk of contracting COVID-19, and the number of providers may become depleted. Many facilities have critical shortages of personal protective equipment (PPE), increasing the risk of transmission to both patients and health care professionals. This has important consequences for all aspects of caring for NET/NEC patients, including clinic visits, blood draws, imaging, chemotherapy/biologic therapy, administration of somatostatin analogs (SSAs), peptide receptor radionuclide therapy (PRRT), interventional radiologic procedures, and selection of patients for surgery.

This document represents suggestions from the North American Neuroendocrine Tumor Society (NANETS) on how health care providers might make modifications to their care of NET/NEC patients in these unprecedented times, with the focus on decreasing risk to patients and health care professionals and preserving resources while delivering acceptable patient care. Portions of this document were built on guidelines produced by other professional organizations, which primarily include the American Society of Clinical Oncology (ASCO), the American College of Surgeons, the Society of Surgical Oncology, the Society of Nuclear Medicine and Molecular Imaging, the American Society of Therapeutic Radiation Oncology (ASTRO), Society of Interventional Radiology, and Centers for Disease Control and Prevention (CDC). We thank these organizations for their contributions, and links to their specific recommendations are included hereinafter. The care of NET/NEC patients should be individualized depending on their specific circumstances and the local conditions, which can change rapidly and could require future updates to this document. Facilities that are inundated with COVID-19 cases may need to ration care, whereas those less affected will need to prepare for a surge of patients and the resulting aftermath. This document is formatted as frequently asked questions regarding different aspects of NET/NEC patient care and the responses of a group of NET/NEC specialists representing NANETS.
1. General: How is treatment for patients with NET/NECs likely to change during the COVID-19 outbreak?

Clinic and infusion center workflows and recommendations are likely to evolve rapidly and may vary by institution and region of country; much will depend on the scale and duration of the COVID-19 outbreak. For now, hospitals and treatment centers are preparing to see more patients with COVID-19, while implementing workflows that will allow for ongoing care of patients with cancer and other conditions (minimizing their risk of infection). Changes in workflow that may impact NET patient care include the following:

- Patients will be screened for risk factors and symptoms of COVID-19 before any in-person visits (and triaged to COVID-19 screening clinics as needed).
- There will be greater adoption of phone and/or video visits (telemedicine visits) for follow-up assessments and new patient consultations.
- Nonessential visits, laboratory tests, and scans will likely be postponed.
- Nonemergent procedures will likely be postponed.
- New enrollments to clinical trials will be very limited. Patients currently enrolled on a clinical trial should coordinate with their study teams, as there may be changes to study procedures and follow-up.
- Patients managed by a team of providers (eg, academic center plus local center) will need to work with their health care team to identify the optimal care plan during the COVID-19 outbreak (eg, minimizing in-person visits to multiple centers, delaying planned treatments, choosing regimens that require minimal follow-up, and receiving essential services in the least dense care setting possible).

2. General: What should providers do to prepare their clinic for patients?

Both the CDC and ASCO have provided extensive guidance related to preparing clinics for patient care during the COVID-19 outbreak (including resources for your practices, phone advice line tools, etc):

a. CDC: Prepare Your Practice for COVID-19: https://www.cdc.gov/coronavirus/2019-ncov/hcp/preparedness-resources.html
b. ASCO: COVID-19 Provider and Practice Information: https://www.asco.org/asco-coronavirus-information/provider-practice-preparedness-covid-19

In general, practices should consider implementing actions that impact staff preparedness, clinic preparedness, and patient scheduling.

- Know how to contact your local health department and learn how to stay up-to-date regarding COVID-19 in your community. Ramp up precautions when cases are increasing in your community. Anticipate your needs; restock supplies now and monitor regularly.
- Staff should be trained on use of standard precautions (https://www.cdc.gov/infectioncontrol/basics/standard-precautions.html) and PPE, how to recognize symptoms, and how to screen patients. Health care workers should be aware of current testing for SARS-COV2 (COVID-19) at your center.
- Waiting rooms and patient rooms should be modified to incorporate social distancing mechanisms.
- Cancer centers should limit access to the facility to one point of entry and screen all patients and visitors outside the facility, clinic, or office for COVID-19 symptoms and fever. Patients should be contacted the day before appointment for screening if symptoms of cough, fever, sore throat, or other flu-like symptoms. If patients have symptoms, they should be rescheduled. In cases where there is suspicion for infection, isolate the patient, provide a facemask, and carry out further testing.
- Know which of your patients are at higher risk of adverse outcomes from COVID-19.
- Along with postponing certain nonurgent visits, telemedicine is recommended for patients not requiring a physical examination, treatment, or in-office diagnostics. The American College of Physicians has created a tutorial for deploying telemedicine services (https://assets.acponline.org/telemedicine/scorecontent/?&_ga=2.50834473.1228759002.1584542301-395527866.1580950498#/).

The ASCO COVID-19 Government, Reimbursement & Regulatory Updates page provides more information regarding expanded access to telemedicine for those on Medicare/Medicaid (https://www.asco.org/asco-coronavirus-information/covid-19-policy-updates).

- Explore the option of in-home collection of routine laboratory testing and/or drug administration in your community.
- The CDC provides guidance for the assessment of risk, monitoring, and work restriction decisions for health care workers with potential exposure to COVID-19. See https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-risk-assessment-hcp.html for details.
- There may be drug shortages as the pandemic progresses. The Food and Drug Administration maintains a list of drugs in shortage, including information on expected duration of shortage and alternative suppliers, when available. Providers should report any critical drug or biological products that are in limited supply or being closely monitored or rationed in your facility. See How to Report a Product Shortage or Supply Issue to the Food and Drug Administration (https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/how-report-product-shortage-or-supply-issue-fda).
- Members of the cancer care team are likely to experience higher levels of stress in the face of the COVID-19 outbreak. Providers should be familiar with local resources to help manage the health of providers and staff, and additional resources including the following:

  - US Department of Veterans Affairs, Managing Healthcare Workers’ Stress Associated with the COVID-19 Virus Outbreak (https://www.ptsd.va.gov/covid/COVID_healthcare_workers.asp)
  - National Academy of Medicine, Duty to Plan: Health Care, Crisis Standards of Care, and Novel Coronavirus SARS-CoV-2 (https://nam.edu/duty-to-plan-health-care-crisis-standards-of-care-and-novel-coronavirus-sars-cov-2/)

3. SSAs: Should octreotide or lanreotide be delayed or stopped in NET?

The balance of potential harms that may result from delaying or interrupting SSA treatment versus the potential benefits of possibly preventing or delaying COVID-19 infection (by minimizing trips to the medical center) in NET patients is very uncertain. Clinical decisions should be individualized between patients and their doctor to consider factors such as the likelihood and consequences of cancer progression if therapy is delayed, modified, or interrupted; whether or not the tumor is functional (making hormones that cause symptoms); and the patient’s tolerance of treatment. Some examples of specific situations are as follows:
• Patients with stable or slowly growing, nonfunctional, metastatic NETs on SSAs may opt to temporarily hold SSAs, switch injections to a provider closer to home, increase the interval between injections, and/or explore the option of home injection.
• Previously untreated patients with stable or slowly growing advanced nonfunctional NETs may opt to postpone starting therapy.
• Patients with resectable NETs may opt to start an SSA as an alternative to up-front surgical resection if treatment is needed. However, a few months of observation without therapy may also be a reasonable strategy in most patients with low-grade NETs waiting for surgery.
• Patients with functional NETs will likely need to start or continue SSAs for symptom control. On a case-by-case basis, such patients should work with their health care providers to explore options including starting lanreotide or octreotide, use of subcutaneous octreotide for breakthrough symptoms, home injections of SSAs, and extended intervals between injections (taking care to avoid exacerbation of symptoms). In some settings, liver-directed therapy (hepatic artery embolization or ablations) may also be considered, although this option may be limited by supply and personnel availability: Oral therapy with antidiarrheals (such as loperamide or diphenoxylate/atropine), telotristat ethyl, and other medications may be considered for additional symptom control.
• Under new Centers for Medicare & Medicaid Services guidance physicians will be allowed to contract with qualified infusion suppliers to perform home infusion/injection under audio/visual supervision of a physician when needed. This may allow a provider to set up a home SSA injection program for those receiving Medicare/Medicaid (https://www.cms.gov/files/document/covid-final-1fc.pdf).
• Information about home SSA injection can be found on these manufacturer websites:
  ○ https://www.ipsencares.com/
  ○ https://www.us.sandostatin.com/carcinoid-syndrome/patient-support/mobile-administration-program/
  ○ Before the COVID-19 pandemic, these programs were not allowed to those on Medicare, Medicaid, US Department of Veterans Affairs, Department of Defense, TRICARE, or who lived in certain states. As in the case of telehealth, these restrictions have been changed and patients may be allowed to participate in these programs.

4. Surgery: Can/should surgery be canceled or delayed?
Health care providers and patients will need to make individual determinations based on the potential harms of delaying needed cancer-related surgery, the specific situation at their hospital, and the increased risk to the patient from COVID-19 exposure. The American College of Surgeons has defined 3 levels of impact of COVID-19, which are very useful for helping to decide on surgical priorities (https://www.facs.org/-/media/files/covid19/acs_triage_management_elective_cancer_surgery_during_acute_and_recovery_phases.xlsx). These include the following:

Phase I: Semiurgent: There are few COVID-19 patients, hospital resources are not exhausted, the institution still has intensive care unit (ICU) ventilator capacity, and the COVID-19 trajectory is not in rapid escalation phase. Surgery is restricted to patients likely to have survivorship compromised if surgery is not performed within the next 3 months.
Phase II: Urgent: There are many COVID-19 patients, ICU and ventilator capacities are limited, operating room supplies are limited, or COVID-19 trajectory within hospital is in the rapidly escalating phase. Surgery is restricted to patients likely to have survivorship compromised if surgery is not performed within the next few days.
Phase III: Hospital resources are all routed to COVID-19 patients, there is no ventilator or ICU capacity, or operating room supplies are exhausted. Surgery is restricted to patients likely to have survivorship compromised if surgery is not performed within the next few hours.

By these criteria, most surgeries for NETs can be postponed. These tumors are generally slow growing, and various medical therapies can reasonably be used when there is a need to delay surgical management. Situations that are considered more urgent and therefore could be considered in phase I or occasionally in phase II scenarios might include the following:

• Symptomatic small bowel NETs (eg, obstruction, bleeding/hemorrhage, significant pain, and concern for ischemia). Perforation, ischemia, or obstruction not responding to nasogastric decompression would require surgery even in phase III.
• Functional pancreatic NETs where symptoms cannot be controlled medically, or nonfunctional pancreatic NETs with symptoms due to local tumor extension, such as bile/pancreatic duct or gastroduodenal obstruction and bleeding could also be considered if failing nonoperative management.
• Well-differentiated lesions with significant or rapid growth

In most situations, other therapies are available, and it may be reasonable to consider alternative treatments up front. For example, one could consider using SSAs, other targeted agents (eg, everolimus or sunitinib), PRRT, or chemotherapy for well-differentiated NETs requiring therapy. Chemotherapy or external beam radiation therapy could be used instead of surgery up front for poorly differentiated NECs or high-grade NETs. In other cases, simply delaying surgery may make sense for “elective” procedures (eg, debulking of low-grade NET liver metastases, removing an asymptomatic primary tumor of the small bowel, resecting asymptomatic pancreatic NETs especially those that are smaller with lower risk of metastases [<3 cm], and surgery for asymptomatic gastroduodenal or rectal NETs). Debulking surgeries and removal or ablation of metastatic tumors should generally be delayed but should be considered on an individual basis, especially if tumors are progressing after multiple therapies (SSAs, chemotherapy or biologic therapy, PRRT) or are causing extreme symptoms despite medical therapy.

The risks of tumor progression with delay in definitive surgery should be weighed against the potential added burden on hospital resources (PPE, staff, ICU care, need for a ventilator), case complexity, and the risk of exposure of patients to COVID-19. However, therapies that require clinic visits and clinician-patient contact, or that themselves could be immunosuppressive, will also be associated with risks to the patient, and this must also be considered when choosing how to treat patients with NETs.

5. Liver-directed therapy: Should liver embolization be performed? Is one modality preferable to another in the context of the COVID-19 outbreak?

Across the country, interventional radiology practices are postponing nonurgent or elective procedures. Determination of what qualifies as nonurgent should be made on a case-by-case basis based on several factors including the indication for the procedure (eg, hormone-mediated symptoms, rate of tumor progression, pain), prior treatment, patient comorbidities, risk of COVID-19 infection
and complications, and institutional resources (including availability of PPE). Additional guidance from the Society of Interventional Radiology can be found at https://www.sirweb.org/practice-resources/covid-19-resources/.

Asymptomatic patients with a low burden of a low-grade tumor and normal liver function, where the intended treatment is percutaneous tumor ablation or (chemo)embolization, can continue imaging surveillance for several months with little risk of an adverse outcome. Patients who are symptomatic or present with a heavy liver tumor burden such that the risk of liver failure threatens survival should undergo liver-directed therapy if hospital resources allow. Embolization should be performed on an outpatient or observation status to minimize contact with the inpatient population and staff. If the community is early on the curve of the epidemic, with low prevalence of infection and ample resources, consider accelerating treatment plans to get NET patients in and out before resources become stressed and exposure risk increases. Follow-up in the Interventional Oncology Clinic should be done by telemedicine, with imaging and laboratory testing done locally for the patient.

6. Lutetium Lu177 DOTATATE PRRT: Should PRRT be delayed if not yet started? Should the next treatment plan be postponed if in the middle of the planned PRRT course?

As with other procedures, the risk of exposure to COVID-19 and the burden on the hospital system should be taken into account when considering initiating or continuing with lutetium Lu177 DOTATATE PRRT. Delaying PRRT can be considered in selected patients, for example, those with slow or no progression before treatment, lower tumor burden, nonfunctional disease, and older patients or those with more comorbidities. A delay of weeks (or longer in some situations) will not impact patient outcome and is considered safe, as it has been practiced for many years in European centers. It is worth noting that, although doses were planned for 8-week intervals in the NETTER-1 trial, subjects could extend the interval to 16 weeks as needed for toxicity. Furthermore, although 4 cycles of therapy were evaluated in the NETTER-1 study, others have reported on the use of 3 cycles of therapy. As such, omitting a cycle of therapy or extending the interval between treatments may be reasonable in selected PRRT patients during the COVID-19 outbreak. Peptide receptor radionuclide therapy should be initiated or continued in patients with difficult to control functional disease, more aggressive disease, higher tumor bulk, those already maximized on SSA, or with multiple prior lines of therapy. If on treatment, patient visits for safety evaluation should be converted to telemedicine if possible, and visits to the hospital (including laboratory appointments) should be minimized to decrease exposure. The decision to extend the interval between treatments and/or omit one or more cycles of therapy in a patient on PRRT will need to be made on a case-by-case basis (considering response and tolerability to date, COVID-19 risk factors, general clinical status, prior therapy, etc) balancing the potential consequences of cancer progression with the potential ramifications of COVID-19 infection. At the present time, the data are insufficient to determine the relative risk of COVID-19 infection and associated complications in the setting of PRRT compared with chemotherapy or use of other systemic agents (eg, everolimus).

7. Iobenguane I 131: Should iobenguane I 131 therapy be delayed if not yet started? Should the next treatment be postponed if in the middle of the planned course of iobenguane I 131 therapy?

As with other procedures, the risk of exposure to COVID-19 and the burden on the hospital system should be taken into account when considering initiating or continuing with iobenguane I 131. Delaying iobenguane I 131 can be considered in selected patients with pheochromocytoma or paraganglioma, for example, those with slow or no progression before treatment, lower tumor burden, nonfunctional disease, and older patients or those with more comorbidities. If there is a pressing need for treatment, one might consider starting with a lower outpatient dose, both to avoid the need to do dosimetry (which would require additional visits to the hospital) and to avoid taking up an inpatient bed (radiation safety rooms at many centers may be located on wards designated for COVID-19 patients). Delaying the second cycle of iobenguane I 131 should be considered as long as the patient is clinically stable.

8. Focal radiation: Should the initiation of radiation be delayed? Can radiation be interrupted or postponed if already in progress?

The risks of delay in treatment for patients with rapidly progressing, potentially curable tumors (eg, localized, poorly differentiated NEC) may outweigh the risks of COVID-19 exposure/infection. However, patients receiving radiation for symptom control or at low risk of harm due to alteration of their schedule for radiation treatment visits could potentially be safely delayed. Patients should check with their radiation oncologist to determine the most appropriate course of action for their treatment. Additional guidance and resources from ASTRO can be found at https://www.astro.org/Daily-Practice/COVID-19-Recommendations-and-Information/Clinical-Guidance.

9. Chemotherapy: Should chemotherapy potentially be stopped, delayed, or interrupted?

As per ASCO guidance, routinely withholding critical anti-cancer or immunosuppressive therapy is not recommended. The potential harm that may result from delaying or interrupting treatment versus the potential benefits of preventing or delaying COVID-19 infection is uncertain. Clinical decisions should be individualized considering factors such as the following: goals of care; urgency of treatment; risk of cancer progression if therapy is delayed, modified, or interrupted; number of cycles of therapy already completed; and the patient’s tolerance of treatment. Some examples of specific situations are as follows:

• For patients with good disease control, stopping chemotherapy may be an option (eg, someone who has had several months of capectabine/temozolomide for pancreatic NET or someone who has had 4–6 cycles of platinum-based therapy for poorly differentiated NEC).
• Some patients may be able to switch from intravenous chemotherapy to oral therapies, which would decrease clinic visits but would require greater vigilance by the health care team to ensure the medication is taken correctly.
• If the COVID-19 outbreak affects a particular cancer center, it may be reasonable to take a chemotherapy break for a few weeks, arrange for infusion at an unaffected satellite site, or transfer treatment to an unaffected facility.
• Use of adjuvant treatment of potentially curable poorly differentiated NEC needs to be considered carefully, as delays or
modifications may be at the expense of compromised disease control and long-term survival.

- Similarly, the risk/benefit assessment for proceeding with platinum-based (or other) chemotherapy in patients with advanced poorly differentiated NEC is potentially different from that of commencing capcitabine/temozolomide in patients with slowly growing well-differentiated NEC.

- In patients on high-risk chemotherapy regimens, prophylactic growth factors, and/or prophylactic antibiotics may be of potential value to reduce the health care burden from urgent visits for febrile neutropenic events.

- At the present time, the data are insufficient to determine the relative risk of COVID-19 infection and associated complications in the setting of chemotherapy compared with PRRT or use of other systemic agents (eg, everolimus).

10. Everolimus and sunitinib: Should everolimus or sunitinib be stopped or interrupted during the COVID outbreak?

No specific guidance is available regarding continuation of oral targeted agents like everolimus and sunitinib during the COVID-19 outbreak. In general, however, decisions to postpone, discontinue, or modify everolimus or sunitinib should consider the overall goals of treatment, risk of cancer progression if treatment is postponed or interrupted, patient tolerance of treatment, and the patient's general medical condition and risk of COVID-19. Each decision requires an individualized risk/benefit assessment between the patient and their provider, for example:

- In an otherwise stable patient on everolimus or sunitinib, it may be reasonable to take a break from therapy entirely, or continue therapy while reducing the interval of laboratory testing, using in-home blood sample collection, or changing to video visits to limit trips to the office (after discussion with the health care provider). Continued use of these agents with reduced clinic visits will require more frequent telephone and video interaction with the health care team to carefully evaluate for potentially serious medication side effects, for example, pneumonitis.

- Patients starting a new therapy will require careful follow-up, and should discuss the pros and cons of initiating a new therapy now, postponing treatment, or considering other alternatives (eg, hepatic embolization and increasing dose of SSA).

- At the present time, the data are insufficient to determine the relative risk of COVID-19 infection and associated complications in the setting of treatment with oral targeted agents compared with chemotherapy or PRRT. However, everolimus is thought to be more immunosuppressive than sunitinib. Furthermore, the pulmonary infiltrates associated with noninfectious pneumonitis in ~20% of everolimus-treated patients could present a diagnostic challenge in the setting of COVID-19.

11. Imaging: Should imaging be postponed?

In general, as recommended by the CDC, any clinic visits that can be postponed without risk to the patient should be postponed. In some cases, it will be prudent to proceed with imaging, particularly if the information will impact the treatment plan (eg, choice or timing of therapy). Some examples of specific situations are noted hereinafter:

- Incidental finding suspicious for NET: Patients who are suspected clinically of disease at low risk of rapid progression (eg, small pancreatic NETs) may potentially delay follow-up imaging.

- Routine surveillance imaging after complete resection of NET/NEC: In any clinic visits that can be postponed without risk to the patient should be postponed. This likely includes routine surveillance in patients considered to be at relatively low risk of recurrence and those who are asymptomatic during the follow-up period. In situations where existing recommendations provide frequency ranges for interventions (eg, every 3–6 months), it is reasonable to delay scheduled interventions to the longest intervals.

- Routine follow-up imaging (on therapy or with known disease in place): Each decision requires an individualized risk/benefit assessment (eg, current therapy, grade of tumor, rate of growth, and symptoms). In situations where existing recommendations provide frequency ranges for interventions (eg, every 3–6 months or every 6–12 months), it is reasonable to delay scheduled interventions to the longest recommended interval.

12. Management of ongoing therapy in COVID-19–positive patients

The general recommendation from multiple expert groups is to interrupt anticancer treatment in patients with active COVID-19 infection, as continuing aggressive anticancer treatments during this time may lead to more serious complications. It is reasonable to hold therapy until all symptoms have resolved and the virus is no longer present (except in patients with rapidly progressing cancers such as NEC, where discussion regarding the risk/benefit ratio of reinitiating therapy earlier may be needed). Currently, it is unclear how long to wait to restart therapy, but ASCO advises following the CDC’s recommendations on the time to discontinuation of transmission-based precautions as a useful guide (https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-hospitalized-patients.html).

Additional information for providers can be found here:

- ASCO: https://www.asco.org/asco-coronavirus-information
- NCCN: https://www.nccn.org/covid-19/
- Society of Surgical Oncology: https://www.surgonc.org/resources/covid-19-resources/
- CDC: https://www.cdc.gov/coronavirus/2019-ncov/index.html
- World Health Organization: https://www.who.int/emergencies/diseases/novel-coronavirus-2019
- ASTRO: https://www.astro.org/Daily-Practice/COVID-19-Recommendations-and-Information/Clinical-Guidance
- American College of Surgeons: https://www.facs.org/covid-19
• Society of Interventional Radiology: https://www.sirweb.org/practice-resources/covid-19-resources/
• Society of Nuclear Medicine and Molecular Imaging: http://www.snmmi.org/COVID-19
• NANETS: https://nanets.net/resources/covid-19-resource-page

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