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Review

Practical recommendations for the management of patients with gastroenteropancreatic and thoracic (carcinoid) neuroendocrine neoplasms in the COVID-19 era

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Abstract Neuroendocrine neoplasms (NENs) are a heterogeneous family of uncommon tumours with challenging diagnosis, clinical management and unique needs that almost always requires a multidisciplinary approach. In the absence of guidance from the scientific literature, along with the rapidly changing data available on the effect of COVID-19, we report how 12 high-volume NEN centres of expertise in 10 countries at different stages of the evolving COVID-19 global pandemic along with members of international neuroendocrine cancer patient societies have suggested to preserve high standards of care for patients with NENs. We review the multidisciplinary management of neuroendocrine neoplasms during the COVID-19 pandemic, and we suggest potential strategies to reduce risk and aid multidisciplinary treatment decision-making. By sharing our joint experiences, we aim to generate recommendations for proceeding to other institutions facing the same challenges.

1. Introduction

1.1. Cancer care in the era of COVID-19

The outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–associated disease (COVID-19) poses an unprecedented challenge globally to all healthcare systems, professionals and patients, and it remains unclear how long this will last [1]. The COVID-19 disease is characterised by rapid human-to-human transmission, and its severity can range from asymptomatic disease to acute respiratory distress syndrome (ARDS) or multiorgan failure requiring aggressive measures, to death [2,3].

Accumulating evidence suggests that patients with cancer may be at higher risk of morbidity and mortality related to COVID-19 infection than the general population because of coexisting chronic comorbidities, underlying malignancy and systemic immunosuppressive states caused by both cancer itself and the effects of antineoplastic therapy or supportive medications such as steroids [4–6]. The current COVID-19 pandemic has transformed and reorganised every aspect of cancer care including deferring clinical activity, adoption of new less-intensive care regimens and innovative ways of care delivery, and curtailed research. The goal has been to maintaining cancer care with minimal risk to patients and staff and shifting resources to COVID-19 care. Remarkable efforts have been made to understand the specificities of cancer patients who develop COVID-19 infection, to overcome the diagnostic and therapeutic challenges and to implement global recommendations for cancer treatment. Oncology societies and national authorities have issued guidelines on cancer care during the pandemic [7–13]. Current pragmatic challenges with the application of these guidelines are i) limited evidence and long-term data defining the risk in various cohorts of cancer patients although this is evolving [14,15], ii) geographic heterogeneity of the COVID-19 pandemic, iii) patient and disease specific risks not evident, and iv) regional variation in resources.

NENs, histologically graded into well differentiated (grade I, II or III neuroendocrine tumours [NETs]) or poorly differentiated neuroendocrine carcinomas (NECs) are a heterogeneous family of rare tumours of challenging diagnosis, clinical management and unique needs that require a multidisciplinary approach [16], with each discipline uniquely affected by the COVID-19 pandemic. Particular challenges with caring for patients with rare cancers in the midst of a pandemic are: the requirement of specialised expertise at centres of excellence, the reliance on a multidisciplinary approach to ensure optimal care, limited access to some treatments and diagnostics, and sometimes the lack of data to guide clinical decision-making [17,18]. In the absence of guidance from the scientific literature, along with the scarce and rapidly changing data available on the effect of COVID-19, sharing collective experiences from academic NEN hospitals in multiple countries at different stages of the COVID-19 pandemic becomes essential especially in rare cancers such as NENs.

2. Methods

The report submitted herein presents a focused set of recommendations that was developed by a multidisciplinary panel of 14 NENs specialists from 12 high-volume NENs centres of expertise in 10 countries (i.e. Canada, France, Germany, Ireland, Israel, Italy, Spain, Sweden, the Netherlands and the United Kingdom) along with members of the International Neuroendocrine Cancer Alliance and the Canadian Neuroendocrine Tumour Society. We rapidly reviewed the published literature and guidelines for COVID-19–related cancer care and applied them to NENs. Each

Table 1
Consensus measures taken by centres for NENs care during the peak stage of the COVID-19 pandemic.

Category	Measures during the pandemic peak for cancer care	Measures during the pandemic peak for NENs care
Hospital-wide	Construct a hospital-wide crisis team responsible for coordinating measures between departments. Instruct patients not to visit the hospital if they have symptoms indicative of possible COVID-19 (unless urgent attention is required). Screen patients at the entrance for symptoms of COVID-19 and fever. Quickly isolate patients with COVID-19 in specialised departments (if possible). Reduce clinical research activities. Enable telephone or video consultations for healthcare professionals who need to self-isolate.	
Outpatient clinic	Critically triage second opinions.	Maintain referrals to centres of expertise for ongoing multidisciplinary supportive care. If not feasible, identification of the optimal care plan during the COVID-19 outbreak with the healthcare team at local hospital.
	Adopt of phone and/or video visits (telemedicine visits) for follow-up assessments and new patient consultations. All patients, regardless if they are off therapy (have completed a treatment or have disease under control) or have "active disease" undergoing active treatment it is mandatory to provide health education: avoid crowded places, wear personal protective equipment (PPE) when attending hospital for visits and treatments, hand hygiene according to World Health Organization (WHO) indications, social distancing with all people, protect yourself to protect others …. When possible, reduce or delay the number of radiological evaluations. Prioritise oral or subcutaneous treatments above infusion-based treatments to reduce time spent in the hospital. Nonessential visits, laboratory tests, or procedures and scans will likely be postponed. Perform blood tests outside the hospital (e.g. at a general practice or at home), when possible. When possible have oral or subcutaneous medications delivered to the patient's home. Maintain multidisciplinary team consultations, remotely if possible. Discuss patient with a multidisciplinary team to consider alternative treatment modalities with less anticipated risk of COVID-19–related complications requiring hospital admission. Inform patients about a possibly increased risk associated with anticancer therapy during the COVID-19 pandemic.	
		Consider switch somatostatin analogues (SSAs) injections to a provider closer to home, or set up a home SSAs injection program with dedicated link with home practitioner/nurse and training on use of PPE. Proactive functional control to avoid hospitalisations in patients with functional NENs.
	• COVID-19 testing should be proposed to all patients undergoing surgery, interventional radiology or radiotherapy. • COVID-19 testing for all patient starting chemotherapy will depend on the incidence of the COVID-19 pandemic and the local guidelines. • Testing should be proposed to all patient with suggestive symptoms of COVID-19 infection, being in active treatment, in follow-up phase or a survivor.	
Chemo care	Consider omitting supportive treatments (e.g. no bisphosphonate infusion, etc)	Consider ongoing supportive treatments if functional NENs.
	In patients on high-risk chemotherapy regimens, prophylactic growth factors, and/or prophylactic antibiotics may be of potential value. Selecting chemotherapy regimens with less need for i.v. fluids, such as carboplatin instead of cisplatin should be considered, as increased i.v. fluids are not recommended in COVID-19 pre–acute respiratory distress syndrome (ARDS). Patient preference must be factored into management during the COVID-19 era.	
	When possible, organise the administration of intravenous maintenance treatments at home, or consider temporary breaks or reductions in the frequency.	Unlikely in NENs.
Management of ongoing therapy in COVID-19 –positive patients	- Cancer patients on surveillance or watchful waiting approaches that test positive for COVID-19 should follow the recommendations for the general population, which may vary by institution and region of country depending on the scale and duration of the COVID-19 outbreak. - For cancer patients receiving anticancer treatment, including NENs, the general recommendation from multiple expert groups is to interrupt anticancer treatment in patients with active COVID-19 infection for a minimum of 14 days and/or until all symptoms have resolved for 14 days and there is some certainty the virus is no longer present (e.g. at least a negative COVID-19 test). Exception could be SSAs for symptomatic secretory NENs (https://www.cdc.gov/coronavirus/2019-ncov/hcp/dispositionhospitalized-patients.html) - Decisions for treatment re-initiation or continuation must be discussed for COVID-19 positive patients if they are asymptomatic or pauci-symptomatic, still fit to be treated and willing to do so after proper risk/benefit explanation.	

PPE, personal protective equipment.

center was invited to provide their approach and recommendations regarding NENs. We identify and discuss many commonalities, but also important local differences, and suggest potential strategies to modify risk during the pandemic and aid multidisciplinary treatment decision making.

3. General recommendations for NEN care during the COVID pandemic

The management of patients with NENs is complex and should be individualised. Factors such as patient comorbidities, performance status, concomitant medication as well as factors that reflect the heterogeneity of NENs, such as tumour-origin, functional status, growth rate, grade, differentiation status, overall disease burden and level of somatostatin receptor expression, will ultimately be taken into consideration when clinicians decide on appropriate treatment pathways for NENs during the COVID pandemic [16–18]. Variation of treatment choices will also depend on local access and availability of treatments as well as the current regional status of the pandemic.

3.1. Maintaining multidisciplinary care in the COVID-19 era

The outcomes of patients with NENs are improved with the multidisciplinary care [19]. During the time of COVID-19, ensuring multidisciplinary care (remotely if necessary) will be essential as different treatments will need to be considered as well as the risk and benefits weighed on an individual patient level. Given the travel restrictions and need for social distancing, multidisciplinary care and case conferences will need to move virtual [16–19]. Developing internal protocols to triage patients into telehealth/virtual versus in-person encounters as well as switching discussions with other health professionals to virtual platforms or phone rather than face-to-face as much as feasible is being universally adopted [7–13,20,21]. We have provided an overview of our approaches and the many commonalities between the general measures applied for cancer care and the particularities that could be applied to the NEN care (summarised in Table 1). This guide is likely to evolve rapidly and may vary by institution and region of country depending on the scale and duration of the COVID-19 outbreak.

3.2. Patient preference in the COVID-19 era

Patient preference must also be factored into management during the COVID-19 era. Educating and engaging patients and caregivers with the most recent COVID-19 guidelines, as well as to educate them on any deviations from the standard of care will ensure a proper understanding of the trajectory of their care. Coordination of tests, imaging, and virtual visits by navigators should be implemented to mitigate potential additional distress for patients and to avoid multiple visits [20,21]. Supportive care needs such as nutrition consultation, social work, palliative care symptoms consultations, therapy education and self-assessment continues to be important for patients with NENs during the pandemic and should be integrated during the transition process to virtual care. Psychological support should be ramped up to adequately meet patient needs, as the emotional toll can be very challenging for NENs patients, including psychological disturbing issues such as treatments delay, delayed access to peptide-receptor radioligand therapy (PRRT), inability to access somatostatin analogues (SSAs) supply from local pharmacies, fear of going to hospital for investigations and appointments, and loss of human interaction. Patients may consider switching to a provider closer to home if available, moving to virtual care, or participating in a home SSAs injection program. If possible, a dedicated link with home practitioner/nurse and training on use of personal protective equipment , as well as to proactively manage functional symptoms control, with potential increased/adjusted doses to avoid hospitalisations is advisable during COVID-19 pandemic. We should collect patient experience data as virtual care is likely here to stay and may benefit NENs patient experience and care, and 'recovery and restoration' plans need to include strategies and the infrastructure to address this increased need as 'normal' care resumes.

3.3. Reevaluating NENs treatment paradigms in the COVID-19 era

During the COVID-19 pandemic any clinic visits or investigation that can be postponed without risk to the patient should be postponed; however an individualised risk/benefit assessment (e.g. patient general condition and medical background, current therapy, tumour characteristics such as ki67 proliferation index, grade of tumour, rate of growth, and symptoms) is required. Telemedicine or virtual care whenever feasible should be implemented, and follow-up visits could be led by a single leading discipline. During the peak of the pandemic wherever possible scans and lab tests should be done locally to reduce travel and in-person hospital visits. Investigations at the time of new NENs diagnosis should be limited only to those that are most necessary. Travel restrictions could have a negative impact on speciality scans such as computed tomography (CT) enterography or ^{68}Ga-somatostatin receptors (SSR) positron-emission tomography (PET) (DOTATOC/DOTATATE/DOTANOC) PET-CT [22,23] that are not usually available in all the centres. The use of ^{68}Ga-SSR PET-CT could be postponed in particular cases, for example, in resected early-stage NENs with no clinical or radiological suspicion for residual disease on conventional imaging. The

Table 2
Specific considerations for locoregional therapy for NENs during the COVID-19 pandemic.

Treatment modality	Proposed treatment recommendations during the COVID-19 pandemic	Other considerations during the COVID-19 pandemic
Surgery	• Based on the American College of Surgeons levels of impact during COVID-19 [12,38], most surgeries for NENs fit under the category of semi urgent and could be safely postponed. • NENs healthcare providers and patients will need to make individual determinations based on the potential harms of delaying surgery, the specific situation at their hospital and the increased risk to the patient from COVID-19 exposure. • In most situations, may be reasonable to consider using bridging alternatives such as somatostatin analogues (SSAs), for well-differentiated, slow growing tumours. • Delaying elective surgeries procedures could be also considered in the following cases: debulking of low-grade NET liver metastases, removing an asymptomatic primary tumour of the small bowel, resecting asymptomatic NETs with low risk of metastases. • Higher priority for surgical indications in NENs might include: - Highly symptomatic small bowel NETs or acute abdominal complications (e.g. obstruction, bleeding/hemorrhage,..) - Functional pancreatic NETs where symptoms cannot be controlled medically • Liver transplantation (LT) consideration should be deferred.	• Regardless appropriateness of surgical delays in NENs, referral to tertiary cancer centres should be still advocated, to allow a process of treatment optimisation based on expert multidisciplinary rounds, an awareness of the best evidence-based care available during the COVID-19 pandemic. Facilitate patient consultations via telehealth. • Preoperative screening for COVID-19 and universal personal protective equipment (PPE) might mitigate this risk. • Postoperative follow-up should use telemedicine options as allowable by local regulatory bodies.
Liver-directed therapy: Transarterial chemoembolisation (TACE), bland embolisation (TAE), radioembolization (TARE), and ablation [radiofrequency (RFA) or microwave ablation (MWA])	• Mandatory discussion in a multidisciplinary tumour board prior to initiation of any liver-directed therapy. Treatment modality will depend on the centre's local expertise, availability of particular technologies and extension/localisation of liver involvement. • Could be particularly considered in highly functioning tumours for symptom control and for tumour growth control in well differentiated NETs instead of a more toxic potentially myelosuppressive therapy such as targeted drugs or systemic chemotherapy. • Non-urgent or elective interventional radiology practices could be postponed on a case-by-case basis evaluation: hormone-mediated symptoms, rate of tumour progression, treatment alternatives, patient comorbidities, risk of COVID-19 infection and complications, and institutional resources (including availability of PPE). • For TACE, consider other liver-directed alternative to reduce the risk of immunosuppression (ie, TAE or TARE).	• Consider testing for COVID-19 before procedure. If the patient is positive, delay the procedure for 7–14 days until the patient has at least one test negative and is asymptomatic. • Standard PPE and respiratory protocols should be instituted. • Establish virtual pre- and post-procedure visits. • Additional guidance from the Society of Interventional Radiology can be found at https://www.sirweb.org/practiceresources/covid-19-resources/.
External beam radiotherapy (stereotactic body radiotherapy (SBRT))	• Treatment alternative in the absence of liver-directed therapy options for high-grade NETs with oligometastatic disease to the	• Consider screening for COVID-19 before radiotherapy simulation.

Table 2 (*continued*)

Treatment modality	Proposed treatment recommendations during the COVID-19 pandemic	Other considerations during the COVID-19 pandemic
	liver, to bridge patients whose cancers are resectable, but resection is not available. • Minimizing the number of radiotherapy fractions delivered is preferable.	• Universal personal protective equipment, use of breathing control devices, and the use of non-invasive tumour motion techniques should be adopted. • If the patient is positive for COVID-19, delay the procedure for 7–14 days until the patient has at least one test negative for COVID-19; Additional information can be found at https://www.astro.org/Daily-Practice/COVID-19-Recommendations-and-Information/Clinical-Guidance.
Palliative radiotherapy (local or metastatic)	• Consider delay preventing multiple outpatient visits, potentially increasing the risk of COVID-19. • Consider best supportive care, and palliative care involvement, and adopt single fraction for symptomatic disease when feasible.	• Consider screening for COVID-19 before radiotherapy simulation, use of universal personal protective equipment, breathing control devices and non-invasive tumour motion techniques might mitigate this risk. Additional information can be found at [13,29].

PPE, personal protective equipment.

use of ^{18}F-FDG-PET is not mandatory in most NENs and should be adopted on an individual basis [22,23]. Given the uncertain timeline of the epidemic, physicians need to assess the risk/benefit ratio of anticancer therapies during the COVID-19 pandemic. Data are insufficient to determine the relative risk of COVID-19 infection and associated complications in the setting of systemic oncologic treatments commonly used in NENs management [17,18,22], but some particularities of NENs patients should be considered:

- Management of NENs patients with uncontrolled functional symptomatology [22,24–27] may necessitate proactive management to avoid hospital visits during the COVID pandemic.
- The common presence of other non-cancer comorbidities (e.g. underlying liver/renal disease, advanced age, diabetes and cardiovascular disease) seen in NENs patients [28] might result in increased morbidity and mortality related to COVID-19.
- Some standard treatment modalities in NENs, such as liver transarterial chemoembolisation [22,29], extensive field radiotherapy or PRRT [30] or systemic targeted therapies (everolimus or sunitinib) [22,31–33] and chemotherapy [22] or supportive medications such as steroids [4–6], may increase the risk of infections and immunosuppression. Targeted agents can also have side-effects such as serious sepsis, pneumonitis or thromboembolic events [31–33] that may facilitate COVID-19 infection and could present a diagnostic challenge in the setting of COVID-19.
- Treatments such as chloroquine and hydroxychloroquine that have been used to combat COVID-19 [34] can have side effects relevant to the NEN management, such as hypoglycemia, which could make more challenging the diagnosis of NENs such as insulinoma, and could interfere with SSAs treatment. In addition, chloroquine, hydroxychloroquine and azithromycin could prolong the QT interval and interfere with SSA treatment or systemic targeted therapies (everolimus or sunitinib) [34]. Chloroquine and hydroxychloroquine have a long half-life (1–2 months) and are substrates for cytochrome P450 enzymes, which could have a sustained effect on the metabolism of sunitinib and everolimus [22,31–33].
- NEN patients receiving antithrombotic therapy for thrombotic disease may develop SARS-CoV-2 infection which predisposes patients to thrombotic disease, with implications for choice, dosing and laboratory monitoring of the antithrombotic therapy, due to potential bleeding risk [35].

During COVID-19, there have been calls for de-escalation of care to minimise risk of exposure [3–8], and the effect of treatment modifications on NENs is unclear. Treatment delays may have little impact in slow-growing disease and may be very reasonable to help reduce impact on the cancer system during COVID. As per the prioritisation-based management guidelines recommended by the oncology societies [7–13], most of the treatment indications for NENs would fit under a lower priority, as given the slow-growing nature of many NENs, the survival of patients is not likely be compromised if treatment intervention is not performed within the next 8 weeks. This recommendation could apply for patients with well-differentiated grade I, slow-growing NETs with Ki-67 <3% and low tumour burden or NETs grade II with low Ki-67 (<5%) with prolonged disease stability on treatment. However, a case by case evaluation is required, and there are examples of treatment indications that should be prioritised in NENs, such as follows:

- Highly functional NENs (e.g. uncontrolled carcinoid syndrome and/or carcinoid heart disease, uncontrolled hypoglycemia, watery diarrhoea in VIPoma, etc).
- Radiologically/clinically progressive grade II NETs.

- High-grade (grade III) NETs or NECs patients.
- High-priority surgical indications: cases where a potential delay would likely close the window of opportunity for surgery or endanger the patient, highly symptomatic small bowel NET patients and/or acute abdominal complications (e.g. obstruction, bleeding/hemorrhage); functional pancreatic NETs patients where symptoms cannot be controlled medically and well-differentiated lesions with significant or rapid growth.
- Prioritised PRRT: in patients with refractory functional disease, those with higher tumour bulk, or those already on increased dose of SSA with lack of alternatives.

Unfortunately, the effects of COVID-19 are not solely limited to the standard-of-care treatment management, but have also had consequences for clinical research. The majority of the centres have halted the initiation of new clinical trials, particularly for those requiring additional actions and/or visits. The impact of the pandemic on clinical and basic cancer research is likely to be severe and could be magnified for those rare tumour entities such as NENs with lack of treatment options.

3.4. Management of COVID-19–positive NEN patients

The specific incidence, morbidity and mortality of COVID-19 among patients with NENs is unknown. For cancer patients receiving anticancer treatment, including NENs, the general recommendation from multiple expert groups is to interrupt anticancer treatment in patients with active COVID-19 infection for a minimum of 14 days and/or until all symptoms have resolved for 14 days, and there is some certainty the virus is no longer present (e.g. at least a negative COVID-19 test) [7–13,36,37]. Exception could be SSAs for symptomatic secretory NENs or life-threatening need for treatment which is rare in NENs.

4. Specific treatment recommendations for NENs care during the COVID-19 pandemic

4.1. Surveillance

Optimal interval timing follow-up for fully resected NENs or for metastatic NENs patients on therapy or routine follow-up is not well established [22,23] and could result in much variation in real-world practice and potentially suboptimal use of resources, which is critical in a pandemic state. In general for asymptomatic slow growing grade I NETs or grade II NETs with low Ki-67 (<5%) patients and prolonged disease stability on treatment it is reasonable to delay scheduled interventions, particularly in countries with high incidence of COVID-19, whereas for grade III NETs or NECs, delay on scheduled follow-up investigations should be individualised. NENs patients on active treatment or surveillance who are suspected clinically of disease progression should proceed with imaging as indicated.

4.2. Specific considerations for locoregional therapy for NENs during the COVID-19 pandemic

4.2.1. Surgery

Surgical programs require substantial resources to provide presurgical assessments and care which have been substantially affected during the pandemic. Based on the American College of Surgeons levels of impact during COVID-19 [12,38], most surgeries for NENs would fit under the category of semi-urgent, as survivorship of NENs patients is not likely compromised if surgery is not performed within the next 3 months and could be safely postponed (e.g. removing an asymptomatic primary tumour with low risk of metastases, debulking of liver metastases of low-grade NETs or palliative debulking surgeries). In addition, surgeons should strictly prioritise curative surgery. Accordingly effort should be made to rule out metastases before operating on NETs patients to avoid de-bulking surgeries that can be generally safely delayed.

For those patients with primary potentially resectable NENs whose elective surgery is being delayed, an alternative upfront approach should be considered to bridge patients while they wait for surgery (SSAs for well-differentiated, slow-growing tumours). Higher priority surgical indications in NENs include the following: highly symptomatic small bowel NETs not controlled with standard medical treatments or acute abdominal complications (e.g. obstruction, bleeding/hemorrhage, etc.) or functional pancreatic NETs where symptoms cannot be controlled medically. Regardless appropriateness of surgical delays, which must be discussed and agreed with patients and caregivers, referral to high-volume NEN centres of expertise should still be advocated. Liver transplantation should be deferred during pandemic [12,22,38] (Additional information is shown on Table 2).

4.2.2. Liver-directed therapy

During the pandemic era, non-urgent or elective interventional radiology practices [22] could be postponed on a case-by-case basis evaluation, including hormone-mediated symptoms, the rate of tumour progression, symptoms, prior treatments, comorbidities, risk of COVID-19 infection and complications, and institutional resources. During COVID-19, liver-directed therapies could be considered in highly functioning tumours for symptoms control and for tumour growth control in well-differentiated NETs instead of more

Table 3
Specific considerations for systemic therapy for GEP- NETs (well-differentiated) during the COVID-19 pandemic.

Treatment modality	Proposed treatment recommendations during the COVID-19 pandemic	Other considerations during the COVID-19 pandemic
Somatostatin analogues (SSAs): octreotide or lanreotide	• Greater adoption of watch-and-wait approach in asymptomatic, newly diagnosed NETs patients with low-grade tumour, Ki-67 (<2%) and low tumour burden. • Consider temporarily hold or increase the interval SSAs injections in non-functional, low-grade tumour, NETs patients with stable or slowly growing disease. • In functional NETs patients, treatment delay or interruption should not be considered. • In NETs patients with slowly progressive disease, and comorbidities, increased SSAs dose or frequency could be considered as a more "gentle" approach.	• Consider switch SSAs injections to a provider closer to home, or set up a home SSAs injection program. • Home injection program will require dedicated link with home practitioner/nurse and training on use of personal protective equipment (PPE).
Targeted therapy: everolimus or sunitinib	• Data are insufficient to determine the relative risk of COVID-19 infection and associated complications in the setting of treatment with oral targeted agents. • Although could represent a more favourable option than intravenous chemotherapy combinations during a pandemic era, given the common related toxicity, the addition of these drugs is not of immediate priority and other treatment alternatives in NENs such as PRRT should be favoured. • If after a case by case evaluation, sunitinib or everolimus are the treatment of choice, dose reductions in those patients starting new drug, or treatment breaks in those with prolonged disease stability should be considered to prevent risk of related toxicity (60% required dose reduction or treatment interruption) and possibly preventing or delaying COVID-19 infection.	• Everolimus toxicity profile including diarrhoea (~30%), infections (20%–29%), pneumonitis (12%–16%), and life-threatening side-effects such as serious infections, sepsis, thromboembolic events, and neutoropenia (6%) may facilitate COVID-19 infection and could present a diagnostic challenge in the setting of COVID-19. • Sunitinib toxicity profile including diarrhoea (59%), vomiting (34%) and lymphopenia (26%) may facilitate COVID-19 infection and could present a diagnostic challenge in the setting of COVID-19. • If feasible, COVID-19 testing should be considered in all patients before starting treatment however this will depend on the incidence of the COVID-19 pandemic and the local guidelines. • Comprehensive patient education, in-home blood sample collection and regular careful follow-up recommended via telemedicine.
Peptide Receptor Radionuclide Therapy (PRRT)-^{177}Lu-DOTATATE	• No specific guidance is available regarding continuation of PRRT during the COVID-19 outbreak or the risk of exposure to COVID-19. • Treatment with ^{177}Lu-DOTATATE is in general well-tolerated and considered safe during COVID-19 era when used appropriately (high uptake on ^{68}Ga-DOTATATE PET CT and difficulty to control functional disease, high tumour load, those patients already on increased dose of SSAs and lack of alternatives or as alternative to everolimus/sunitinib) and with the right safety precautions. • Delaying PRRT by weeks, omitting a cycle of therapy or extending the interval between treatments may be considered in selected patients, for example, those with slow or no progression before treatment, lower tumour burden, nonfunctional disease.	• Regular careful follow-up recommended via telemedicine. • COVID-19 testing should be considered in all patients before starting treatment. • Transient grade III–IV neutropenia or lymphopenia 2% and 9% of patients treated with ^{177}Lu-DOTATATE respectively. • 3–4% of the patients may develop irreversible cytopenia and bone marrow toxicity such as leukaemia or bone marrow dysplasia. • Hormonal crisis may occur soon after PRRT and requires careful follow-up.
Chemotherapy	• As per the most updated oncology societies guidelines routinely withholding anticancer therapy is not recommended. The potential risk from delaying or interrupting treatment versus the potential benefits of preventing or delaying COVID-19 infection is uncertain.	• In patients on high-risk chemotherapy regimens, prophylactic growth factors, and/or prophylactic antibiotics may be of potential value to reduce the healthcare burden from urgent visits. • If feasible, COVID-19 testing should be considered in all patients before starting treatment however

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Table 3 (*continued*)

Treatment modality	Proposed treatment recommendations during the COVID-19 pandemic	Other considerations during the COVID-19 pandemic
	• Goals of care; urgency of treatment; risk of cancer progression if therapy is delayed, modified, or interrupted, number of cycles of therapy to be completed, must be considered on a case by case basis. • There are no data to support adjuvant therapy in NETs G1/G2/G3. • In advanced rapidly progressive pancreatic-NETs, NETs G2 with Ki-67 close to NET G3, and NET G3, streptozotocin/5-fluoracil (STZ/5-FU) or temozolomide alone or in combination with capecitabine, which would be a more favourable option than intravenous chemotherapy combinations during pandemic, could be considered during pandemic.	this will depend on the incidence of the COVID-19 pandemic and the local guidelines. • Selecting chemotherapy regimens with less need for i.v. fluids, such as carboplatin instead of cisplatin should be considered, as increased i.v. fluids are not recommended in COVID pre- (acute respiratory distress syndrome).
IFNα	• IFNα can be considered for antiproliferative therapy if other treatment options have been exploited or are not feasible, however given the toxicity profile with common flu like symptoms can be misinterpreted for COVID-19 its use must be considered with caution.	• If feasible, COVID-19 testing should be considered in all patients before starting treatment however this will depend on the incidence of the COVID-19 pandemic and the local guidelines.
Functional Control	• Long-acting SSAs, Rescue s.c. octreotide injections and/or telotristat ethyl (in carcinoid syndrome with high 5-HIAA levels and refractory diarrhoea) treatments should continue during COVID-19 era as clinically indicated. • Interferon alpha (IFNα) could be used as an add-on treatment to SSA in patients with refractory syndrome, however toxicity concerns may be an issue during COVID-19 era. • Telotristat ethyl can be recommended an add-on treatment to SSAs in patients with carcinoid syndrome, high 5-HIAA levels and refractory diarrhoea.	• Consider switch SSAs injections to a provider closer to home, or set up a home SSAs injection program. • Home injection program will require dedicated link with home practitioner/nurse and training on use of (PPE). • Proactive functional control to avoid hospitalisations.

PRRT, Peptide Receptor Radionuclide Therapy; Grade 1/Grade 2/Grade 3; IFNα, Interferon alpha; PPE, personal protective equipment.

toxic, potentially myelosuppressive, therapies such as targeted drugs or systemic chemotherapy, although this may be controversial and should be discussed with patients and likely will be dependent on center resources (Additional information is shown on Table 2) [29].

4.2.3. External beam radiotherapy (stereotactic body radiotherapy)

In the absence of liver-directed therapy options, external beam radiation could be considered for high-grade NENs to bridge patients for potential deferred surgery, solitary or oligometastatic disease, and refractory functional grade III NETs. Additional guidance can be found at https://www.astro.org/Daily-Practice/COVID-19-Recommendations-and-Information/Clinical-Guidance [13] and https://www.sirweb.org/practiceresources/covid-19-resources/ [29] (Additional information is shown on Table 2).

4.2.4. Palliative radiotherapy for symptomatic disease

Delay of palliative radiotherapy for symptomatic disease, while ensuring supportive palliative care management, could be considered as would prevent multiple outpatient visits. Adoption of single fraction is recommendable when feasible. Additional guidance from the Society of Interventional Radiology can be found at https://www.astro.org/Daily-Practice/COVID-19-Recommendations-and-Information/Clinical-Guidance [13] and https://www.sirweb.org/practiceresources/covid-19-resources/ [29] (Additional information shown on Table 2).

4.3. Specific considerations for systemic therapy for NENs during the COVID-19 pandemic

4.3.1. SSAs: octreotide or lanreotide

In newly-diagnosed, asymptomatic, low-grade and Ki-67 (<3%) NETs, preferably in small bowel NETs, with low tumour burden, a watch-and-wait approach may be

Table 4
Specific considerations for systemic therapy for GEP- NECs (neuroendocrine carcinoma) during the COVID-19 pandemic.

Treatment modality	Proposed treatment recommendations during the COVID-19 pandemic	Other considerations during the COVID-19 pandemic
Somatostatin analogues: octreotide or lanreotide	• There are no data from randomised clinical trials to support the use of SSAs as antiproliferative treatment in NECs.	
Targeted therapy: everolimus or sunitinib	• There are no data from randomised clinical trials to support the use of everolimus or sunitinib in NECs.	
Peptide Receptor Radionuclide Therapy (PRRT)-^{177}Lu-DOTATATE	• There are no data to support the use of PRRT in NECs outside clinical trial.	
Chemotherapy	• As per the most updated oncology societies guidelines routinely withholding anticancer therapy is not recommended. The potential risk from delaying or interrupting treatment versus the potential benefits of preventing or delaying COVID-19 infection is uncertain. • Goals of care; urgency of treatment; risk of cancer progression if therapy is delayed, modified, or interrupted (particularly in those patients with disease stability or NECs patients with stable disease after 4–6 cycles of platinum-etoposide therapy); number of cycles of therapy to be completed, and tolerance, must be considered on a case by case basis. • FOLFOX may be considered instead of platinum/etoposide, particularly in elderly or more fragile patients or prone to bone marrow suppression. • Although in aggressive NECs, platinum-based adjuvant chemotherapy might be considered, during the pandemic, a case by case evaluation is required and pros and cons need to be thoroughly discussed with patients.	• In patients on high-risk chemotherapy regimens, prophylactic growth factors, and/or prophylactic antibiotics may be of potential value to reduce the healthcare burden from urgent visits. • Consider carboplatin instead of cisplatin, less need for home hydration. Cisplatin associated with higher volume of i.v. fluids - not recommended in COVID pre–acute respiratory distress syndrome (ARDS). • Consider dose reduction in elderly NEC patients with comorbidities. • If feasible, COVID-19 testing should be considered in all patients before starting treatment however this will depend on the incidence of the COVID-19 pandemic and the local guidelines..
Functional Control	• Long-acting SSAs, Rescue s.c. octreotide injections and/or telotristat ethyl treatments should continue during COVID-19 era as clinically indicated. • Interferon alpha (IFNα) could be used as an add-on treatment to SSA in patients with refractory syndrome; however toxicity concerns may be an issue during COVID-19 era. • Telotristat ethyl can be recommended an add-on treatment to SSAs in patients with carcinoid syndrome, high 5-HIAA levels and refractory diarrhoea.	• Consider switch SSAs injections to a provider closer to home, or set up a home SSAs injection program. • Home injection program will require dedicated link with home practitioner/nurse and training on use of (PPE). • Proactive functional control to avoid hospitalisations.

NECs, neuroendocrine carcinoma; s.c., subcutaneous; PPE, personal protective equipment.

reasonable during the COVID era; however treatment with SSAs is considered safe during COVID-19 given its favourable toxicity profile. This is dependent on a safe and reliable way for patients to get the drug and must be balanced against the risk of a healthcare visit, particularly in areas with a high baseline COVID prevalence or high community spread. For those asymptomatic patients with low-grade, slow-growing tumours that are already on SSAs, delaying, interrupting SSA treatment, and/or exploring options for self-injected SSAs could be considered if health resources dictate [22,39,40]. Home delivery of SSAs should be encouraged wherever possible, with extra care taken by healthcare providers. SSAs treatment should always continue in patients with functional NETs. Increased SSA dose or frequency, especially for those NETs patients with comorbidities and/or slowly progressive disease on standard SSA dose [22], could be considered to avoid the use of other systemic agents that are more toxic such as everolimus, sunitinib or PRRT. In SSR–positive thoracic carcinoids, SSAs are in general used as an initial treatment particularly in newly diagnosed patients with comorbidities

Table 5
Specific considerations for systemic therapy for Thoracic (Carcinoid) NENs during the COVID-19 pandemic.

Treatment modality	Proposed treatment recommendations during the COVID-19 pandemic	Other considerations during the COVID-19 pandemic
Somatostatin analogues (SSAs): octreotide or lanreotide	• Patients starting a new therapy could discuss SSAs as alternative to everolimus, particularly in those patients with comorbidities and somatostatin receptors (SSR) positive tumours. SSAs should be used in functional thoracic carcinoids.	• Consider switch SSAs injections to a provider closer to home, or set up a home SSAs injection program. • Home injection program will require dedicated link with home practitioner/nurse and training on use of personal protective equipment (PPE).
Targeted therapy: everolimus	• Data are insufficient to determine the relative risk of COVID-19 infection and associated complications in the setting of treatment with oral targeted agents. • Everolimus may be started at a lower dose to prevent risk of related toxicity (60% required dose reduction or treatment interruption), and possibly preventing or delaying COVID-19 infection. • Consider treatment breaks or delays in those with prolonged disease stability.	• Everolimus toxicity profile including diarrhoea (~30%), infections (20%–29%), pneumonitis (12%–16%), and life-threatening side effects such as serious infections, sepsis, thromboembolic events, and neutropenia (6%), may facilitate COVID-19 infection and could present a diagnostic challenge in the setting of COVID-19. • If feasible, COVID-19 testing should be considered in all patients before starting treatment however this will depend on the incidence of the COVID-19 pandemic and the local guidelines. • Comprehensive patient education, in-home blood sample collection and regular careful follow-up recommended via telemedicine.
Peptide Receptor Radionuclide Therapy (PRRT)-^{177}Lu-DOTATATE	• Although there are no data from randomised clinical trials to support the use of PRRT-^{177}Lu-DOTATATE in thoracic (carcinoid) NENs, in the context of COVID-19, PRRT-^{177}Lu-DOTATATE could be considered as alternative to everolimus, in case the general requirements of this treatment are fulfilled such as SSR expression.	
Chemotherapy	• In the context of COVID-19, recommendation of chemotherapy in pulmonary carcinoids should be avoid. There are no data from randomised clinical trials to support the use of chemotherapy in thoracic (carcinoid) NENs.	
Functional Control	• Long-acting SSAs, Rescue s.c. octreotide injections and/or telotristat ethyl treatments should continue during COVID-19 era as clinically indicated. • Interferon alpha (IFNα) could be used as an add-on treatment to SSA in patients with refractory syndrome; however toxicity concerns may be an issue during COVID-19 era. • Telotristat ethyl can be recommended an add-on treatment to SSAs in patients with carcinoid syndrome, high 5-HIAA levels and refractory diarrhoea.	• Consider switch SSAs injections to a provider closer to home, or set up a home SSAs injection program. • Home injection program will require dedicated link with home practitioner/nurse and training on use of personal protective equipment (PPE). • Proactive functional control to avoid hospitalisations.

s.c., subcutaneous.

[22,41] and should be considered during COVID (Additional information is shown on Tables 3–5).

4.3.2. Targeted therapy: sunitinib or everolimus

Everolimus is approved in pancreatic, gastrointestinal and thoracic NETs with progressive disease. Sunitinib is approved in progressive pancreatic NETs only. No specific guidance is available regarding continuation of oral targeted agents during the COVID-19 outbreak. Given the common related toxicity, including lymphopenia (26%) and diarrhoea (59%) induced by sunitinib, and induced immune-suppression (neutropenia and lymphopenia 6%), diarrhoea (~30%), risk of diabetes (13%) and risk for pulmonary side effects (pneumonitis 12%–16%) by everolimus [22,31–33] the addition of these drugs is not of immediate priority and should be avoided and other treatment alternatives such as PRRT may be favoured. However, these treatments could represent a more favourable option than intravenous

chemotherapy combinations. If after a case by case evaluation, sunitinib or everolimus are the treatment of choice, dose reductions in those patients starting treatment, or treatment breaks in those with prolonged disease stability should be considered. In thoracic carcinoids where there are no other approved treatments than everolimus, SSA use should be considered if supported by SSR expression (Additional information shown on Tables 3–5).

4.3.3. Peptide receptor radionuclide therapy — ^{177}Lu-DOTATATE

No specific guidance is available regarding continuation of PRRT during the COVID-19 outbreak or the risk of exposure to COVID-19 [22,33]. However a recent report has not shown increased susceptibility to risk of viral infections in cancer patients treated with PRRT during the COVID-19 pandemic, advocating thus for PRRT treatment continuation when used appropriately (high uptake on ^{68}Ga-DOTATATE PET CT, difficulty to control functional disease, high tumour load, those patients already on increased dose of SSAs and lack of alternatives or as alternative to everolimus/sunitinib) and with the right safety precautions [42]. Delaying PRRT by weeks, omitting a cycle of therapy or extending the interval between treatments should be individually weighed against the possible risk of a COVID-19 infection during radionuclide therapy, but may be considered in selected patients, for example, those presenting grade III–IV neutropenia or lymphopenia (2% and 9% of patients treated with ^{177}Lu-DOTATATE respectively); or those with slow or no progression before treatment, low tumour burden and non-functional disease where the treatment is less urgent (Additional information is shown on Tables 3–5).

4.3.4. Chemotherapy

At the present time, data are insufficient to determine the relative risk of COVID-19 infection and associated complications in the setting of chemotherapy, and as per the most updated oncology societies guidelines [7–11] routinely withholding anticancer therapy is not recommended. Therefore, treatment prioritisation, risk/benefit assessment, number of cycles of therapy, chemotherapy breaks (particularly in those patients with disease stability or NECs patients with stable disease after 4–6 cycles of platinum-etoposide therapy), possible dose reductions, and goals of care should be considered on a case by case basis. There are no data to support adjuvant therapy in NETs, although in aggressive NECs in which platinum-based chemotherapy might be considered [22], a case-by-case evaluation is required during the pandemic, and pros and cons need to be thoroughly discussed with patients. In advanced rapidly progressive pancreatic NETs, NETs grade II with Ki-67 close to grade III NETs, and grade III NETs, temozolomide alone or in combination with capecitabine represents a more favourable option than intravenous chemotherapy combinations during pandemic [22]. To minimise risk of COVID-19, alternative schedules, with reduced STZ treatment duration [43,44], or dose reductions, could be considered. If feasible, COVID-19 testing should be considered in all patients before starting treatment; however this will depend on the incidence of the COVID-19 pandemic and the local guidelines. In patients on high-risk chemotherapy regimens, prophylactic growth factors, and/or prophylactic antibiotics may be of potential value to avoid unplanned hospitalisations and emergency department visits. Selecting chemotherapy regimens with less need for intravenous (i.v.) fluids, such as carboplatin instead of cisplatin should be considered, as increased i.v. fluids are not recommended in COVID-19 pre-ARDS [45]. FOLFOX may be considered instead of platinum/etoposide, particularly in elderly or more fragile patients or prone to bone marrow suppression [46,47] (Additional information is shown on Tables 3–5).

4.3.5. Interferon α

Interferon can be considered for antiproliferative therapy if other treatment options have been exploited or are not feasible; however given the toxicity profile with common flu–like symptoms that can be misinterpreted for COVID-19 its use must be considered with caution [22,48] (Additional information is shown on Tables 3–5). In severe carcinoid syndrome, however, low-dose interferon may be used to improve symptoms of the carcinoid syndrome in combination with SSAs and to avoid hospitalisations (e.g. renal insufficiency due to profuse diarrhoea).

4.3.6. Telotristat ethyl

For functional control, telotristat ethyl can be recommended an add-on treatment to SSAs in patients with carcinoid syndrome, high 5-HIAA levels and refractory diarrhoea [22,49–51] (Additional information is shown on Tables 3–5).

5. Preparing for the future, research priorities, mitigation strategies and window of opportunities

The management of cancer patients, including NEN patients, during the COVID-19 era is influenced by country-specific strategic choices for COVID-19 control and to what extent the oncological communities needs to re-organise their healthcare systems depending on the scale and duration of the COVID-19 outbreak. Although low-grade NETs may be some of the optimal cancers to delay treatment given their prolonged survival, we must however take into account the patient perspective. Many NENs patients have experienced a well described diagnostic delay [22], and further delays may have a psychological impact.

The resolution of the current crisis may become a lengthy process and healthcare providers, including those focused on NENs care, need models and data with which to enable systematic, evidence-based assessments of the risk/benefit ratio of anticancer therapies and treatment interventions during the COVID-19 pandemic. To better inform strategies to mitigate the impact of COVID-19 in NENs patients, it is critical that centres collect as much 'real-world' information including i) the symptomatic and asymptomatic incidence of COVID-19 by large-scale serological testing on both surveillance and on active treatment patients to quickly assess the effects of adjustment and de-escalation of treatment regimens on the outcomes of cancer patients; ii) to determine the treatment's additional risk for COVID-19–related morbidity and mortality in NENs patients on active treatment and iii) to develop an epidemiological model with which to estimate the cumulative incidence of COVID-19 for a NENs patient within a specific timeframe. Currently, data are insufficient to determine the relative risk of COVID-19 infection and associated complications in the setting of systemic oncologic treatments commonly used in NENs management [52]. A world-wide data collection for SARS-CoV-2–positive NEN patients is undergoing (INTENSIVE [**I**nter**N**a**T**ional r**E**gistry o**N** **S**ars-cov-2–pos**I**ti**V**e n**E**uroendocrine neoplasm patients]; NCT04444401)] and will provide relevant clinical information to better characterise the clinical characteristics, treatment prioritisation and outcome for SARS-CoV-2–positive NENs patients. The impact of the pandemic on clinical and basic cancer research is likely to be severe and could be magnified for those rare tumour entities such as NENs with limited treatment options. During the pandemic, there is a need to carefully reconsider the clinical cancer research processes and procedures that contribute to data integrity and patient safety versus tasks that might ultimately detract from cancer research goals. The impact of the adoption of virtual cancer care on the management of NENs and patient experience should be evaluated in future research.

6. Conclusions

By sharing our joint experiences, we have shown how multidisciplinary NENs specialists from high-volume NENs academic centres worldwide, at different stages of the COVID-19 pandemic, have suggested potential modifications to preserve high standards of care for patients with NENs while battling shortages and the quickly evolving and multidimensional challenges posed by the pandemic. We have provided an overview of these experiences and the many commonalities in general measures and goals for our NENs patients. Unfortunately, solid scientific data are often lacking to guide adjustments to standard-of-care treatment regimens in rare diseases such as NENs, and thus we hope may offer a practical guidance to other institutions facing the same challenges during this unprecedented era. These recommendations need to be supported by real-world data in the future. Dedicated local registries actively collecting data on NENs patients infected by COVID-19 may provide better information regarding the therapeutic approach and related outcomes in the future. Multiple countries are now experiencing the diverse trajectory of the pandemic and future waves of COVID-19 are possible; therefore working together and collecting 'real-world' information of the impact of COVID-19 in NENs patients are critical steps to better inform our future healthcare strategies and treatment interventions.

6.1. Search strategy and selection criteria

We search Pubmed using the search terms "COVID-19, coronavirus, novel coronavirus, SARS-CoV-2", "cancer", tumour malignancy", and neuroendocrine neoplasms, neuroendocrine tumour, neuroendocrine cancer" to identify articles for this Rapid Review published between 1st December 2019 and 1st June 2020. We reviewed only articles published in English. We selected up-to-date and evolving management guidelines related to the neuroendocrine neoplasms, original research articles, letters and reviews on the basis of their clinical relevance to each section of this rapid review.

Contributors

VRF, AT and SS drafted the outline and planned this rapid review. VRF, AT and SS contributed to the initial drafting of the manuscript and drafted the tables. All authors who contributed opinions based on their individual expertise and the policies of their centres critically reviewed the manuscript. Each author contributed to content of the manuscript and helped in preparation of manuscript. All authors contributed equally. All authors agreed to submit the final version of the manuscripts. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

Ms. Kolarova reports grants from Novartis Pharmaceuticals Corporation, grants from Advanced Accelerator Applications SA, grants from IPSEN PHARMA, grants from ITM Isotopen Technologien.

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Dr. Valle reports personal fees from Agios, personal fees from AstraZeneca, personal fees from Debiopharm, personal fees from Delcath Systems, personal fees from Genoscience Pharma, personal fees from Imaging Equipment Limited, personal fees from Incyte, personal fees from Ipsen, personal fees from Keocyt, personal fees from Merck, personal fees from Mundipharma EDO, personal fees from Novartis, grants, personal fees and non-financial support from NuCana, personal fees from PCI Biotech, personal fees from Pieris Pharmaceuticals, and personal fees and non-financial support from Pfizer, personal.

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References

[1] www.worldometers.info/coronavirus.

[2] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507–13. https://doi.org/10.1016/S0140-6736(20)30211-7.

[3] https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html.

[4] Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China Lancet. Oncol 2020;21(3):335–7. https://doi.org/10.1016/S1470-2045(20)30096-6.

[5] Wang B, Li R, Lu Z, Huang Y. Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. Aging 2020;12(7):6049–57. https://doi.org/10.18632/aging.103000.

[6] Dai M, Liu D, Liu M, Zhou F, Li G, Chen Z, et al. Patients with cancer appear more vulnerable to SARS-CoV-2: a multicenter study during the COVID-19 outbreak. Canc Discov 2020;10(6):783–91. https://doi.org/10.1158/2159-8290.CD-20-0422.

[7] The Medical Journal of Australia. Managing haematology and oncology patients during the COVID-19 pandemic: interim consensus guidance. Available at: https://www.mja.com.au/journal/2020/212/10/managing-haematologyand-oncology-patients-during-covid-19-pandemic-interim. Accessed March 26, 2020.

[8] Ontario Health Cancer Care Ontario. Pandemic planning clinical guideline for patients with cancer. [cited 2020 Apr 9]; available from: https://www.accc-cancer.org/docs/documents/cancerprogram- fundamentals/oh-cco-pandemic-planning-clinicalguideline_ final_2020-03-10.pdf?sfvrsn=d2f04347_2].

[9] ESMO COVID-19 and cancer. [cited 2020 Apr 9]; available from: https://www.esmo.org/covid-19-and-cancer].

[10] ASCO coronavirus resources. [cited 2020 Apr 9]; available from: https://www.asco.org/asco-coronavirus-information].

[11] NCCN. Coronavirus disease 2019 (COVID-19) resources for the cancer care community. [cited 2020 Apr 9]; available from: https://www.nccn.org/covid-19/].

[12] American College of Surgeons. ACS: COVID-19 and surgery. [cited 2020 Apr 10]; available from: https://www.facs.org/covid19/clinical-guidance. https://www.essoweb.org/news/esso-statementcovid-19/.

[13] American Society for Radiation Oncology (ASTRO). COVID-19 recommendations to radiation oncology practices. [cited 2020 Apr 10]; available from: https://www.astro.org/Daily-Practice/%20COVID-19-Recommendations-and-Information.

[14] Lee LYW, Cazier JB, Starkey T, Turnbull CD. UK Coronavirus Cancer Monitoring Project Team, Kerr R, Middleton G. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. Lancet 2020;S0140-6736(20):31173–9. https://doi.org/10.1016/S0140-6736(20)31173-9.

[15] Kuderer NM, Choueiri TK, Shah DP, Shyr Y, Rubinstein SM, Rivera DR, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. Lancet 2020;S0140-6736(20):31187–9. https://doi.org/10.1016/S0140-6736(20)31187.

[16] Hallet J, Law CH, Cukier M, Saskin R, Liu N, Singh S. Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. Cancer 2015;121(4):589–97. https://doi.org/10.1002/cncr.29099.

[17] Bergsland EK, Halperin DM, Dillon JS, Dasari NA, Kunz PL, Soares HP, et al. North American neuroendocrine tumor society guide for neuroendocrine tumor patient health care providers during COVID-19. Pancreas 2020. https://doi.org/10.1097/MPA.0000000000001561.

[18] Ramirez RA, Bren-Mattison Y, Thiagarajan R, Boudreaux JP, Marsala AJ, Ryan P, et al. A neuroendocrine tumor specialty center in new Orleans' (NOLANETS) response to patient care during the COVID-19 pandemic. Oncologist 2020. https://doi.org/10.1634/theoncologist.2020-0279.

[19] Singh S, Law C. Multidisciplinary reference centers: the care of neuroendocrine tumors. J Oncol Pract 2010;6(6):e11–6. https://doi.org/10.1200/JOP.2010.000098.

[20] Liu R, Sundaresan T, Reed ME, Trosman JR, Weldon CB, Kolevska T. Telehealth in oncology during the COVID-19

outbreak: bringing the house call back virtually. JCO Oncol Pract 2020:OP2000199. https://doi.org/10.1200/OP.20.00199.
[21] Meti N, Rossos PG, Cheung MC, Singh S. Virtual cancer care during and beyond the COVID-19 pandemic: we need to get it right. JCO Oncol Pract 2020:OP2000281. https://doi.org/10.1200/OP.20.00281.
[22] Pavel M, Öberg K, Falconi M, Krenning E, Sundin A, Perren A, et al. Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2020;S0923-7534(20):36394–8. https://doi.org/10.1016/j.annonc.2020.03.304.
[23] Singh S, Moody L, Chan DL, Metz DC, Strosberg J, Asmis T, et al. Commonwealth neuroendocrine tumour collaboration (CommNETS) follow-up working group. Follow-up recommendations for completely resected gastroenteropancreatic neuroendocrine tumors. JAMA Oncol 2018;4(11):1597–604. https://doi.org/10.1001/jamaoncol.2018.242.
[24] Modlin IM, Kidd M, Latich I, Zikusoka MN, Shapiro MD. Current status of gastrointestinal carcinoids. Gastroenterology 2005;128:1717–51.
[25] Fink G, Krelbaum T, Yellin A, Bendayan D, Saute M, Glazer M, et al. Pulmonary carcinoid: presentation, diagnosis, and outcome in 142 cases in Israel and review of 640 cases from the literature. Chest 2001;119:1647–51.
[26] Modlin IM, Oberg K, Chung DC, Jensen RT, de Herder WW, Thakker RV, et al. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol 2008;9:61–72.
[27] Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer 2003;97:934–59.
[28] Shen C, Dasari A, Gu D, Chu Y, Zhou S, Xu Y, et al. Costs of cancer care for elderly patients with neuroendocrine tumors. Pharmacoeconomics 2018;36(8):1005–13. https://doi.org/10.1007/s40273-018-0656-z.
[29] https://www.sirweb.org/practiceresources/covid-19-resources.
[30] Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. Phase 3 Trial of (177)Lu-Dotatate for midgut neuroendocrine tumors. N Engl J Med 2017;376:125–35.
[31] Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 2011;364:514–23.
[32] Pavel ME, Baudin E, Öberg KE, Hainsworth JD, Voi M, Rouyrre N, et al. Efficacy of everolimus plus octreotide LAR in patients with advanced neuroendocrine tumor and carcinoid syndrome: final overall survival from the randomized, placebo-controlled phase 3 RADIANT-2 study. Ann Oncol 2017;28:1569–75.
[33] Raymond E, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C, et al. Sunitinib malate for the treatment of pancreaticneuroendocrine tumors. N Engl J Med 2011;364:501–13.
[34] Ferner RE, Aronson JK. Chloroquine and hydroxychloroquine in covid-19. BMJ 2020;369:m143.
[35] Khan IH, Savarimuthu S, Leung MST, Harky A. The need to manage the risk of thromboembolism in COVID-19 patients. J Vasc Surg 2020;72(3):799–804. https://doi.org/10.1016/j.jvs.2020.05.015.
[36] https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-hospitalized-patients.html.
[37] https://www.nice.org.uk/guidance/ng161.
[38] https://www.facs.org//media/files/covid19/acs_triage_and_management_elective_cancer_surgery_during_acute_and_recovery_phases.ashx.
[39] Rinke A, Müller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol 2009;27:4656–63.
[40] Caplin ME, Pavel M, Ćwikła JB, Phan AT, Raderer M, Sedláčková E, et al. Anti-tumour effects of lanreotide for pancreatic and intestinal neuroendocrine tumours: the CLARINET open-label extension study. Endocr Relat Canc 2016;23:191–9.
[41] Baudin E, Hayes AR, Scoazec JY, Filosso PL, Lim E, Kaltsas G, et al. ENETS 2016 munich advisory board participants; ENETS 2016 munich advisory board participants. Unmet Medical Needs in Pulmonary Neuroendocrine (Carcinoid) Neoplasms Neuroendocrinology 2019;108(1):7–17. https://doi.org/10.1159/000493980.
[42] Brabander T, Hofland H. Radionuclide therapy in the time of COVID-19. Eur J Nucl Med Mol Imag 2020:1–2. https://doi.org/10.1007/s00259-020-04921-9.
[43] Moertel CG, Hanley JA, Johnson LA. Streptozocin alone compared with streptozocin plus fluorouracil in the treatment of advanced islet-cell carcinoma. N Engl J Med 1980;303:1189–94.
[44] Eriksson B, Öberg K. An update of the medical treatment of malignant endocrine pancreatic tumors. Acta Oncol 1993;32:203–8.
[45] Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol 2020;17(5):259–60. https://doi.org/10.1038/s41569-020-0360-5.
[46] Hadoux J, Malka D, Planchard D, Scoazec JY, Caramella C, Guigay J, et al. Post-first-line FOLFOX chemotherapy for grade 3 neuroendocrine carcinoma. Endocr Relat Canc 2015;22(3):289–98. https://doi.org/10.1530/ERC-15-0075.
[47] Spada F, Antonuzzo L, Marconcini R, Radice D, Antonuzzo A, Ricci S, et al. Neuroendocrinology 2016;103(6):806–14. https://doi.org/10.1159/000444087.
[48] Yao JC, Guthrie KA, Moran C, Strosberg JR, Kulke MH, Chan JA, et al. Phase III prospective randomized comparison trial of depot octreotide plus interferon alfa-2b versus depot octreotide plus bevacizumab in patients with advanced carcinoid tumors: SWOG S0518. J Clin Oncol 2017;35:1695–703.
[49] Modlin IM, Pavel M, Kidd M, Gustafsson BI. Review article: somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine (carcinoid) tumours. Aliment Pharmacol Ther 2010;31:169–88.
[50] Cella D, Beaumont JL, Hudgens S, Marteau F, Feuilly M, Houchard A, et al. Relationship between symptoms and health related quality of life benefits in patients with carcinoid syndrome: post-hoc analyses from TELESTAR. Clin Therapeut 2018;40(12):2006–2020.e2. https://doi.org/10.1016/j.clinthera.2018.10.008.
[51] Oberg K. Interferon in the management of neuroendocrine GEP-tumors: a review. Digestion 2000;62(Suppl 1):92–7.
[52] Di Fiore F, Bouché O, Lepage C, Sefrioui D, Gangloff A, Schwarz L, et al. COVID-19 epidemic: proposed alternatives in the management of digestive cancers: a French intergroup clinical point of view (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, SFR). Dig Liver Dis 2020;52(6):597–603.