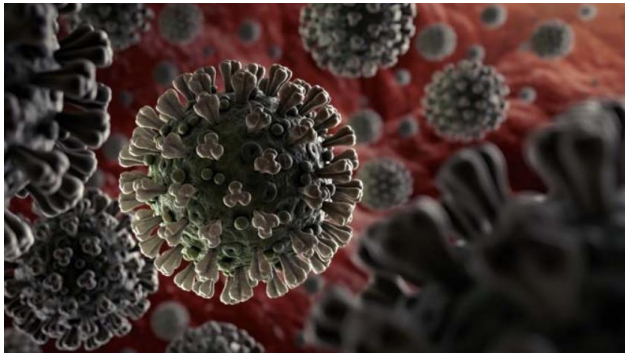
NENs Care During and Beyond the Covid-19 Pandemic



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Objectives

- To discuss issues facing NETs patients during the COVID19 pandemic
- To examine possible alterations in NETs care during the COVID 19 pandemic
- To explore further opportunities to understand the impact of COVID19 on NETs

So many unknowns..

Cancer Care During the COVID-19 Pandemic

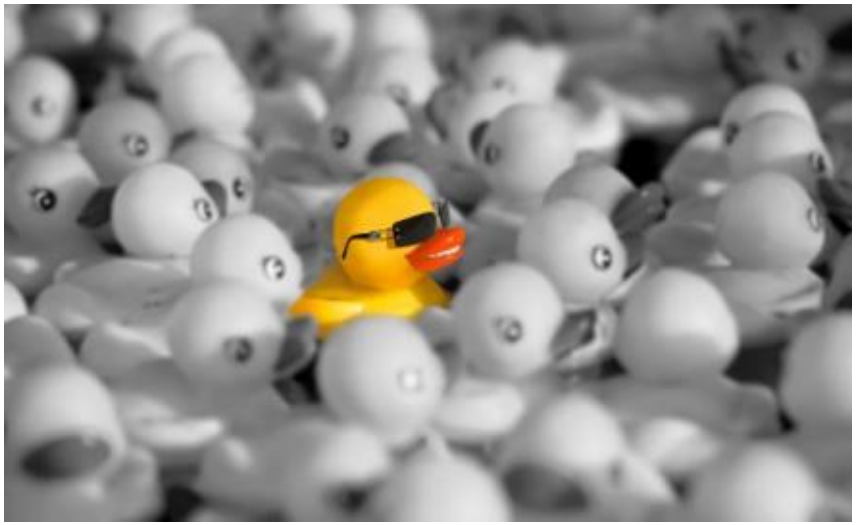
- Has resulted in massive reorganization of cancer care in short time

- Do Cancer Patients have an increased risk of contracting SARS-CoV-2 infection?
  - limited experience reported to-date: similar to the global population (1)
- Increased risk of morbidity related COVID-19 (2,3)
  - Risk factors: age, ECOG-PS, smoking status, active and progressing status of cancer, hematological cancer, lung cancer and comorbidities.
  - Chemotherapy or anticancer treatments may not necessarily increase the risk of mortality (4).
- WE do not know what the optimal care for NETs patients is during the pandemic
  - Have to revert to first principles…

Still many questions to be answered….

1. J. van de Haar, et al. Nat Med 2020
2. Dai MY , et al. Cancer Discov 2020
3. Liang W, et al. Lancet Oncol 2020
4. Lee LY, et al. Lancet 2020

Each place is different…



- What is the community rate of infection?
- What is the status of the health care system?
- What is the patient individual circumstances?
- What are institutional circumstance?
- What is the patient preference?

General Aspects for NENs care during the COVID-19 pandemic

- Management should be **individualized** and requires **multidisciplinary** approach

- Each discipline has been uniquely affected

- Associated challenges with caring uncommon cancers:
  - requirement of specialized expertise
  - limited access to some treatments and diagnostics
  - lack of data to guide clinical decision making

Can we use COVID to improve our patients care?

A crisis is a terrible things to waste….

Paul Romer, Nobel Prize Winning Economist
Stanford University

Virtual Care

- May be both a patient friendly and resource friendly way to deliver care during COVID19 and beyond
  - Financial toxicity, time toxicity
- Telephone, Virtual (e.g. Zoom, Facetime, WhatsApp)
- Multi-disciplinary care
- Access to experts, more opinions

Virtual Care

- Data driven
  - Effectiveness, Provider experience, Patient experience
- Person centered care (including larger care team)
- Equitable delivery
- Appropriateness
- Privacy and Confidentiality

Testing

- Universal routine testing for COVID-19 in asymptomatic?:
  - General population recommendation vs vulnerable cancer population?

- Universal routine testing to who?:
  - Patients requiring admission to hospital for cancer treatment
  - Ambulatory patients at risk, or those whom knowledge of COVID-19 infection status would impact on the management
  - The Ontario provincial Ministry of Health guidelines:
    - Testing within 24-48 hours prior to treatment
    - Where resources are limited, testing patients with symptoms and exposure to COVID-19 will be prioritized

Management of COVID-19 positive NENs

- incidence, morbidity and mortality of COVID-19 among NENs is unknown
  - risk of interrupting cancer treatment versus the still poorly defined risk of adverse COVID-19 outcomes
- Unclear how long a delay after the infection has resolved
- Particularities of NENs:
  - rapidly progressing cancer - life threatening: rare in NENs
  - SSAs for symptomatic secretory NENs: should continue regardless test results

Reevaluating NENs treatment paradigms
During the COVID-19 pandemic

- Adapted to the pandemic scenario and to health facilities and resources.
  - Cancer Care Ontario categories:
    - (A) patients who are deemed critical and require immediate services/treatment
    - (B) patients who require services/treatment, but whose situation is not critical;
    - (C) patients who are generally healthy, whose condition is deemed as non-life threatening where treatment can be delayed without anticipated change in outcome
- Most of the treatment indications for NENs would fit under a lower priority (C)
  - Slow-growing nature and survival not likely compromised if treatment intervention is delay
  - Particularly: well-differentiated grade 1, slow growing NETs with Ki-67 (<2%) and low tumour burden or NETs grade 2 with low Ki-67 (<5%) with prolonged disease stability on treatment.

Reevaluating NENs treatment paradigms During the COVID-19 pandemic :prioritized indications

- Highly functional NENs, (e.g., uncontrolled carcinoid syndrome and/or carcinoid heart disease,…etc).
- Radiologically/clinically progressive grade 2 NETs.
- High-grade (grade 3) NETs or NECs patients.
- Prioritized PRRT: in patients with refractory functional disease, higher tumor bulk, or those already on increased dose of SSA with lack of alternatives.

- High priority surgical indications:
  - Cases where a potential delay would likely close the window of opportunity for surgery
  - Highly symptomatic small bowel NETs patients and/or with acute abdominal complications (e.g., obstruction, bleeding/ hemorrhage);
  - Functional pancreatic NETs patients where symptoms cannot be controlled medically

Don’t forget…support the patients

Patients are the partners in care…

- Engage patients and caregivers with the most recent COVID-19 guidelines
- Educate on any deviations from the standard of care
- The risks of travel for the patient and SARS-CoV-2 exposure need to be considered.
  - Facilitate a provider closer to home, participating in a home SSAs injection program, if available
- Proactively manage functional symptoms control to avoid hospitalizations

- Wellness interventions and supportive care needs (nutrition monitoring, health education, medical adherence, social work, and palliative care consultations) should be integrated into the virtual care.

- Psychological support should be ramped up to adequately meet patient needs
  - Patients are scared, WE are ALL Scared.

Diagnosis and Surveillance

- Investigations at diagnosis should be limited only to those that are **most necessary**
- Optimal interval timing follow-up for fully resected NENs or metastatic NENs is not well established:
  - Potentially suboptimal use of resources during pandemic
  - ^{68}Ga-SSR PET-CT could be postponed in resected early-stage NENs with no suspicion for residual disease.
  - ^{18}F-FDG-PET is not mandatory in most NENs, and should be adopted on an individual basis.
  - Telemedicine or virtual care whenever feasible should be implemented
- Delay scheduled interventions particularly in countries with high incidence of COVID-19:
  - Individualized risk/benefit assessment: ki67 index, grade, rate of growth, symptoms…
  - Asymptomatic slow growing NETs grade 1 or NETs grade 2 with low Ki-67 (<5%) and prolonged disease stability on treatment
  - Not recommended in NETs grade 3 or NECs
- Remember NETs already have a diagnosis delay….and patients need answers COVID or not!!!

Surgery

- Based on The American College of Surgeons levels of impact during COVID-19, most surgeries for NENs would fit under the category of semi-urgent:
  - Survivorship of NENs is not likely compromised if surgery is not performed within the next 3 months, and could be safely postponed (eg, removing an asymptomatic primary tumor with low risk of metastases, debulking of liver metastases of low-grade NETs or palliative debulking surgeries)
- If surgery is being delayed, alternative approach should be recommended:
  - SSAs for well-differentiated, slow growing tumours

- Appropriateness of surgical delays must be discussed and agreed with patients and caregivers.

Liver directed therapy

- Non-urgent or elective interventional radiology practices could be postponed on a case-by-case basis evaluation based on several factors, including:
  - hormone-mediated symptoms,
  - rate of tumor progression,
  - prior treatments,
  - comorbidities,
  - risk of COVID-19 infection and
  - institutional resources

- During COVID-19, liver directed therapies could be particularly considered in:
  - Highly functioning tumors for symptoms control and for tumor growth control in well differentiated NETs instead of a more toxic systemic approach

- Appropriateness of Liver directed therapy must be discussed and agreed with patients and caregivers

- Pretreatment screening for COVID-19 and PPE should be provided.

SSAs

- Treatment with SSAs is considered safe during COVID-19
- Newly-diagnosed, asymptomatic, low-grade and Ki-67 (<2%) NETs, preferably in small bowel-NETs, with low tumour burden:
  - Watch-and-wait approach? particularly in areas with a high COVID prevalence
- For those asymptomatic, slow growing NETs, already on SSAs:
  - Delaying, interrupting SSA treatment, and/or exploring options for self-injected SSAs, could be considered
- Home delivery of SSAs should be encouraged wherever possible
- SSAs treatment should always continue in patients with functional NETs
- Increased SSAs dose or frequency, especially for those NETs patients with comorbidities and/or slowly progressive disease could be considered to avoid the use of other more toxic systemic agents
- In somatostatin receptors (SSR) positive thoracic carcinoids, should be considered during pandemic as first line treatment.

Targeted therapy- Sunitinib or Everolimus

- No specific guidance is available regarding continuation of oral targeted agents like everolimus and sunitinib in NENs during the COVID-19 outbreak.

- Maybe more favorable option than intravenous chemotherapy, however given the common related toxicity, the addition of these drugs is not of immediate priority and should be avoided.
  - Sunitinib: lymphopenia (26%), diarrhea (59%)
  - Everolimus: immune-suppression (neutropenia and lymphopenia 6%), diarrhea (~30%), risk of diabetes (13%) and risk for pulmonary side effects (pneumonitis (12%–16%),
  - Overlapping diagnosis challenges with the COVID-19 symptoms

- If after a case by case evaluation, sunitinib or everolimus are the treatment of choice, consider:
  - Dose reductions in those patients starting a new drug,
  - Treatment breaks in those with prolonged disease stability
  - Supportive measures such as therapy education, remote follow-up and self-assessment is relevant during the pandemic.

PRRT

- No specific guidance is available regarding continuation of PRRT during the COVID-19 outbreak or the risk of exposure to COVID-19
  - Recent report has not shown increased susceptibility to or risk of viral infections when used appropriately

- Delaying PRRT by weeks, omitting a cycle or extending treatment interval may be considered in selected patients:
  - Presenting grade 3-4 neutropenia or lymphopenia (2% and 9% of patients treated with ^{177}Lu-DOTATATE respectively)
  - or those with slow or no progression before treatment, low tumor burden and non-functional disease where the treatment is less urgent.

Chemotherapy

- Data are insufficient to determine the relative risk of COVID-19 infection and associated complications with chemotherapy,
  - But routinely withholding anticancer therapy is not recommended.
  - Treatment prioritization and risk/benefit assessment is the key

- Alternative approaches should be considered on a case by case basis:
  - Number of cycles of therapy, dose reductions
  - Chemotherapy breaks
  - Goals of care
- Chemotherapy indications in advanced, metastatic NENs during pandemic:
  - Rapidly progressive pancreatic-NETs,
  - NETs high grade 2 or grade 3
- Consider oral agents when possible

NENs Care Beyond the Covid-19 Pandemic

- The resolution of the current crisis may become a **lengthy** process

- Development of strategies to mitigate the impact of COVID-19 in NENs:
  - Collection of 'real-world' information including:
    - Symptomatic and asymptomatic incidence of COVID-19 in NENs on both surveillance and on active treatment: large-scale serological testing
    - Characterize the clinical characteristics, treatment prioritization and outcome for SARS-CoV-2 positive NENs patients
      - INTENSIVE registry (**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

- The impact of the pandemic on clinical and basic cancer research is likely to be severe
  - We need to advocate for clinical trials to continue for our NET patients

Lets bring our “A” game…

Thank you…