Sponsor:	Istituto Europeo di Oncologia
Protocol Title:	**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 **INTENSIVE** *(Registro internazionale di pazienti affetti da neoplasia neuroendocrina positivi per SARS-CoV-2)*
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1. Background, rationale and objectives

In late December 2019, a number of cases of pneumonia of unknown origin were epidemiologically linked to a seafood and wet animal wholesale market in Wuhan, Hubei Province, China. On 30 December 2019, a previously unknown beta-coronavirus was identified with RT-PCR of samples got from a bronchoalveolar lavage of a patient with pneumonia of unknown etiology in Wuhan Jinyintan Hospital [1]. This new coronavirus, named 2019-nCoV, was later named SARS-CoV-2 due to its association with severe acute respiratory syndrome (SARS). The related disease, mainly pulmonary initially, was called coronavirus disease 19 (COVID-19). Information on the epidemic was notified to WHO on 3 January 2020. After that the outbreak spread outside China and the first western case occurred in Italy on January 30th. On 30 January 2020, the WHO declared COVID-19 as the sixth public health emergency of international concern. On 11 March 2020 the WHO general director, Dr Tedros Adhanom Ghebreyesus, said that SARS-CoV-2 outbreak became a pandemic.
At the date of this version of the protocol just below 4 million of total confirmed cases of COVID-19 have been recorded from 215 Countries all over the world, with roughly 270,000 deaths.
As cancer patients are historically been considered at a higher risk of infection and related complications the main oncological Societies published general guidances on their websites. An international collaborative group proposed some practical measures for the management of cancer patients based on the available data [2].
It has been reported that cancer patients were more susceptible to viral infections, particularly SARS-CoV-2-related [3]. Furthermore, according to a recently published Chinese cohort, patients with cancer had a significantly higher risk of developing severe events (mainly intensive care unit - ICU - admissions) compared with patients without cancer (39% vs 8%, p=0·0003) [4].
Some types of cancers, like the thoracic ones, and clinical underlying conditions, such as immunosuppressive concurrent therapies or immune-related comorbidities, are potentially at a higher risk for infection and complications of COVID-19 for cancer patients.
However it is difficult to understand where and how to locate neuroendocrine neoplasms (NENs) patients within this context. It is well know that NENs represent a rare and heterogeneous group of malignancies and their clinical behavior and response to treatment is various. Some therapies, such as peptide receptor radionuclide therapy (PRRT), are specific of this disease. Prognosis can be very different between for instance a patient with a fast growing high burden neuroendocrine carcinoma (NEC) and a patient with an indolent metastatic small bowel neuroendocrine tumor (NET). Moreover in the first case is probable that the patient is receiving a conventional platinum-based chemotherapy whereas in the other case just a somatostatin analog (SSA). Therefore it is clear that global recommendations from scientific societies about NEN patients management during COVID-19 pandemic should take into account all these difference.
However at the moment there are not data about the risk of infection, disease and complications of NEN patients during COVID-19 pandemic.
In Italy according to the Istituto Superiore di Sanità (ISS)'s report on May 7th 2020 the 16% of patients had an active cancer over the past five years among the patients dead due to COVID-19. Unfortunately this information regards just 2,621 patients (out of 27,955) died for SARS-CoV-2 infection, that is less than 10% of the total number of patients died so far. This information was extracted reviewing charts of patients died in hospital as reported in the online published document from ISS.
On the basis of what above reported we think that it will be difficult to have reliable and reproducible data about the risk of infection and risk of disease/complications for cancer patients

and SARS-CoV-2. Other than difficult it is probably too early to find the ideal approach for cancer patients in the middle of the pandemic. Unfortunately the number of cancer patients COVID-19 positive will increase and guidances will have to be updated. What it is clear so far is that the management of cancer patients must be dynamic and tailored to every patient's condition, every hospital's resources and every physician's experience/expertise.
All of this will be even more complex for NEN patients, because of the aforementioned heterogeneity and rarity.
Therefore we propose a global collection of data through an international database to describe and monitor NEN patients with COVID-19. This retrospective/prospective collection of data can create a large basis to check frequence of events, clinical management, clinical outcome, demographic, geographical, clinical and biological correlations. All this will be helpful for the clinical and scientific community to get reliable information for a homogeneous clinical management of NEN patients during COVID-19 pandemic.

This protocol will be submitted to the attention of the executive boards of the main NEN societies and international oncological societies for their endorsement. Furthermore each single center dealing with NEN patients all over the world will be welcome to participate into this global registry. The aim is to get the as wide as possible representativity of the world situation.

2. Study design and patient population

This is a retrospective and prospective observational international multicentric trial on Sars-CoV-2 positive NEN patients.
Centers all over the world will be invited to participate in this study filling in a web application (REDCap) which reports clinical characteristics of patients, NENs and COVID-19. Specific questions will address clinical management and outcome.
During the revision of the clinical history and using the hospital chart, will be collected the following parameters in an electronic case report form:
Age, sex, place of residence, Center, major comorbidities, ongoing therapies for comorbidities, diagnosis of NEN, type of NEN, stage of NEN, treatment of NEN, duration of treatment of NEN, NEN response status, date of RT-PCR diagnosis of COVID-19, symptoms/signs of COVID-19, COVID-19-related CT-scan, therapy of COVID-19, biochemical exams regarding COVID-19, clinical behavior of NEN, clinical behavior of COVID-19, outcome of COVID-19, NEN-treatment management during COVID-19.

3. Duration of the study

The duration of the study will be approximately five months in total and four months for enrollment.

4. Eligibility criteria

Inclusion criteria

Patients with a NEN of any type with an RT-PCR positive COVID-19

Patients can have one of the following characteristics:

- Clinical symptoms/signs, including : fever (persistent T > 37.5 °C) and/or reduced O2 saturation and/or cough and/or rhynorrea and/or dyspnea at rest and/or extertional dyspnea and/or hypo-/anosmia and/or dys-/ageusia and/or diarrhea and/or myalgia and/or artralgia and/or conjunctivitis)
- Radiological sings of COVID-19 pneumonia at CT-scan
- No symptoms/signs, no radiological imaging or alterations
- Signed written informed consent for patients enrolled in the prospective part

Exclusion criteria

- Patients with NEN and symptoms suspected for COVID-19 without an RT-PCR positivity confirmation

5. Study Objective

Endpoints

- major demographic features;
- prevalence of major comorbidities;
- proportion of severe events overall including deaths;
- proportion of NET patients who received chemotherapy;
- proportion of NEC patients who received chemotherapy;
- proportion of NET patients who received everolimus;
- surgery, radiotherapy, immune check point inhibitors, chemotherapy, everolimus, in the last 2 months before COVID-19.

6. Statistical considerations

Sample size

This is mainly a descriptive study with no formal a priori hypothesis to be tested. As a consequence no formal statistical sample size has been computed.

Data analysis

Patients characteristics will be summarized by means of counts and percentages for categorical variables and by using the mean and standard deviation (DS) or median and quantiles for continuous variables.
Parametric and non-parametric tests for comparisons between groups (i.e. the Pearson Chi-Square or the Fisher Exact test for comparisons between categorical variables, the Mann- Whitney or the Kruskal-Wallis test for comparisons between continuous and categorical variables) will be eventually performed with explorative purposes as well as the use of logistic regression with multiple explanatory variables.
Time to event endpoints such as, DFS and OS will be mainly described by means of Kaplan-Meier curves. Multivariable regression models, such as the Cox model, will be eventually used with purely explorative intents.

7. Database management and CRF completion

Data for this study will be collected in a REDCap® (Research Electronic Data Capture) database. REDCap is a secure web platform for building and managing online databases and surveys. REDCap's streamlined process for rapidly creating and designing projects offers a vast array of tools that can be tailored to virtually any data collection strategy. REDCap provides an intuitive user interface that streamlines project development and improves data entry through real-time validation rules (with automated data type and range checks). REDCap also provides easy data manipulation (with audit trails for reporting, monitoring and querying patient records) and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). Investigators who have received appropriate institutional research approval (i.e., Institutional Review Board or Institutional Ethics Committee) will be given a web link with a survey where they can enter data about their specific patients. Guidelines about the data collection and to properly enter the data will be developed.
The Promoter/Study Coordinator Centre is the legal owner of the collected data and has the right to manage it (including the data collected by the centers involved)
in the case of a multi-site study, the sharing of data to any satellite centres is at the discretion of the Coordinator Centre under existing contractual agreements
the regulation regarding protected health information (PHI) is also valid in Italy: it is therefore not possible to enter sensitive data of the subjects enrolled in the study or any other data (such as hospital codes/labels/SDO) that can lead to their identity; that's why when a subject is inserted into the platform, the system assigns it a unique identifier
The id/name-lastname code decoding is the responsibility of the PI of each experimental center (and should not be shared with the Coordinator Center). Each experimental center will then be the only one to be able to decode the IDs assigned to the subjects managed by its center.
For experimental studies, the date of birth is usually encoded by keeping only month and year or year only according to the specifics of the study; observational studies should follow the same rule but it is "borderline" as dynamic, even today the actual date of birth is often collected without particular criticism by the regulators
As for the timing of data retention, it depends on the contract you have with the server on which it is collected; all web-based information transmission is encrypted. REDCap was developed specifically around HIPAA-Security guidelinesMore information about the consortium and system security can be found at http://www.projectredcap.org/.
Investigators will access the medical record of their patient, enter required data into the database. The protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project. Future research, that is not defined in this protocol, wishing to access the REDcap database will need institutional review board/ethic review board approval before obtaining access to the REDcap database.
The investigator will ensure the staff dedicated to the study is available so that CRF will be adequately completed, and in timely fashion. As much as possible queries will be resolved when needed.
De-identified data only will be managed. Missing data will have to be carefully documented for patients who are lost to follow-up or with blocks or slides not available for the study. The database will contain information that enables the samples to be linked to personal data.

8. Ethical considerations

All the study procedures will be in accordance with the precepts of Good Clinical Practice and the declaration of Helsinki. According to the regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016, the following requirements regarding personal data will be guaranteed: pseudonymisation and encryption, the confidentiality, integrity, availability and resilience of treatment systems and services, the ability to restore the availability and access of data in the event of a physical or technical accident.
This study will be conducted in compliance with the protocol, adhering to the principles current local legislation.

9. Independents Ethical Committee and Legal Arrangements

All the documents required by the national law and any other informative documents that may be requested will be submitted for review to an independent Ethics Committee whose procedures and operations meet the national legal requirements.
The Health Authorities according to the legal requirements will authorize the study.
Selection of the patients will not start before approval of the Ethics Committee has been obtained and the study has been authorized by the Health Authorities.

10. Enrollment

For the prospective study all patients giving informed consent can be enrolled. When the informed consent is signed (signed and dated by the patient and the physician) the patient will be assigned a progressive number.
All inclusion/exclusion criteria will be checked during the registration procedure. As soon as the eligibility is verified the patient is registered.

11. Patient information and Consent

Confidentiality

The investigator must ensure that the subject's confidentiality is maintained. In case report forms (CRF) and other study-related document subjects should be identified by their unique subject study number only.
Source documents are original documents, data, and records from which the subject's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, radiographs, and correspondence. Case report form entries may be considered source data if the case report form is the site of the original recording (ie, there is no other written or electronic record of data).
For other patient the informed consent process is under investigator's responsibility.
The information and consent document will be made in duplicate: the original copy to be kept by the investigator, one copy will be given to the patient.

12. Publications

Property of data is of the European Institute of Oncology, IEO, IRCCS; Milan, Italy.
The main results of the clinical trial will be published in a peer-reviewed scientific journal.
The final publication will be written on the basis of the final analysis performed by the European Institute of Oncology and Statistical Center.
Organizational committee members will be co-authors.
Investigators will be able to be included among the co-authors on the basis of the active recruitment of the center and/or their participation in the design and drawing up of the research project.
All publications, abstract or presentations including data related to the present trial will be submitted for review to the Chair of the Study, who is the Director of Division of Gastrointestinal Medical Oncology and Neuroendocrine Tumors of European Institute of Oncology, prior to submission.
Trial results will not be released before data maturity has been reached for the primary endpoint of the trial. Publication will be done in case of positive study results as well as negative results.

13. References

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3. Yu J, Ouyang W, Chua MLK, Xie C. SARS-CoV-2 Transmission in Patients With Cancer at a Tertiary Care Hospital in Wuhan, China. JAMA Oncol 2020.
4. Liang W, Guan W, Chen R et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol 2020; 21: 335-337.