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Nuclear Medicine in the time of Covid-19 pandemic

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The modifications brought about by the COVID-19 pandemic to Nuclear Medicine practice

Vasiliki Chatzipavlidou MD, Interim Editor in Chief of Hell J Nucl Med, President of the Hellenic Society of Nuclear Medicine

Nuclear Medicine Consultant, Head of Nuclear Medicine Department of Cancer Hospital of Thessaloniki Theagenio

Corresponding author:

Vasiliki Chatzipavlidou MD, Nuclear Medicine Consultant, Head of Nuclear Medicine Department of Cancer Hospital of Thessaloniki Theagenio, Al Symeonidis 2 str, P.C 54007 Thessaloniki, Greece, Tel: +302310898180/+306944331146, Email: hpavlidou@gmail.com

Nearly 19.9 million cases and more than 730 thousand disease-related deaths have been confirmed in the months that followed WHO's assessment that the novel coronavirus COVID-19, first emerged in Wuhan China on December 2019, could be characterized as a pandemic [1]. The aforementioned coronavirus affected 188 countries as of 8.10.2020 [2]. Despite the continually increasing number of COVID-19 cases reported to CDC, at national level, the percentage of visits to outpatient providers and emergency departments has decreased and mortality rates attributed to COVID-19 have declined compared to the previous weeks, still above the baseline [3]. It is common knowledge that the coronavirus pandemic has reshaped societies and economies around the globe, affecting all aspects of everyday life. Public health systems as a whole have been globally affected since they had to face extraordinary demands over a long period of time, which, in turn, required rapid adjustments in the operating procedures that were already in use, in order to provide high-standard health services, while respecting patients quality of life [4].

Over half of deaths in low-income countries are caused by communicable diseases, maternal causes, conditions arising during pregnancy and childbirth, and nutritional deficiencies. On the contrary, this percentage is less than 7% in high-income countries. Noncommunicable diseases cause 71% of deaths globally, ranging from 37% in low-income countries to 88% in high-income countries. However, in terms of absolute number of deaths, 78% of global NCD deaths occurred in low-and middle-income countries [5]. This partially explains why recent developments in medicine were mostly focused on chronic illnesses, including cardiovascular disease, cancer, chronic respiratory diseases and type 2 diabetes, rather than focusing on infection and inflammation progress. The COVID-19 pandemic and the subsequent burden it placed upon health systems to deal with infectious and non-infectious diseases in a poor environment, can become an opportunity to update the field of medical research and change the

governmental policies in place that have been stagnant and/or inefficient and ill-managed [6]. This way, health systems will be equipped with better and faster protocols and best practices in order to manage efficiently any other pandemic that might emerge in the future.

In this context, Nuclear Medicine departments should reconsider and update their practices, by altering routines and workflows in order to comply with the new sanitary standards, triaging their appointments, or introducing new diagnostic methods like Tele-Medicine / Tele Nuclear Medicine and Artificial Intelligence applications.

This special edition of Hellenic Journal of Nuclear Medicine has as its main purpose to introduce and communicate those new practices and protocols/standard operating procedures, in order for the scientific community, health public institutions, affected individuals and their families to be duly informed.

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SARS-CoV2: Diagnostic tests available to the clinician

Paul Hadweh, Timoklia Orfanidou, Maria Tsiamita, Grigorios Timologos, Theofanis Papadopoulos

KARYO Ltd, Molecular Diagnostics Laboratory, Ermou 51 str, P.C 54623, Thessaloniki, Greece

Corresponding author:

Theofanis Papadopoulos, KARYO Ltd, Molecular Diagnostics Laboratory, Ermou 51 str, P.C 54623, Thessaloniki, Greece, email: papadopoulos@karyo.gr

Abstract

On December 2019, a new coronavirus disease (COVID-19) emerged in China and spread worldwide, causing acute severe respiratory syndrome. Due to the increased transmission rate of the virus, it became of great importance the early diagnosis of the disease. The coronavirus pandemic led to the development of numerous tests in order to mass screening population for active viral load and for the identification of antibodies for epidemiological purposes. This review summarizes the different diagnostic tests available to the clinicians for the diagnosis and follow up of the SARS COV-2 infections.

Introduction

On December 2019, a new coronavirus emerged in China and caused an acute respiratory disease now known as coronavirus disease 2019 (COVID-19) [1]. The virus was identified to be a betacoronavirus related to severe acute respiratory syndrome coronavirus (SARS-CoV) and thus was named SARS-CoV-2 [2]. In less than two decades, this virus is the third known coronavirus to cross the species barrier and cause severe respiratory infections in humans after SARS-CoV in 2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, yet with unprecedented spread compared with the previous two viruses [3].

SARS-CoV, SARS-CoV-2 and MERS-CoV have the largest positive-stranded RNA genomes among the RNA viruses (27-32kb) [4]. The genome of SARS-CoV-2 encodes 27 proteins, among whom the RNA-dependent RNA polymerase (RDRP) as well as four structural proteins: small envelope protein (E), matrix protein (M), nucleocapsid protein (N) and spike surface glycoprotein (S) [5]. Among the structural proteins, the S glycoprotein is responsible for the virus binding to host cells by a cellular receptor [6]. A human protease is responsible for priming the S protein recognized by the angiotensin-converting enzyme 2 (ACE2) engaged as a receptor for the entry of SARS-CoV-2 to the host cells [7].

SARS-CoV-2 is highly infectious. The incubation time varies between 4-8 days infecting people from all groups of age, with older people with comorbidities being at higher risk [8].

Diagnostic testing for SARS-CoV-2 is critical for epidemiological surveillance, but the accuracy (sensitivity and specificity) and clinical utility (impact on health outcomes) of the current diagnostic methods used for SARS-CoV-2 detection are not known.

This review summarizes the different diagnostic tests available to the clinicians for the diagnosis and follow up of the SARS COV-2 infections.

Types of diagnostic testing

At present two major categories of tests are available; the diagnostic ones based on the molecular recognition of the active viral infection and the immunological assays for the recognition of antibodies of individuals that have been exposed to the virus.

Nucleic acid testing: Reverse transcriptase polymerase chain reaction

Diagnostic assays for SARS-CoV detection were rapidly developed after the identification of the SARS-COV-2. Testing of suspected cases helped considerably to contain the outbreak and understand the rapid disease progression observed in some of the patients. SARS patients had detectable viral RNA between three and 30 days after the first symptoms appeared, with high viral loads in lower respiratory tract and fecal samples.

Quantitative real-time reverse transcription polymerase chain reaction (qRT-PCR) assays were the first assays that helped identify and subsequently isolate patients who were actively shedding the virus [9]. It was reported that viral RNA could be detected by qRT-PCR up to 30 days post onset of illness (dpoi) [10].

A number of SARS-related viral genome sequences were aligned aiming to detect conserved regions used in designing primers and probes suitable for the development of diagnostic reverse transcription polymerase chain reaction (RT-PCR) kits [11]. Three regions of the genome with conserved sequence were detected and are those of RdRP, the E-gene and the N-gene, with the first two having higher analytical sensitivity. Designed assays are highly recommended to use a two-target system, one detecting numerous coronaviruses including SARS-CoV-2 whereas the second detects exclusively SARS-CoV-2. Many RT-PCR kits were developed successfully by various institutions around the world such as Charité in Berlin [11], U.S. CDC, Chinese CDC, and institute Pasteur in Paris among other [12].

Mucus samples collected from the nose or the throat, were examined with molecular tests. Although the molecular test is the method of choice for the detection of active coronavirus infection by identifying renal genetic material, the accuracy of the result might be compromised by the collecting process of the samples along with inappropriate specimen maintenance and transport [13]. The specificity of the qRT-PCR assays has also been questioned because of the potential for nucleic acid contamination in the laboratories where many SARS-CoV samples were processed [14]. The use of standard operating procedures concerning decontamination methods and processing the samples under specific conditions minimizes the above risks, rendering quantitative real-time reverse transcription polymerase chain reaction assays as golden standard for the detection of the virus.

Nucleic acid testing: Reverse transcriptase loop-mediated isothermal amplification

Although RT-PCR is a sensitive and reliable method for SARS-CoV-2 detection, it is a method dependent on specific detection devices and equipment. Loop-mediated isothermal amplification (LAMP) is a method able to amplify DNA rapidly at constant temperature involving six primers binding with extremely high specificity to the targeted sequence, making a thermal cycler dispensable [15]. Using a suitable warm stable reverse transcriptase, LAMP can also be used to amplify RNA targets (RT-LAMP). This method has been formerly used in pathogen detection of viruses and bacteria [16-20]. Huang et al. achieved to develop a sensitive and rapid diagnostic test using primers targeting Orf1ab gene and N gene without any RNA extraction from the specimen, whereas the final product of the amplification is visualized optically using a pH dependent indicator leading to colorimetric change in the reaction due to the dropping pH positive samples [21].

The specifications of this method allow installing it in facilities with frequent testing needs such as airports, railway stations, borders, medical care units etc., making it possible this way to perform tests everywhere and prevent spreading the disease. The sensitivity of this test was determined at 2 viral target RNA copies/25µl reaction. This sensitivity though is considered a disadvantage as many false positive samples occur due to carry-over contamination. For this reason, the positive results obtained by this method are suggested to be retested using quantitative real-time reverse transcription polymerase chain reaction assays.

Serological assays

Validated serological assays are crucial for patients' contact tracing, identifying the viral reservoir hosts, and epidemiological studies. Epidemiological studies are urgently needed to help uncover the burden of disease, especially the rate of asymptomatic infections, and to get better estimates on illness and death. In addition, these epidemiological studies can help identify the extent of virus spread in households, communities, and specific settings, which could help guide control measures. Serological assays are also needed for the evaluation of results of vaccine trials and development of therapeutic antibodies.

Although highly accurate molecular diagnostic tests can be rapidly developed whenever the viral sequence is known, the technology used for the development of serological tests is different and more time consuming. In particular distinct proteins forming the viral coat should be recognized and antibodies to these specific proteins present during immune response upon viral infection should be identified. Finally, these proteins should be tested for specificity, meaning that they do not have cross-reactivity with other coronaviruses [22].

Numerous different serological assays have been developed based on a variety of methodologies such as western blot, ELISA, chemiluminescence and immunofluorescence platforms.

Among the 4 coronavirus structural proteins, the spike (S) and nucleocapsid (N) proteins are the main immunogens [23]. Okba et al., recently described the development of serological assays for the detection of virus neutralizing antibodies and antibodies to the N-protein and various S-protein domains, including the S1 subunit, and the receptor-binding domain (RBD) of SARS-CoV-2 in an ELISA format [24]. Using a well-characterized cohort of serum samples from PCR-confirmed SARS-CoV-2 patients and patients PCR-confirmed to be infected with other seasonal coronaviruses and respiratory pathogens, they validated and tested various antigens in

different commercial platform [24]. Okba and his team found that commercial S1 IgG or IgA ELISAs were of lower specificity, and sensitivity varied between the 2 assays; the IgA ELISA showed higher sensitivity. Overall, the validated assays described can be instrumental for detection of SARS-CoV-2 specific antibodies for diagnostic, seroepidemiologic, and vaccine evaluation studies.

In general, in published studies the sensitivity of serological assays ranged from 0-100% and their specificity from 78%-100% with most assays performing better in symptomatic patients after 14 days of the onset of their symptoms. Recently developed assays are based on fully automated chemiluminescence immunoassays on high throughput laboratory instrumentations. However limited performance assays are available in order to conclude which test is preferable to use in clinical practice [22].

Rapid antigen test

Rapid antigen tests would theoretically provide the advantage of fast time to results and low-cost detection of Covid19 antibodies without getting tested in a central laboratory.

They are ready to use tests, developed for the detection of both IgM and IgG SARS COV2 antibodies in blood from finger prick. They are LFIA assays (lateral flow assays) where a membrane strip is coated with two layers of colloidal gold nanoparticle. In the first layer antibody conjugates are present and bind antibodies on the second layer. When blood is placed on the membrane, proteins are drawn through capillary action and as they pass through the first layer, the antigens binds to the gold nanoparticle antibody conjugate and the complex flows across the membrane. If the concentration of antibodies is low the rapid test can reveal a false negative result. Published results up to date describe a sensitivity of rapid tests ranging from 9% to 88.6% and specificity 88.9% to 91.7%. At present it is suggested that although rapid test devices might provide some information to clinicians for epidemiological purposes, their performance is inadequate for most diagnostic applications [22]. Recent study by Scohy et al. suggested that COVID-19 Ag rapid test should not be used alone for COVID-19 diagnosis and shows no benefit in reducing the use of RT-qPCR [25]. Novel approaches to concentrate antigen, or to amplify the detection phase are needed if these methods are to have clinical utility. Timing of specimen collection, when viral titres are highest, may improve the diagnostic sensitivity of rapid antigen tests for HCoV-229E [26].

Cell culture

Isolation of the virus and subsequent cell culture is a crucial method for characterization of the virus, for testing of possible therapeutic molecules and for the development of new vaccines [26]. However this method is not used for diagnostic purposes, since it is a time consuming method which needs permissive cell lines, currently unavailable along with the lack of commercial antisera for culture confirmation. The method is currently based on growing SARS-CoV, MERS-CoV and SARS-CoV-2 in primary monkey cells and commercially available cell lines such as Vero and LLCMK2. However, cell culturing should be avoided in suspected cases in routine diagnostic laboratories in order to avoid contamination and spreading of the virus [27, 28].

Radiographic tests

Chest imaging is a key component of the diagnostic work-up for patients with suspected infection. Several studies find that bilateral pneumonia is the most frequent clinical feature, on chest radiography [29-30]. On the other hand, computed tomography is regarded as more sensitive than radiography, with several cohort studies reporting that most patients had ground glass opacities. Compared with nasopharyngeal sampling, chest computed tomography may be more sensitive than an RT-PCR test at a single time point for the diagnosis of COVID-19, due to false-negative results of RT-PCR mostly due to inappropriate sampling or laboratory malpractice [31-33]. Radiographic tests are extremely useful in epidemic areas during urgent periods when regional hospitals are overloaded and laboratory test results are delayed. However, these radiological findings are not completely specific to COVID-19 and do not exclude a co-infection or an alternative diagnosis [34].

Conclusion

The coronavirus pandemic led to the development of numerous tests available to the clinical doctors. Two major categories of tests are available; the diagnostic ones based on the molecular recognition of the active viral infection and the immunological assays for the recognition of antibodies of individuals that have been exposed to the virus. The qRT-PCR assays are currently the method of choice, since a positive test reveals active infection of SARS-COV2. However, there is an increasing need for a serological assay to be developed with increased sensitivity and specificity for the detection of immune response produced by the virus. Currently a negative antigen test of a patient with clinical symptoms suggestive to Covid-19 does not rule out an infection by the virus and the patient is retested using a molecular test. Additionally, an accurate serological test is needed since seroconversion can lead to reassurance of patients with a positive result.

As time passes more results are available to the scientific community, which will lead to comparative studies, validating across different populations and leading to serological assays with increased sensitivity and specificity.

Having better tests will help recognizing the patients affected by coronavirus, even when asymptomatic, in order to take appropriate measures and minimizing the spreading of the disease.

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Invited contribution

The consequences of COVID-19 pandemic in the routine of Nuclear Medicine Departments

Emmanouil Papanastasiou MSc, PhD

Medical Physics Laboratory, School of Medicine, Aristotle University of Thessaloniki, Greece

Keywords: *COVID-19 pandemic, Nuclear Medicine*

Corresponding author:

Emmanouil Papanastasiou, Medical Physics Laboratory, School of Medicine, Aristotle University of Thessaloniki, Greece. Email: empapana@auth.gr

Abstract

The outbreak and spreading of the COVID-19 pandemic have affected billions of people around the world, severely disrupting many aspects of their lives. Although not at the frontline of the pandemic response, Nuclear Medicine departments have to adopt their clinical routine to the new environment. A series of protective measures, including among others spatial arrangements to promote social distancing, meticulous hand hygiene and use of personal protective equipment, workload reduction, patient screening at admission and examination protocol adjustments, have to be adopted in order to minimize the risk of spreading the infection and ensure the safety of both their patients and staff. As the pandemic seems to slowly recede, the valuable experience gained should help everyone be much better prepared for a possible new outbreak.

Introduction

Since last December, first China and gradually the rest of the world, is experiencing an unprecedented hygienic crisis with an enormous cost in human lives and unforeseeable social and economic consequences. Until the 14th of May 2020, coronavirus SARS-CoV-2, causing COVID-19 disease, has infected more than 4.250.000 people and has been responsible for more than 294.000 deaths in 215 countries around the globe [1].

Highly esteemed health care systems in many countries were driven far beyond their limits, being unable to cope with the increasing demand for intensive care beds, ventilators and other support equipment for their COVID-19 patients and protective equipment for their staff.

It is true that Nuclear Medicine (NM) departments and their staff were not found in the front line of the pandemic response. Nevertheless, along with all other health care providers, they also experienced a dramatic change in their clinical routine and had to adopt their standard

practices to the new environment. Several national and international organizations have issued guidance documents to help NM staff cope with suspected or verified COVID-19 patients [2-5]. The International Atomic Energy Agency (IAEA) has recently assembled an international experts panel and broadcasted a live webinar entitled “Coronavirus disease (COVID-19) Pandemic: Challenges for the Nuclear Medicine Departments” in order to disseminate their experiences along the NM community. The recorded webinar is still available through the IAEA website [6]. In the present article, an attempt is made to outline some measures and actions that can be taken in NM departments, in order to maintain (as much as possible) a safe working environment for their patients and staff. The information presented here is by no means exhaustive; it is drawn from national and international guidance, discussions with colleagues and modest personal experience.

Facility preparation

NM departments are already designed in a way as to minimize prolonged close contacts of patients with members of the staff, for radiation protection purposes. However, there are some protective measures that can further reduce the risk of SARS-CoV-2 spread.

The NM reception booth should be partly isolated from the reception area using glass or plastic screens, behind which reception staff should be sited. The seats in the pre-injection and the post-injection waiting rooms must be rearranged in a way that a distance of at least 1.5m is maintained between patients, and, if possible, the remaining seats must be removed. The use of multi-seat couches is discouraged.

Hand hygiene, for both patients, accompanying persons and staff, cannot be overstressed. Wall-mounted hand sanitizing dispensers should be installed at the entrance, the exit and at key sites of the department. Proper signs and posters urging patients and staff to continuously wash and/or disinfect their hands should be placed accordingly. Such posters and signs could also display information about the most common COVID-19 symptoms (to promote awareness) and advice for keeping social distancing.

Personal Protective Equipment (PPE)

Availability of all proper PPE (face masks, safety goggles or face shields, disposable gloves, shoe covers and isolation gowns) into the department is essential. Unfortunately, especially during the first weeks of the pandemic, many hospitals have experienced serious shortages of elementary PPE, such as face masks, as the outburst in demand had far surpassed availability.

Medical face masks are obligatory for all hospital staff. Face masks are also obligatory for patients and caregivers. NM staff involved in the injection of radiopharmaceuticals are also advised to wear safety goggles or, preferably, plastic face shields. Disposable latex gloves are routinely used by NM staff anyway, in order to protect them from radioactive contamination. The complete set of PPE must be used by all NM staff members who will be involved in the handling of a suspected COVID-19 patient who is referred for a NM scan. Appropriate training concerning the correct procedure to wear and remove the PPE needs to be provided to all staff by hospital experts.

It is indeed fortunate that the majority of NM personnel, being used to work with unsealed

radioactive sources for their entire professional careers, are well acquainted with the use of many kinds of PPE and had much less difficulty in adopting to the new routine. The radiation protection culture that is being continuously developed among NM departments has paid off in a surprisingly new way, none could have imagined some months ago.

Adequacy of radiopharmaceutical supplies

The worldwide lockdown and the dramatic decrease in the availability of international flights has created serious problems in the production and the distribution of radiopharmaceuticals. Even though the request for many NM examinations has been reduced during the COVID-19 pandemic, radiopharmaceuticals shortage can cause further disruptions in the department's schedule. An effort must be made to maintain a stock of cold kits sufficient for at least 2-3 months, if possible.

Scheduling appointments

According to national guidance, hospitals designated as COVID-19 reference hospitals have postponed all outpatient appointments during the lockdown, in order to minimize patient traffic. As a result, most NM diagnostic scans (primarily performed on an out-patient basis) were also postponed during the peak of the pandemic. There were cases where it was requested that NM resources (for example hybrid SPECT/CT and PET/CT scanners) were made available to Radiology departments, to assist them in dealing with the increased demand for CT scans, provided that the CT component was indeed a fully operational diagnostic CT scanner.

Depending on each Hospital policy, the number of NM scheduled scans was generally reduced. NM physicians had to decide which non-essential NM procedures could be postponed, and which essential procedures (diagnostic or therapeutic) had to proceed as scheduled. There has been guidance to avoid performing examinations which are associated with the production of aerosols, such as lung ventilation studies [2, 4], due to an anxiety for airborne transmission of SARS-CoV-2, which could be further facilitated by the airflow generated by central or non-central air-conditioning units, continuously operating in NM imaging suites.

The day before each scheduled appointment, the NM reception staff should communicate with the patients and ask them whether they have had any suspicious symptoms related to COVID-19 and whether they have come in close contact with COVID-19 patients. Patients need to be reminded to come to the NM department wearing a face mask and without being accompanied by relatives. If it is absolutely necessary, a patient can be accompanied by a single caregiver, preferably without any risk factors. Patient may be advised not to arrive at the department more than 5-10 minutes before their scheduled appointment, in order to avoid crowded waiting areas.

Patient admission

Upon arrival, all patients and caregivers must be instructed to clean their hands using the hand sanitizing dispensers at the department entrance. All patients should be asked whether they have had any symptoms of COVID-19. It is good practice for the reception staff to read to the patients an appropriate questionnaire, with the most common clinical signs (fever) or symptoms (dry

cough, dyspnea, unusual fatigue, myalgia, diarrhea, anosmia, hyposmia, dysgeusia, or ageusia) and fill it in with their responses. Temperature control using skin contact electronic thermometers or non-contact infrared thermometers can be used, but it should be kept in mind that it cannot safely identify COVID-19 patients. Increased vigilance is required to identify and isolate as soon as possible any suspicious case. It is important that all NM patients and relatives be considered as being asymptomatic virus carriers.

Every effort must be taken as to keep patients and relatives from continuously moving around the Hospital. Any administrative procedures that can be completed without the physical presence of the patient to other Hospital departments, should be properly arranged.

In the case when a COVID-19 patient is identified, both the patient and any accompanying person should be isolated in a separate waiting area and immediate consultation with the hospital's infectious diseases team should be sought.

Examination protocol adjustments

Whenever possible, examination protocols can be appropriately modified, in order to minimize the time patients remain in the department and the time NM staff spends in close proximity to them. As an example, myocardial perfusion imaging can be performed using a single-day, stress-first protocol. Pharmacological stress should be preferred over exercise stress testing to minimize droplet exposure to exercise staff [3].

Patient scanning

Patient table must be covered with single use disposable covers, which must be disposed accordingly after the completion of the scan. Patients must be instructed not to remove their masks during scanning. After scanning, the scanner and any other surfaces in the scanning room that might have come in contact with patient's respiratory droplets must be disinfected.

Scanning a COVID-19 suspected patient should be scheduled as the last appointment of the working day [2] and, if possible, after every other patient has left the NM department. Only the necessary number of staff needed to properly handle the patient should remain on site, who must have enough time to prepare themselves (wear the appropriate PPE and refresh all necessary procedures).

Radioiodine therapies

After the initial guidance to postpone non-urgent radioiodine therapies [7], because of the radiation protection issues that would arise if these patients needed to be admitted to an Intensive Care Unit, it was realized that COVID-19 pandemic would be around us for many months, therefore treatments could not be postponed for such a long time. The Royal College of Radiologists has recently issued revised guidelines on the subject [8].

Teleconsultation before and after radionuclide therapies can be used to minimize patient visits into the NM department.

On the other hand, let us point out here that providing radiation protection guidance to a

hyperthyroid of thyroid cancer patient who is going to receive radioiodine treatment has never been easier: before the pandemic, many patients were expressing difficulties in abiding with the rules of social distancing, the meticulous hand hygiene and all the other required radiation protection measures. For better or worse, all these have become part of everybody's daily routine, and it seems that they may have come to stay with us for a long time.

Stay alert

None knows how the SARS-CoV-2 will behave in the near future. Following the extensive lockdown, the pandemic seems to slowly recede in most countries, but everyone is afraid of a new outburst during next autumn or winter. However, this time the health community will be better prepared. Infrastructure and resources in the health systems have been reinforced, new scientific knowledge and experience on the efficacy of the available treatments for COVID-19 disease have been accumulated and several vaccines against SARS-CoV-2 are being clinically evaluated. But until scientists come up with an effective treatment or an effective vaccine, the most important action that each one of us has to take in order to successfully confront a second pandemic outbreak is to stay alert, to continue keeping the necessary precautions even when the danger seems to fade and to help maintain the high level of preparedness in our departments.

Conclusion

The COVID-19 pandemic has changed the lives of billions of people worldwide and has pushed health systems in many countries far beyond their limits. Nuclear Medicine practice could not have remained unaffected but has managed to overcome the initial shock and begins to resume all its activities, as the pandemic slowly seems to recede. The lessons learned and the practices that were adopted during these months constitute an invaluable experience for all of us and will help us make sure that NM laboratories and healthcare systems in general will be better prepared should the pandemic outbreaks again.

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Challenges and priorities in skeletal, gastrointestinal, hepatobiliary, genitourinary and lung scintigraphy during the COVID-19 pandemic

John Koutsikos^{1,2} MD, George Angelidis³ MD

1. Nuclear Medicine Department, 401 General Army Hospital, Athens, Greece, 2. Nuclear Medicine Department, Henry Dunant Hospital Center, Athens, Greece, 3. Nuclear Medicine Laboratory, University of Thessaly, Larissa, Greece

Corresponding author:

John Koutsikos MD, Nuclear Medicine Department, 401 General Army Hospital, Athens, Greece,
Email: jtkoutsik@yahoo.gr

Introduction

On December 29, 2019, a hospital in the City of Wuhan, Hubei Province, in Central China, admitted four individuals with pneumonia. The hospital reported this occurrence to the local center for disease control (CDC), which lead Wuhan CDC staff to initiate a field investigation with a retrospective search for pneumonia patients [1]. On December 31, 2019, the World Health Organization (WHO) was alerted by the Chinese authorities for several cases of pneumonia of unknown origin in the City of Wuhan [2]. On January 7, 2020, a novel virus was identified as the causative agent, belonging to the *Coronaviridae* family (Severe Acute Respiratory Syndrome Coronavirus 2, SARS-CoV-2). Within the same month, the virus spread to other provinces of China, as well as a number of neighbouring countries. On February 11, 2020, the WHO announced that the SARS-CoV-2 - caused infection would be called coronavirus disease 2019 (COVID-19). On February 15, 2020, the first death due to COVID-19 in Europe was reported; a Chinese tourist who died in France. The first COVID-19 case was diagnosed in Greece on February 26th. The WHO declared COVID-19 a pandemic on 11 March 2020. On March 12th, movie theaters, gyms and courtrooms were closed in Greece and on March 13th, with 190 confirmed cases and 1 death, malls, cafés, restaurants, bars, beauty parlors, museums and archaeological sites were also closed.

So far, COVID-19 pandemic has affected the way people live and work globally, and has resulted in extreme strain on the healthcare systems worldwide [3]. Most of the nuclear medicine studies are performed on an out-patient basis. Therefore, without effective implementation of the required preventive measures, there is a significant risk for viral transmission when visiting nuclear medicine departments, particularly in periods of high community spread.

Nuclear Medicine departments and COVID-19 pandemic

Nuclear Medicine studies are necessary for medical management. They should be scheduled at the earliest possibility, but require judicious balancing of risks associated with a test or a treatment postponement versus associated risks of exposure to SARS-CoV-2 by patients and personnel [4]. An advantage in nuclear medicine is that most of the scans and therapies tend to be outpatient, elective cases, while the in-patients would have been screened for COVID-19 on the wards, before being transferred for nuclear medicine applications [5]. However, the segregation of the patients into high- and low-risk groups, with respect to COVID-19 suspicion, could help in reducing the possibility of intra-institutional spread, as well as in facilitating contact-tracing [2]. Patients' segregation can be achieved in term of space and/or time. Space segregation involves the designation of separated zones within the department for different types of risk. On the other hand, temporal separation could be even more useful in facilities with constraints with regard to layout of the department. In general, the nuclear medicine technologists, nurses and healthcare assistants are considered to be at higher risk for exposure to SARS-CoV-2 [5].

General measures for COVID-19 prevention and control in Nuclear Medicine departments

Several general measures have been proposed for the prevention and control of COVID-19 pandemic in nuclear medicine departments [6]. First, the reception staff must be protected with the placement of plastic screens. A questionnaire, mainly regarding possible COVID-19 clinical features, the travel history, and history of close contacts with known clusters of the disease, could be provided to the patients on arrival [2, 6]. Initial triage is of great importance for the early identification of suspected COVID-19 cases in order to avoid further spread of the virus, and temperature-taking at entrances acts as a guard, despite the fact that not all infected patients are symptomatic nor febrile [2, 6]. The stay of accompanying persons in the departments should be discouraged, particularly with respect to patients in good physical condition. Undoubtedly, confirmed or suspected COVID-19 cases must be separated in dedicated areas. The purpose of this isolation practice is to provide safe areas away from other patients, where the suspected (in particular) cases can be reviewed by the specialized institutional team for further management [2]. Taking into account the procedures requiring close contact to the patients, physical distancing is still considered as the main protective measures against COVID-19. Therefore, crowding should be avoided in the waiting areas and the hot-rooms. Hand sanitizers must be available in certain stations across the departments, while all patients must wear a face mask. It may be also useful to display posters on hand hygiene and infection prevention in the departments. Finally, barriers could be applied to prevent contamination of the scanners, and proper procedures should be implemented to clean and/or disinfect the gantry, bed, computer screens, keyboards, etc.

As far as the staff welfare, the application of personal protective equipment (PPE) should be consistently implemented. However, it should be noted that PPE does not substitute physical distancing measures, especially during verbal communications, and optimal hand hygiene. In assigning Healthcare Personnel to specific roles at a Nuclear Medicine Department, a risk-adapted approach is recommended with consideration given to the significantly higher case-fatality rates from COVID-19 among older people and those with chronic diseases [4].

Furthermore, staff members should be cautiously monitored for symptoms and signs of infection. In larger departments, the staff could be segregated according to alternating duty rosters, in an attempt to avoid wide spread of the virus among staff members. Without compromising imaging findings, scan protocols should be adjusted, aiming to minimize patients' stay at the departments. Further, service hours could be also adapted for a better application of the protective measures, when possible.

Under the circumstances associated with the COVID-19 pandemic, the use of modern technologies and on-line applications is highly advisable, in order to avoid close contact, such as that observed in the reading rooms and the multidisciplinary meetings. Apparently, this includes remote studies reporting, virtual meetings, as well as tele-consultations with the patients [2].

Specific recommendations with respect to the study type

Nuclear medicine techniques can provide important information regarding the diagnostic investigation and follow-up of patients in multiple conditions. However, due to the risk of COVID-19 transmission, certain (non-urgent) studies may be advisable to be deferred and possibly held in a queue, in periods of high SARS-COV-2 community spread [3, 6]. In further detail, examinations with no immediate impact on the patient management may include surveillance studies in oncology, hepatobiliary studies, or renal (non-transplantation related) studies. On the other hand, studies with immediate effect on the patient management should be performed as soon as possible, taking special precautions for the adoption of all general protective practices [6]. This recommendation includes examinations linked to the loss of treatment opportunities when diagnostic and prognostic information is missing, such as studies in oncology for staging and therapeutic response assessment, pulmonary studies, and examinations aiming at revealing sites of infection. Patient prioritisation for bone, gastrointestinal, hepatobiliary, genitourinary, and lung studies are presented in Table 1.

Table 1. Patient prioritisation in nuclear medicine with regard to the coronavirus disease 2019 pandemic.

Type of studies	Phase A (pandemic)	Phase B (recovery)	Phase C (post-pandemic)
Bone	<ul style="list-style-type: none"> Oncology (staging, treatment assessment) 	<ul style="list-style-type: none"> Oncology Investigation for sites of infection 	All indications
Gastrointestinal	<ul style="list-style-type: none"> Gastrointestinal bleeding Meckel's scan 	<ul style="list-style-type: none"> Gastrointestinal bleeding Meckel's scan 	
Hepatobiliary	None	None	
Genitourinary	<ul style="list-style-type: none"> Dynamic study after kidney transplantation 	<ul style="list-style-type: none"> Dynamic study after kidney transplantation Static and Dynamic studies as well as GFR measurements as a pre-transplantation procedure 	
Pulmonary	<ul style="list-style-type: none"> Lung perfusion (only) study SPECT/CT (if available) 	<ul style="list-style-type: none"> Lung perfusion (only) study SPECT/CT (if available) 	<ul style="list-style-type: none"> Lung ventilation/perfusion study

The task of postponing and re-scheduling of studies would require rigorous efforts, both by the medical personnel and the administration staff [3]. Commonly, there are several studies booked over the upcoming weeks, and the evaluation of the risk of postponement should be the key factor in the decision process. In particular, patient appointments should be carefully prioritised; patients suffering from chronic, stable, or mild conditions may have lower priority, in comparison to patients with acute, progressive, or severe conditions. Additionally, the studies should not be re-booked until further advice has been received by the local authorities [3].

Special considerations for the pulmonary studies

During the COVID-19 pandemic, an increase in pulmonary study referrals is expected, and has already been recorded in some departments. Main cause is the suspicion of pulmonary embolism in SARS-CoV-2 infected patients [2]. Indeed, there are overlapping symptoms between suspected cases of pulmonary embolism and the infected patients. Furthermore, the increased number of patient referrals for pulmonary studies may represent an effort to relieve the radiology departments, which are directly involved in COVID-19 diagnostic investigation, based on institutional recommendations [2].

SARS-CoV-2 is known to spread through the aerosolization of airway secretions, causing infection of the upper respiratory tract in contacts [7]. In the healthcare settings, it is crucial to identify procedures with a potential to lead to aerosolized secretions. Obviously, in the field of nuclear medicine, the main candidate technique is the ventilation/perfusion examination for the detection of pulmonary embolism. The typical protocol involves a low-dose ventilation study, followed by a higher dose perfusion study. During the ventilation study, there is a risk for aerosolized secretions contaminating personnel within the imaging suite, while the patients often cough after the inhalation of the radiopharmaceutical, increasing the risk of contamination. In an effort to mitigate the risk, the use of N95 (or higher level) respirators, eye protection, gloves, and gowns is indicated for the personnel performing aerosolized secretions - generating procedures, according to the US Centers for Disease Control and Prevention (CDC) [7]. Although this approach can permit the uninterrupted performance of the ventilation/perfusion technique, appropriate PPE may be in short supply, mainly due to increased demands in other departments of the hospital, such as emergency departments and intensive care units. Moreover, decontamination of the γ -camera and imaging suite would be needed in cases of suspected aerosolization, a process that can affect significantly the patient throughput. Consequently, during COVID-19 pandemic, a shift to a perfusion-only diagnostic algorithm is considered as the most advisable strategy in order to minimize the potential for COVID-19 transmission due to ventilation study [7].

Another option (wherever available) is the performance of a perfusion-only single photon emission computed tomography (SPECT)/computed tomography (CT) study, the hybrid technique which also involves the performance of a low-dose CT (without contrast enhancement). Based on previous studies, using low-dose CT instead of the ventilation scan results in similar sensitivity with regard to the pulmonary embolism investigation, although the rate of false-positive studies was found to be higher [8]. In particular, several non-thromboembolic abnormalities may be depicted on the low-dose CT images, such as parenchymal changes (e.g. emphysema,

pneumonia) or extrinsic vascular compression that may explain the perfusion defects. Notably, the performance of a perfusion-only SPECT/CT examination in patients with suspected pulmonary embolism may reveal findings of COVID-19 - associated pneumonia (C-19AP) [9]. Therefore, it is crucial, for the prevention of viral transmission, the findings of C-19AP to be recognized early, and the patient to be reported to the designated COVID-19 team in each institution.

Conclusions

In general, COVID-19 transmission could be restricted with the adoption of good personal and institutional infection control practices. These measures are awaited be appropriate to the overall situation, as well as the different levels of transmission risk among the patients. Therefore, recommendations for the practice of nuclear medicine during the period of high SARS-CoV-2 transmission and in the post-pandemic era, should take into account the epidemic status, patient characteristics regarding the suspicion of infection, and department resources.

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Nuclear Cardiology practice in COVID-19 era

Anna Paschali¹ MD, Constantinos Anagnostopoulos² MD, PhD, FRCP, FRCR, FESC

1. PET/CT Oncology Center 'Theageneio', Thessaloniki, Greece, 2. Biomedical Research Foundation of Academy of Athens, Athens, Greece

Corresponding author:

Anna Paschali MD, PET/CT Oncology Center 'Theageneio', Al Symeonidis 2 str, P.C 54007 Thessaloniki, Greece, Email: a_pashali@yahoo.gr

Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic is the biggest shock in decades to the well developed healthcare system and resources worldwide. Although there was a wide variation in the level of preparedness, the transition was tough even for the most renowned healthcare systems. Increasing the capacity and adapting healthcare for the needs of COVID-19 patients is described by the WHO as a fundamental outbreak response measure [1].

However, while the system is preoccupied with a pandemic infection, patients suffering from other illnesses are in high risk to get infected, also being compromised by the imperative shift in medical resources and significant restrictions on routine medical care. For example patients with cardiovascular disease and others referred for nuclear cardiology procedures are frequently greater than 60 years of age and have other comorbidities (e.g. hypertension, diabetes, chronic lung disease, and chronic renal disease) that place them at a high-risk for adverse outcomes with COVID-19, providing unique challenges for their management in healthcare facilities, as well as for the care of health care personnel [2-4].

Numerous medical specialty societies and governmental agencies issued guidelines aiming at the specification of preventive measures and amendments in everyday clinical practice during the escalation and peak of the pandemic. In accordance, the American Society of Nuclear Cardiology (ASNC) and the Society of Nuclear Medicine and Molecular Imaging (SNMMI), issued a common statement in late March 2020, which was provided as an initial response to this pandemic, offering specific recommendations for adapting nuclear cardiology practices at each step in a patient's journey through the lab—for inpatients, outpatients and emergency department patients. One of the main recommendations was cancelling or delaying of all non-urgent nuclear cardiology studies [5].

As COVID-19 follows a different time course in different geographic regions and lockdowns begin to lift in many countries, the issue of re-establishment of non-emergent care, in nuclear cardiology laboratories amongst others, has to be addressed in a watchful and balanced

way, keeping in mind that the COVID-19 crisis is far from over. Furthermore measuring what is happening in the current crisis is essential to ensuring preparedness for a possible next wave of the pandemic.

Recently the ASNC, SNMMI, the International Atomic Energy Agency (IAEA) and the Infectious Disease Society of America (IDSA), issued an information statement which describes a careful approach to reestablishment of non-emergent care in nuclear cardiology laboratories reflecting diverse settings from the United States and worldwide [6]. In the same spirit it is also the reintroduction guidance issued by North American Cardiovascular Societies [7].

In this paper we provide a synopsis of the basic steps of adapting nuclear cardiology practice in the era of COVID-19 in order to balance between the risk of viral transmission while also providing crucial cardiovascular assessments for our patients.

Considerations about staff safety

At all phases of the pandemic, medical and paramedical staff in nuclear cardiology laboratories are required to stay up to date and conform to local health policies (e.g. record symptoms and temperature), and to strictly adhere to the protective measures including: personal hygiene, physical distancing and appropriate use of personal protective equipment (PPE) [8-11]. Importantly, a transparent collaborative plan for COVID-19 testing and PPE use must be in place before a safe reintroduction of procedures and tests can occur [6-7].

At all phases of the pandemic every effort should be made to minimize the number of staff in contact with the patient and also to minimize the number of staff working in the same room. For that purpose, rotating staff schedules should be considered as well as the use of technology is encouraged whenever possible for off-site work. Furthermore it is essential to minimize in-person image review with referring services, opting for telephone discussions instead [5]. Covid-19 pandemic may be an opportunity to exploit and establish cutting edge technologies in order to work safely and effectively in the post-Covid-19 era.

Operational changes

1. Prioritizing the study requests

During the COVID-19 pandemic it is very important the nuclear medicine laboratories to prioritize study requests according to the benefit/hazard ratio and adapt their workload accordingly. The American Society of Nuclear Cardiology (ASNC) and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) in their recent common statement provide a classification of priority for all indications for γ -camera and PET nuclear cardiology studies, according to the level of urgency and estimated benefit: Priority 1: perform test as scheduled. Priority 2: postpone test by 2-4 months. Priority 3: postpone test by >4 months. Such classification of procedures requires clinical judgment and preferably discussion with the referring provider. During the escalation and peak phase of the pandemic nuclear cardiology laboratories are recommended to perform only studies classified as priority 1, which are those that are expected to drive a meaningful treatment change that could be implemented in the immediate future and would have a clear short-term

benefit [5].

In patients who are known to have active COVID-19 virus infection, there is limited role for performing nuclear cardiac stress tests, as the results would be very unlikely to alter short-term patient management in most cases [5]. Patients with high-risk exposures, who do not have an urgent need for testing should have their testing deferred [5,8]. Interestingly, ¹⁸F-FDG PET should be considered for endocarditis in a febrile patient with bacteremia (priority 1), as an alternative to transesophageal echocardiography, which carries a very high droplet risk exposure for operators [5]. There is also the provision that patients whose exams are deferred, should be in contact with their provider if their condition changes.

As the COVID-19 pandemic abates, urgent patients should continue to be tested first, while patient's exams previously deferred should be scheduled according to their clinical state considering also their waiting time [6]. It is important to review the indication for testing and contact the patient before rescheduling, to ensure that the test is still indicated and to ask for changes in symptoms and/or health status may either render the test not indicated or demand a different test [6].

Patients whose exams have been deferred because they were COVID-19 positive or highly-suspected, should be reevaluated clinically before rescheduling, depending on local health policies [6].

It is acknowledged that there will be a reasonable and gradual ramp up period to allow the backlog of patient tests to be completed, however this should be balanced with availability of staff and key equipment [6,12]. For example, 25% of a standard case load might be planned for the first 1-2 weeks, 50% case load in weeks 3 and 4, and then greater caseloads if conditions permit [6]. Importantly, if during the opening phase, COVID-19 admissions and deaths start to increase, there must be a rescheduling in the operation of nuclear cardiology laboratories towards to a cessation of most elective invasive procedures in accordance to regional public health policies [7].

2. Screening of the patients prior to testing

At all phases of the pandemic, the laboratory team needs to contact patients the day prior to the scheduled nuclear cardiology testing, in order to:

- Screen patients by history following latest local infection control recommendations for COVID-19 exposure risk. It is important to ensure that the patient is not experiencing clinical signs or symptoms suggesting possible occult COVID-19 infection, and that they have not been exposed to any case or high-risk subjects in the preceding 2 weeks, and have not travelled to high COVID-19 risk areas. If the patient refers suspicious symptoms, should be consulted to telephone his doctor or emergency department, if not done already. In most laboratories these patients are being cancelled or rebooked depending on the course of the respiratory illness and the urgency of the test.

- Suggest patients to arrive for the test alone, if feasible. If the patient must be accompanied, the accompanying person should also be screened for history of COVID-19 exposure risk.

It is very important to obtain the medical history of the patient the day before in order to make a judgment about the stress protocol to be used, to inform the patient about the procedure and ideally to obtain a verbal consent. This will allow reducing face to face interaction at the day

of the exam.

Considerations for the patients in NM department

At all phases of the pandemic the following measures are of critical importance [5-8]:

- Measuring temperature of all patients at arrival to the healthcare facility and/or nuclear cardiology laboratory. Consider non-contact thermometer if available.
- Face covering or masks.
- Physical distancing in waiting areas, ideally with 2 meters between persons.
- Limitation of interaction between inpatients and outpatients.
- Proper infection control of the scanners and equipment.

Protocol changes

If possible, consider pharmacologic testing preferably using vasodilator stress agents to decrease droplet exposure risk and minimize close contact between staff and patients [5-10]. Regadenoson may be the preferred stress agent if available and not contraindicated for the patient, since it requires a single 10 second infusion, after which providers can maintain distance from the patient. For laboratories with access to myocardial perfusion PET, this modality is preferred because of its time efficiency.

If after careful consideration, exercise testing is determined to be necessary, it is recommended to use a higher- level PPE for staff and surgical mask or face covering and gloves for patients [5-8, 13].

Image interpretation/Reporting

For patients tested with SPECT/CT or PET/CT instrumentation in regions with heavier COVID-19 outbreaks, some laboratories recommend a policy of reviewing the chest CT images before the patient leaves the laboratory in order to detect patients with infiltrates who might be unknowingly infectious with COVID-19 [14].

Conclusions

The ongoing Covid-19 pandemic has put an enormous strain on healthcare systems worldwide with severe disruptions in many medical services, including nuclear cardiology laboratories. As the pandemic is evolving, nuclear cardiology laboratories have to keep adapting according to the phase of the curve in order to balance between the safety of patients and healthcare professionals while also providing crucial cardiovascular assessments. This document could serve as a summary of guidance in COVID-19 era for healthcare professionals in nuclear cardiology, urging them to be vigilant, facing the challenges and coming out of it stronger than before.

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COVID-19 pandemic: Implications for radionuclide therapy in Nuclear Medicine departments

S. Koukouraki¹ MD, PhD, N. Kapsoritakis¹ MD, O. Bourogianni¹ MD

1. Department of Nuclear Medicine, School of Medicine, University of Crete, Greece

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Corresponding author:

S. Koukouraki, MD, PhD, Nuclear Medicine Physician, Assoc. Professor, School of Medicine, University of Crete, Greece, Head of the Department of Nuclear Medicine, University Hospital, Heraklion, Crete, Email: koukour@uoc.gr.

Introduction

The global COVID-19 health and economic crisis has forced people to adopt challenging rules of social distancing and self-isolation. Health care staff has been advised to change working routines to keep themselves and their patients safe.

Radionuclide therapy has had an increasing role in clinical practice. Most therapeutic radionuclide procedures have applications in oncology. Cancer patients are an especially fragile and vulnerable population with higher risk due to co morbidities and immunosuppression. COVID-19 is another risk that must be considered in treatment planning. Therapeutic, prophylactic, and supportive interventions may require changes for these patients [1].

The most common radionuclide therapies involve patients with differentiated thyroid cancer (DTC) who need radioiodine therapy (RAI), patients with neuroendocrine tumours (NETs) who need peptide receptor radionuclide therapy (PRRT), patients with hepatocellular carcinoma (HCC) who need therapy with radiolabelled microspheres, and patients with prostate cancer and bone metastasis who need radionuclide palliative therapy.

If infected, cancer patients could be at a higher risk for serious COVID-19 disease. Treatment decisions for thyroid cancer and NETs are challenging in this environment. Any decision to postpone therapy must be carefully considered, balancing risks and benefits. A risk of worsened prognosis due to delayed or suboptimal cancer treatment must be weighed against the risk of severe COVID-19 illness [2].

Dilemmas for decision making

Two main dilemmas affect the decision making: a) which patients can safely avoid treatment, or have their treatment be deferred and how long for; b) which patients need no changes in therapeutic management, and which ones need adaptations during the pre therapeutic period, during therapy, or during follow-up. Moreover, the most important issue is whether a patient will develop COVID-19 during the high-risk days after therapy.

Unfortunately, at present, no guidelines or strong recommendations are available regarding therapeutic management of cancer patients who need radionuclide therapy. Some recommendations are given in the literature, but they are broad and must be adapted to country- and hospital-specific resources and infrastructure. Nuclear medicine physicians must modify their everyday clinical practice, keeping in mind the safety of patients and staff.

The European Society of Medical Oncology (ESMO) and National Health Service (NHS) have suggested priorities for cancer therapy during the pandemic, taking into account the benefits of treatment. Priority must be considered when a therapeutic procedure is able to cure, to increase overall survival, to relieve symptoms and improve quality of life, or to minimise complications that could threaten the patient's life. On the other hand, the risk of COVID-19 must be assessed, considering the incidence of infection in the community and the likelihood of severe disease in cancer patients [3].

The National Institute for Health and Care Excellence (NICE) issued a prioritisation statement, amended in April 2020, considering the level of immunosuppression and functional capacity issues. Priority 1 includes patients with a high chance of cure (>50%); priority 2, intermediate chance of success (20% to 50%); priority 3, low chance of cure (10% to 20%); priority 4, very low curative ability (0% to 10%); priority 5, palliative therapy (chance of success >50%); and priority 6, palliative therapy (chance of success 15% to 50%) [4].

The most important consideration is the risk of postponement. In this regard, the British Society of Nuclear medicine (BNMS) has suggested a traffic light system (green, amber, and red categories) for cancelling a patient's appointment. The red category includes diagnostic and therapeutic procedures that should not be cancelled unless the patient is at risk. The amber category includes all procedures that could be cancelled or postponed after discussion with the clinician. The green category includes procedures that could be cancelled and rescheduled without discussion with a clinician. Most radionuclide therapies are in the red category [5].

Several variables must be considered before the final decision to administer radionuclide therapy some of them are cancer type (grading), incidence of COVID-19 in the community, patient age, performance status (ECOG >2), severity of immunosuppression, and co morbidities.

Peptide receptor radionuclide therapy for Neuroendocinetumors (PRRT)

Side effects of PRRT are more severe than those of radioiodine therapy (RAI). Myelosuppression, nephrotoxicity, and gastrointestinal symptoms are the most prevalent [6]. Several recommendations are given for patients with neuroendocrine tumors (NETs) who are candidates for PRRT but there are limited data on the risks of PRRT associated with COVID-19 disease.

Inclusion criteria and contraindications must be carefully considered. The decision to postpone therapy is based on the toxicity, the frequency of severe complications and bone marrow suppression, the histopathological report, and the status of the pandemic (severity, waves

of infection, peak incidence). For patients with low risk NETs, it may be safe to postpone PRRT for several months. However, intermediate- and high-risk patients need more specific consideration than low risk since the impact of delayed therapy on recurrence and mortality in this group remains unclear. PRRT, a salvage therapy, is included in the red traffic light category suggested by the BNMS [5]. More careful consideration is needed due to higher bone marrow suppression. It may be safer to defer treatment for a few months despite the limited risk due to the necessary self-isolation. Moreover, the scenario in which a patient becomes symptomatic of COVID-19 whilst radioactive complicates the decision.

In early March 2020, we recommended an individualised approach to manage candidates for radionuclide therapy during the COVID-19 outbreak, allowing for the safest conditions for both patients and hospital staff. For the pre therapeutic period, the following recommendations were suggested: a) contact by phone the day before the procedure to check for COVID-19 symptoms; b) suggest fourteen-day quarantine before the procedure, minimising the possibility of infection; c) consider a swab test 24-72h before treatment if available; and d) reconsider the dose to minimise the time of hospitalisation.

During therapy and the inpatient stay, the following adjustments are proposed: a) intensify general protective measures (masks, gloves); b) minimise staff contact with patients; and c) screen for COVID-19 symptoms before entering the therapeutic unit and minimise the patient stay in hospital.

Follow-up must be adapted in the COVID-19 era. A detailed medical report including information about the injected dose and radiation restrictions should be given. Radioprotection instructions must be provided to intensive care staff in case of admission for COVID-19 symptoms.

Palliative therapy for bone metastasis

Bone metastases occur in many patients with advanced prostate cancer. Bone pain interferes with quality of life and palliative therapy is required. Patients with bone metastasis are candidates for therapy with bone seeking radionuclide agents such as radium-223 dichloride ($^{223}\text{RaCl}_2$). Generally, short time side effects are mild and data concerning long term side effects are not available. Radium-223 dichloride can be administered as an outpatient procedure, so the risk of hospitalisation is low. Moreover, its uptake in cortical bone does not contribute significantly to marrow toxicity. Since the decision to postpone therapy is based on the toxicity, frequency of severe complications and bone marrow suppression, the impact of delayed therapy on recurrence and mortality in this group should be considered. No guidelines are available regarding radionuclide palliative therapy [4].

Conclusion

There are no evidence based international guidelines regarding the therapeutic management of cancer patients during the COVID-19 There is no "one size fits all" approach. Each patient must be assessed on an individual basis, taking into account the performance status, age, local prevalence of COVID-19 (state, region) the overall goals of treatment, and the risk of disease

progression if radionuclide therapy is postponed.

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Invited contribution

Nuclear Medicine and Oncology in the COVID-19 pandemic era

Emmanouil Panagiotidis MD, MSc, PhD, FEBNM

PET/CT Oncology Center 'Theageneio', Thessaloniki, Greece

Keywords: COVID-19 pandemic -Nuclear Medicine -Oncology -PET/CT

Corresponding author:

Emmanouil Panagiotidis MD, MSc, PhD, FEBNM, PET/CT Oncology Center 'Theageneio', Al Symeonidis 2 str, P.C 54007 Thessaloniki, Greece, Email: manospanagiotidis@yahoo.gr

Introduction

The coronavirus disease 2019 (COVID-19) global pandemic poses a significant challenge to the national health systems. Not only China, the first country that experienced the health crisis since last December, but the rest of the world, is facing an unprecedented global health crisis, the most serious crisis in a century, with social and economic impact. However, the most important impact of the new pandemic is the human impact. Till 4th of June 2020, coronavirus SARS-CoV-2, causing COVID-19 disease, has infected more than 65000.000 people and has been responsible for more than 386000 deaths globally [1].

The first priority of public health authorities is to contain and mitigate the spread and infection rate of the coronavirus SARS-CoV-2, distributing the number of infections over time and, if possible, reduce the incidence of the disease (COVID-19) it causes. A critical task for health systems confronted with the spread of the coronavirus is to protect the health of all citizens, so this requires that both diagnosis/testing and appropriate care should be readily available, affordable, and provided in a safe environment.

The health care systems of many developed countries failed to demonstrate a satisfactory response to the increased demand for acute care hospital beds, ventilators, emergency services, diagnostics tests, support equipment for their COVID-19 patients, availability of essential medicines, protective equipment for their staff etc.

Nuclear Medicine (NM) departments and their staff, in spite of the fact that not being in the front line of the pandemic response, have experienced a dramatic alteration in their daily clinical activity, trying to adapt their clinical routine to the new environment. There are several issued guidance from national and international organizations, trying to help to cope with

suspected or verified COVID-19 patients [2-12].

Patients with cancer are thought to be more susceptible and have higher morbidity and mortality rates from COVID-19 than the general population [13].

In the current article, our aim is to present measures, guidance and thoughts that should be considered for the cancer patients.

Cancer patients

It is well established that cancer patients are more susceptible to infections because of the immunosuppressive state caused by both anticancer treatments and surgery. A recent study shows that the risk of developing severe events in COVID-19 is statistically significant higher in patients with cancer, with a hazard ratio of 3.56 [14]. The authors suggest that postponing adjuvant chemotherapy or elective surgery for less aggressive cancers should be considered and that the increased risk for personal protection provisions should be emphasized for patients with cancer or cancer survivors [14]. Furthermore, more intensive surveillance or treatment should be considered for those patients with cancer who are infected with SARS-CoV-2. There are several COVID-19 cancer care guidelines to be followed [15-17].

ESMO tiered approach

The European Society of Medical Oncology (ESMO) has published recommendations that should be used as guidance for prioritizing the various aspects of cancer care in order to mitigate the negative effects of the COVID-19 pandemic on the management of cancer patients [17].

The tiered approach of ESMO in delivering a guidance for cancer patients during the COVID-19 pandemic is designed across three levels of priorities, namely: tier 1 (high priority intervention), 2 (medium priority) and 3 (low priority) - defined according to the criteria of the Cancer Care Ontario, Huntsman Cancer Institute and ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS), incorporating the information on the value-based prioritization and clinical cogency of the interventions [17].

High priority: Patient's condition is immediately life threatening, clinically unstable, and/or the magnitude of benefit qualifies the intervention as high priority (e.g. significant overall survival [OS] gain and/or substantial improvement in quality of life [QoL]).

Medium priority: Patient's situation is non-critical but delay beyond 6 weeks could potentially impact overall outcome and/or the magnitude of benefit qualifies for intermediate priority.

Low priority: Patient's condition is stable enough that services can be delayed for the duration of the COVID-19 pandemic and/or the intervention is non-priority based on the magnitude of benefit (e.g. no survival gain with no change nor reduced QoL).

Oncology and financial toxicity

The situation is evolving, and pragmatic actions may be required to deal with the challenges of treating patients, while ensuring their rights, safety and wellbeing.

Nevertheless, in addition to the apparent threats the COVID-19 poses, both to single individuals and health systems, this epidemic hides subtle menaces, like the distraction effect. It is mandatory, especially in a finite resource system, to balance the potential benefit of containment measures, such as postponing scheduled procedures, with negative health and social costs. Diverting the attention exclusively to the COVID-19 situation and overshadowing the everyday clinical practice may have substantial negative implications, especially for cancer patients. Re-allocating an excessive amount of health care personnel, both nurses and doctors, to the COVID-19 triage and management may stretch an already fragile system and potentially leave uncovered some vital activities, such as treatment administration, surgeries, and inpatient assistance. It is well established that delayed oncologic surgery may lead to disease progressions and result in tumors no longer resectable, leading to worse survival outcomes [18].

The same should be considered for neoadjuvant or adjuvant chemotherapy regimens administered with suboptimal timing. It should be emphasized that we are dealing with patients potentially cured by oncologic treatments. Therefore, any delay of these fundamental procedures, either intentional or due to shortage of personnel, should be avoided. The same risk is present for the people who have scheduled screening or staging activities (e.g. staging ^{18}F -FDG PET/CT for the staging of Hodgkin's lymphoma). People should be advised to maintain their scheduled appointments, if the procedure is feasible safely, or at least to promptly reschedule their appointment when the epidemic is expected to slow its pace. For patients with advanced disease, as oncologists know the enormous negative impact from disease progression in terms of both survival time and quality of life [18]. The inability to deliver palliative care to patients unable to move from their homes and the management of treatment side-effects are other significant concerns from a forced quarantine [19]. Patients with advanced disease, and no suggestive symptoms of COVID-19, should keep receiving planned chemotherapy or radiotherapy treatment and all the necessary diagnostic tests such as ^{18}F -FDG PET/CT, without unnecessary delays. Moreover, although postponing follow-up and cancer prevention appointments is a strategy to be considered, an excessive accumulation of visits or examinations risks burdening the national public health system over the next few months.

Nuclear Medicine aspect

Nuclear Medicine departments are already designed in a way as to minimize prolonged close contacts of patients with members of the staff, for radiation protection purposes. Therefore, some protective measures could be beneficial reducing the risk of SARS-CoV-2 spread. According to national and international guidance, hospitals designated as COVID-19 reference hospitals have postponed all outpatient appointments during the lockdown, to minimize patient traffic [5, 8]. As a result, most NM diagnostic scans (primarily performed on an out-patient basis) were also postponed during the peak of the pandemic [9].

In some cases where the demand for CT exams is high, NM resources (hybrid SPECT/CT and PET/CT scanners) were made available to Radiology departments to deal with, given that the

CT component was indeed a fully operational diagnostic CT scanner.

In March 2020, the "COVID-19 standardized reporting working group" of the Dutch Association for Radiology (NvVR) proposed a CT scoring system for COVID-19 [20]. They called it CO-RADS (COVID-19 Reporting and Data System) to ensure CT reporting is uniform and replicable. This assigns a score of CO-RADS 1 to 5, dependent on the CT findings. In some cases, a score of 0 or 6 may need to be assigned as an alternative. If the CT is uninterpretable then it is CO-RADS 0, and if there is a confirmed positive RT-PCR test then it is CO-RADS 6v [20,21]. The first study investigating the use of CO-RADS found a reasonable level of interobserver variation, with a Fleiss' kappa score of 0.47 (cf. 0.24 for PI-RADS and 0.67 for Lung-RADS) [21].

Nuclear medicine practitioners should be prepared for incidental findings of COVID-19 when patients undergo ^{18}F -FDG PET/CT scans for routine oncologic indications. An initial small case series published demonstrated that ^{18}F -FDG uptake is increased in ground-glass opacities in those with presumed COVID-19 [22]. A commentary in the same issue of the journal as this paper suggested that those with higher SUVs in lung lesions take longer to heal [23].

It should not be difficult to realize the urgency to delay the start of PRRT therapies and to postpone crucial for staging or recurrence PET/CT exams that are necessary for commencement of chemotherapy. One should weigh the consequences of exposing our susceptible patients and small cancer workforce to COVID-19 while ignoring oncology principles that we previously did not dare to disregard [24].

Critical decisions should be made because many patients with cancer present with locally advanced disease, and delaying treatment will result in progression and deterioration of their cancer as well as higher out-of-pocket expenditure for treatments, leading to further psychological distress. A crucial question in NM department regarding daily activities to be answered would be what will happen to an oncological patient that will develop a fever before PET/CT or SPECT/CT study. Should the patient be referred to an overstretched/overused and possible under-sourced COVID-19 medical team or the medical oncology team should investigate the high possibility of neutropenic fever?

Elective procedures and physical meetings are cancelled, and a small number of patients are to be seen per day. Patients are educated about possible additional risk while receiving chemotherapy (i.e., of contracting COVID-19 and having poorer treatment outcomes) and appointments are rescheduled [13]. Patients with a fever are referred to the emergency room. A minimum number of essential staff (in protective gear when available) will be rotated, prescriptions refilled remotely, and second-line and third-line palliative chemotherapy halted [24]. Subsequently, adjuvant therapy will be reduced when the risk of COVID-19 outweighs the benefit of treatment to decrease avoidable cancer deaths [24].

Nowadays that most countries are trying to gear up to normality, depending on each Hospital policy, the number of NM scheduled scans is generally increased [10]. Nuclear Medicine physicians had to decide which non-essential NM procedures could be postponed, and which essential procedures (diagnostic or therapeutic) had to proceed as scheduled. At this moment, we cannot tell when the current outbreak will end, as this will happen when the number of infected people fall to a critical threshold (the Critical Community Size), which is too low to sustain viral spread. In practice, this is going to be a result of the interplay of containment, emerging immunity,

viral evolution and weather [18].

However, looking back at past outbreaks and pandemics, complete eradication of a pathogen after its emergence is rarely achieved. It involves available and effective intervention methods to interrupt transmission, preferably vaccines that elicit immunity in broad segments of society.

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Nuclear thyroidology in pandemic times: The paradigm shift of COVID-19

Evanthia Giannoula¹ MD, MSc, PhD, Alexis Vrachimis² MD, PhD, Luca Giovanella³ MD, PhD, Vasiliki Chatzipavlidou⁴ MD, MSc, Ioannis Iakovou¹ MD, MSc, PhD

1. Academic Department of Nuclear Medicine, University Hospital AHEPA, School of Medicine, 54621 Thessaloniki, Greece, 2. Nuclear Medicine Department, German Oncology Center, University Hospital of the European University, Limassol, Cyprus, 3. Nuclear Medicine Department, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland, 4. Nuclear Medicine and PET/CT Department Theagenio Cancer Hospital, Thessaloniki, Greece

Corresponding author:

I. Iakovou, Academic Department of Nuclear Medicine, University Hospital AHEPA, School of Medicine, PC 54621 Thessaloniki, Greece, Email: iiakovou@auth.gr

Abstract

Since its outbreak in Wuhan, China the SARS-CoV-2 has become a public health emergency of international concern, impacting all areas of daily life, including medical care. Although not in the front line nuclear medicine practice should adjust their standard operating procedures. The adaptations and the flexibility that nuclear thyroidology, among other fields of nuclear medicine, should show during the pandemic, must focus not only in minimizing the risk of infection to staff, patients, and family members, but also in controlling the transmission of the virus while continuing to provide health care services which do not jeopardize patients' prognosis and quality of life. Favorable prognosis and indolent symptoms of most cases of thyroid diseases, allows postponements and rescheduling as well as alternative procedures, provided that they are cautiously considered for each case individually. The objective of the current paper is to provide guidance on how diagnostic and therapeutic management of patients with thyroid diseases can be safely and effectively adjusted during pandemic, in nuclear medicine settings.

Introduction

The crisis of COVID-19 (Coronavirus disease 2019) resulting from SARS-CoV-2 (severe acute respiratory coronavirus 2) infection has affected societies and economies around the globe and will permanently reshape our world as it continues to unfold. Since its outbreak in Wuhan, China in December 2019, the COVID-19 was characterized as a pandemic by the WHO in March 11th, 2020, and has already become an unprecedented challenge with very severe consequences [1].

As of May 26, 2020, the virus had been identified in 188 countries, accounting for 5.5 million confirmed cases and over 347.59 confirmed deaths [2]. On February 26, 2020, the first documented case in Greece was registered at the University General Hospital of Thessaloniki AHEPA and at the time of writing, there were 2889 confirmed cases and 173 confirmed deaths in the country [3]. Healthcare systems worldwide continue to struggle under the weight of the pandemic. Under these circumstances it is critical for health care settings, including nuclear medicine departments to rapidly adjust their standard operating procedures to cope with the pandemic cases and deliver their services. Several reports have been issued to serve as guidance on all aspects of nuclear medicine practice, in order to prevent a potential spread of the virus while being at the same time effective, safe and preserving their quality of essential services [4].

Nuclear thyroidology procedures are frequently not urgent e.g. due to the natural history/excellent survival of most cases of differentiated thyroid cancer [5] or by the possibility to cover/bridge with drugs in benign diseases [6]. However, imaging and treatment procedures for patients with thyroid conditions should always be identified and prioritized. Postponements and rescheduling as well as alternative procedures should be considered for each case individually [7]. The adaptations and the flexibility that nuclear thyroidology should show during the pandemic, must focus not only in minimizing the risk of infection to staff, patients, and family members, but also in controlling the transmission of the virus while continuing to provide health care services which do not jeopardize patients' prognosis and quality of life. Hence, the objective of the current paper is to provide a guidance on how diagnostic and therapeutic management of patients with thyroid diseases can be safely and effectively adjusted during pandemic, in nuclear medicine settings.

In April 1st 2020 the NHS published the list of cases characterized as extremely clinically vulnerable to, or at highest clinical risk from, COVID-19 [8]. The highest case-fatality rates have been reported in elderly and comorbid patients, particularly in those with cardiovascular or chronic respiratory diseases, diabetes, hypertension and cancer [9]. Although the majority of patients with autoimmune and malignant thyroid diseases are not included in them, the question arises as to what impact the novel coronavirus may have on them, to adjust their diagnostic and therapeutic management.

Benign thyroid conditions

Both hyper- and hypothyroidism are usually caused by autoimmune conditions. Since the outbreak of the pandemic, concerns have been raised on the risk of SARS-CoV-2 infection and related complications among patients affected by systemic autoimmune diseases [10]. Thyroid autoimmune disease is not known to be associated with increased risk of viral infections in general, nor is there an association with severity of the viral infection. However, there are studies arguing that Graves' disease (GD) is associated with neutropenia in one in seven patients at diagnosis [11]. On the contrary, it has been documented that viral infection may represent the initial inductive step in precipitating autoimmune thyroid disease in persons predisposed by virtue of having an immunoregulatory defect in the first place [12]. Since COVID-19 is a novel virus there are still not any reliable data suggesting that this group of patients are more vulnerable to (severe/

critical) illness or whether it can induce thyroid autoimmunity. However, patients on antithyroid drugs (ATDs) or steroids, although rarely may show adverse events associated with higher risk of infection [13]. ATDs have been associated with idiosyncratic neutropenia and agranulocytosis [14] occurring in 0.2%-0.5% of patients [15], which may lead to severe COVID-19 infection. Patients suffering from GD orbitopathy that are on steroid therapy at immunosuppressive dosage or other immunosuppressive agents such as mycophenolate are at higher risk as well [16], requiring individualized approach. Rare life-threatening thyroid emergencies resulting from decompensated thyrotoxicosis (thyroid storm), with resultant morbidity, could also be associated with higher risk for critical illness [17].

All the aforementioned cases that are at higher risk of (severe/ critical) infection with COVID-19, including patients with comorbidities or pregnant women, are advised to social distancing or self-isolation. Specifically, they are advised to stay at home and shielding by not attending any gatherings and strictly avoid contact with people displaying symptoms of COVID-19. There are also general principles they should follow to prevent the spread of airway and chest infections caused by respiratory viruses, including frequent and careful handwashing and respiratory hygiene [18].

Except for the impact of COVID-19 on patients who have been already diagnosed with thyroid diseases, it is not yet validated whether, a possible infection could affect thyroid function or hypothalamic-pituitary-thyroid axis in previously healthy population. Brancatella and colleagues presented recently the first case of subacute thyroiditis (SAT) related to SARS-CoV-2 [19]. SAT is a self-limited inflammatory thyroid disease characterized by neck pain, general symptoms, and thyroid dysfunction characterized by triphasic course (thyrotoxicosis, hypothyroidism, and euthyroidism) that usually lasts 3 months [20]. It is usually preceded by an upper respiratory tract infection. Direct and indirect evidence support a viral or postviral origin of this disease, and many viruses have been reported as potentially causative agents including COVID-19 [21]. Radioactive iodine uptake (RAIU), and thyroid scintigraphy (TS) are included in the diagnostic algorithm of SAT [22]. The risk of hypothalamitis potentially leading to central hypothyroidism in COVID-19 patients after remission has been raised as well. However, further data are required to evaluate it [23]. Therefore, nuclear medicine physicians should be alerted about the possibility of these additional clinical manifestations related to SARS-CoV-2 infection, not only in order to facilitate differential diagnosis but also to contribute in the tracing and management of persons, who had contact with COVID-19 cases and consult them accordingly [24].

In this context, until normalisation of the situation in our opinion it may be appropriate, for most cases with autoimmune thyroid disease, to adapt the thyroid related procedures as stated in Table 1.

Table 1. Procedures that should be adopted during the COVID-19 emergency for benign thyroid diseases.

Recommendations	Alternatives	Exceptions
Postponement of diagnostic and follow-up appointments for all patients with un/newly diagnosed thyroid diseases and those under treatment.	Telemedicine consultation and E-health services	Patients with thyroid emergencies (thyroid storm)
Postponement of any scheduled outpatient examinations including complete blood count (CBC), biochemical and serological labs for all cases	A block and replace regimen for management of thyrotoxicosis should be considered for patients with significant symptoms [25]	Patients with thyroid emergencies (thyroid storm)
		High risk patients for GD associated neutropenia at first diagnosis before any treatment
Postponement of any scheduled outpatient imaging/ functional test (Ultrasonography US, ^{99m}Tc / ^{123}I / ^{131}I scintigraphy with or without % uptake)	Discuss with clinician if there is a need to cancel/rebook	Patients with significant symptoms, indicating critical for life events (e.g. pressure to trachea, breathing difficulties) suggesting large goiter can undergo US (always with precaution and risk / benefit assessment).
	In case of high suspicion for SAT, evaluation of clinical manifestations should replace imaging/ functional tests. Glucocorticoid administration must be avoided.	Critical symptoms during acute phase of SAT may require administration of glucocorticoids [26]
Postponement of any scheduled outpatient follow up examinations	Rebook and consider a block and replace regimen for management of poorly controlled thyrotoxicosis	Patients with thyroid emergencies (thyroid storm)
Postponement of all non-urgent surgery	Rebook and administrate ATDs (always with precaution and risk / benefit assessment)	Patients with large goiter causing regional critical for life events (e.g. pressure to trachea, breathing difficulties) (always with precaution and risk / benefit assessment).
		Severely symptomatic Graves' disease that has not responded to medical therapy [27]
Postponement of all radioactive iodine (^{131}I) therapeutic administration	Rebook and consider a bridging with ATDs until definitive therapy unless contraindicated	Patients at risk for ATD's neutropenia/ agranulocytosis
Administrate ATDs in all thyrotoxic cases unless contraindicated		Patients at risk for ATD's induced neutropenia/ agranulocytosis

Malignant thyroid disease

Delivering care for patients with cancer during this crisis is challenging given the serious complications from SARS-CoV-2, and the likely higher lethality of COVID-19 in immunocompromised hosts [28]. The prevalence of cancer in those with COVID-19 varied across reports from 1% to 6% [29, 30], while 8% of the patients admitted to the intensive care unit [ICU] for COVID-19 have been documented to have either active or prior history of malignancy [31]. Current literature argues that the likelihood of a severe illness from COVID-19 is higher among adult patients with cancer, particularly those with hematologic malignancies and lung cancer [32].

Luckily, this is not the case for the majority of thyroid cancer (TC) patients. TC patients who have previously received treatment for thyroid cancer such as surgery, with or without radioiodine (remnant ablation or radioiodine therapy), as well as the vast majority of those with suspicious thyroid nodule(s) or neck lymphadenopathy due to TC are not considered at higher risk of viral infection including from COVID-19 [33] with the exception of stage IV patients with severe lung metastatic disease or in case of other comorbidities. On the other hand, interestingly, the significant oncogenicity and metastatic potential, due to changes to the tumor microenvironment, subsequent to viral infection, has been documented for thyroid cancer [34, 35]. However, there are no data available supporting the oncogenic potential of the novel coronavirus.

It is well known that the minority of TC patients that are receiving multikinase inhibitors (MKIs), or other systematic treatments are at increased risk of developing adverse events [36], jeopardizing a possible infection and more critical illness from coronavirus [37]. Furthermore, patients who have previously received external beam radiotherapy (EBRT) to the neck may be at increased risk of severe illness as well [38]. All the aforementioned cases that are at higher risk of (severe/ critical) infection with COVID-19, including patients with comorbidities or pregnant women, are advised to social distancing or self-isolation as well as to following general principles to prevent a possible infection. Their therapeutic and diagnostic management in the nuclear medicine setting should be cautious, individualized and performed prior to careful risk assessment of each case (Table 2).

Except for the patients who have been previously diagnosed with TC, clinicians are also asked to manage newly or still undiagnosed cases of thyroid malignancies. The most common manifestation of TC is thyroid nodules. Although thyroid nodules are quite common findings in general population, depending on the diagnostic approach [39], a small minority of them turn to be malignant [40]. There is still no evidence that patients with thyroid nodules are more vulnerable to a possible infection. However, their clinical management including thyroidectomy or procedures such as Fine Needle Aspiration (FNA) biopsies, thyroid ultrasonography and scintigraphy which are by definition non-urgent and scheduled in advance, may increase that risk when performed without appropriate preventive measures [41, 42]. Since less than a half of COVID-19-infected individuals are documented to be asymptomatic [43], elective procedures should be performed with special attention to avoid virus transmission. Moreover, recent data suggest that surgery may accelerate and exacerbate disease progression of COVID-19 [44]. Hence, they should be performed strictly when they are considered to be medically necessary. Special recommendations for most cases with thyroid cancer management are listed in Table 2 [6].

Table 2. Procedures that should be adopted during the COVID-19 emergency for thyroid cancer.

Recommendations	Alternatives	Exceptions
Postponement of diagnostic appointments for all patients with un/newly diagnosed thyroid cancer and those under suppressive treatment.	Telemedicine consultation and E-health services	Patients with a history, clinical characteristics and laboratory examinations indicating aggressive thyroid disease e.g. anaplastic (ATC), medullary (MTC), metastatic or other diseases e.g. lymphoma
Postponement of any scheduled outpatient examinations including biochemical and serological labs for all cases	Reschedule	Patients suspected of thyrotoxicosis in the setting of metastatic thyroid carcinoma
		High risk patients on serious suspicion for recurrence, under special precautions
Postponement of any scheduled outpatient imaging/ functional test (Ultrasonography US, post-thyroidectomy ¹²³ I/ ¹³¹ I scintigraphy with or without %uptake, ¹⁸ F-FDG PET/CT)	Discuss with clinician if there is a need to cancel/rebook	Patients with significant symptoms, indicating critical for life events (e.g. pressure to trachea, breathing difficulties) suggesting large goiter can undergo US (always with precaution and risk / benefit assessment).
Postponement of any scheduled FNA biopsy	Reschedule or consider reevaluation of previous clinical, imaging and functional findings that enable differential diagnosis.	In cases of calcitonin levels >10 pg/ml, FNA should be offered as early as possible
	Telemedicine consultation and E-health services	
	Assessment of calcitonin levels in patients with with family history of MTC	
Postponement of any scheduled outpatient follow up examinations	Rebook or consider serum Tg and TgAbs measurements with or without stimulation (under appropriate precautions).	High risk patients on serious suspicion for recurrence, under special precautions
Postponement of all non-urgent surgery even those for cytologically confirmed differentiated thyroid cancer (due to limited availability of personal protective equipment, staffing, bed capacity and the possibility of acceleration and exacerbation disease progression of COVID-19)	Rebook	Patients with large goiter causing regional critical for life events (e.g. pressure to trachea, breathing difficulties)
		When there are clinical or paraclinical signs pointing to an aggressive form of cancer, including gross extrathyroidal extension, recurrent nerve palsy, local invasion with esophageal, vascular or tracheal involvement, massive lymph nodes infiltration, ATC & MTC.

		Pediatric patients with preoperative > cT3cN1 tumors, of cytological/imaging features indicating higher risk disease
Postponement of all radioactive iodine (¹³¹ I) therapeutic administration:	Rebook	Treatments in which a redifferentiation therapy has taken place.
Patients on suppressive doses of levothyroxine (i.e have a TSH target of <0.1mU/l) should continue their current dose	Modify via telemedicine consultation	Patients with non previously existing symptoms of hypo/hyperthyroidism
Postponement of any MKIs or chemotherapy	Discuss with clinician if there is a need to cancel/rebook	Imminently threatening disease progression expected to require intervention and/or to produce morbidity or mortality in <6 months (e.g. pulmonary lesions or lymphadenopathy likely to rapidly invade airways, produce dyspnoea, or cause bronchial obstruction)
Postponement of any external beam radiation therapy	Discuss with clinician if there is a need to cancel/rebook	Very strictly selected cases to cope with "local phenomena"(e.g. pressure to trachea, breathing difficulties) (always with precaution and risk / benefit assessment).

General principles

Atomic Energy Agency (IAEA) has developed guidelines to help nuclear medicine departments adapt operating procedures to minimize the risk of COVID-19 infections among patients, staff and the public, based on WHO's "COVID-19: Operational Guidance for maintaining essential health services during an outbreak" [45]. Among other suggestions, specific training of all staff members in identifying COVID-19 symptoms, hygiene procedures, handling COVID-19 patients, disinfection procedures, and use of personal protective equipment (PPE) and establishment of effective patient flow (screening, triage, and targeted referral) at all level and identifying mechanisms to maintain the availability of essential equipment and supplies are sine qua non to ensure safe and effective nuclear medicine services and should be religiously adapted when treating patients with thyroid conditions[4].

Conclusions

The COVID-19 outbreak has become a public health emergency of international concern, impacting all areas of daily life, including medical care. Although not in the front line, there are many issues raised for nuclear medicine departments concerning the current COVID-19 outbreak. Among other fields, nuclear thyroidology should rapidly adjust standard operating procedures to cope with the pandemic cases and deliver their services safely and effectively, by ensuring both patients' favorable prognosis and prevention of viruses' transmission. Nuclear thyroidology

procedures are elective and frequently non urgent due to the natural history of most cases of benign and malignant thyroid disease. However, special and cautious considerations and measures should be taken to protect our patients and staff. The lessons learned from the current experience should improve preparedness and address possible deficiencies in case of new outbreaks in the future.

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Non-Oncological PET/CT imaging during SARS-CoV-2 pandemic

P. Exadaktylou¹ MD, MSc, N. Papadopoulos² N. MD, MSc, V. Chatzipavlidou² MD, MSc, F. Giammarile³ MD, PhD

1. 3rd Department of Nuclear Medicine, Aristotle University of Thessaloniki Medical School, Papageorgiou General Hospital, 56403 Thessaloniki, Greece, 2. Nuclear Medicine Department, Theagenio Cancer Hospital, 54007, Thessaloniki, Greece, 3. Nuclear Medicine and Diagnostic Imaging Section, Division of Human Health, International Atomic Energy Agency, PO Box 100, 1400, Vienna, Austria.

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Corresponding author:

Paraskevi Exadaktylou MD, MSc, 3rd Department of Nuclear Medicine, Aristotle University of Thessaloniki Medical School, Papageorgiou General Hospital, 56403 Thessaloniki, Greece, TEL: +306947271674, Email: voulaexadaktylou@hotmail.com

Introduction

In December 2019 a new β -CoV, Severe Acute Respiratory Coronavirus- 2 (SARS-CoV-2), has been identified in Wuhan Hubei Province, China. Within a few months it spread rapidly to more than 114 countries and the disease, Coronavirus disease 2019 (COVID-19), was declared pandemic on 11th February 2020 by the World Health Organization (WHO) [1]. Until 20 June 2020 8:09 am, 8,465,085 cases of COVID-19 were confirmed globally, with 454,258 deaths [2]. The first incidence in Greece was documented on 26 February 2020 in Thessaloniki and up to 20 June 2020 8:09 am, 3,227 confirmed cases of COVID-19 were reported, with 188 deaths [3]. At the time of writing USA and Brazil, are the countries with the highest disease burden [4]. Governments have imposed a variety of suggestions and restrictions in order to control the spread of the virus, focusing mainly on social distancing, self-isolation, personal hygiene and personal protective equipment (PPE) [5]. Greece was one of the countries that implemented early drastic measures [6] thus succeeding in controlling the virus transmission; having a profound economical effect though.

SARS-CoV-2 background

Coronaviruses (CoVs), are RNA viruses of Coronaviridae family (order Nidovirales) which are divided into four genera, α -CoVs, β -CoVs, γ -CoVs and δ -CoVs, and are the cause of respiratory and intestinal infections to humans [7]. SARS-CoV-2 is a member of β -CoVs, like SARS coronavirus (SARS-CoV) and MERS coronavirus (MERS-CoV). To our existing knowledge, bats are the natural hosts of CoVs, and in the case of SARS-CoV-2 pangolin is regarded to be the intermediate animal host, through which human transmission occurred. This new RNA virus enters the cells via endocytosis, through angiotensin-converting enzyme 2 (ACE2), a glycoprotein receptor which is expressed in lung alveolar epithelial cells, heart, kidney, and intestine [8]. COVID-19 has miscellaneous manifestations, as it can present from asymptomatic infection to mild or severe pneumonia and acute respiratory distress syndrome (ARDS), leading to incubation and death [9]. Older age, male sex and comorbid diseases such as cardiovascular disease, diabetes, chronic respiratory disease, hypertension and cancer, are associated with high mortality rates [10, 11]. The WHO publishes online guidance for health care workers such as, directions for screening and management of COVID-19 patients [12], catalogue with all the essential medical devices and equipment [13], as well as criteria for releasing patients from isolation [14], and is constantly updated as the disease progresses and knowledge is enriched.

Non oncological PET/CT

Positron emission tomography/computed tomography (PET/CT) is a valuable diagnostic tool for the diagnosis, staging and assessment of therapeutic response, of both malignant and non-malignant diseases. As for the latter, the field is steadily growing and it encompasses infectious, inflammatory and granulomatous diseases as well as neurological and cardiac conditions [15, 16]. In Greece, non-oncological PET/CT applications embrace all the mentioned conditions above, except for the neurological ones. Patients referred to nuclear medicine departments for a non-oncological PET/CT scan, are in the majority outpatients, however with a history of many hospital visits during the diagnostic workup, or are already hospitalized. The majority has been tested for Covid-19 thoroughly, but the risk of nosocomial transmission is high.

At the peak of the pandemic, the number of routine PET/CT scans performed had been reduced, in consultation with the referee clinician as necessary, but as the daily workflow returns to “normality”, all the personnel should be on alert. At the time of writing there are no guidelines published regarding the prioritization of PET/CT examinations and most nuclear medicine departments have implemented their own “traffic light system” [17] in compliance with the local disease burden and patient’s flow.

The following measures are guidance and not guidelines, based on our daily practice and review of the literature.

General precautions [18-23]:

- Appropriate training of nuclear medicine staff for correct use of PPE [24], personal and environmental hygiene and early recognition of symptoms of Covid-19.
- Schedule all appointments by phone while receiving a detailed medical history including symptoms related to Covid- 19 (fever, cough, fatigue, dyspnea, nausea/vomiting, diarrhea, abdominal pain, pink eye/conjunctivitis, runny nose/nasal congestion, loss of taste or sense of

smell), occupational history, travelling history to countries or territories with increasing cases of Covid-19 and contact history (Fever, Travel to high-risk areas, Occupational history, Contact history and Clustering of cases, FTOCC questionnaire). The examination should be postponed when Covid-19 is suspected and a RT-PCR test should be performed for SARS-CoV-2.

- One day prior to examination patients should be contacted for their attendance and medical status.
- Patients should arrive 15 minutes before their appointment, preferably alone or accompanied with one person when it is required, with the proper PPE and hand hygiene. Perform FTOCC questionnaire and consider temperature screen.
- Patient's waiting area should not be crowded and must be equipped with hand sanitizers, tissue boxes and masks. Keep three feet distance between sited patients. All areas should be disinfected appropriately at least once every two hours.
- NM departments with more than one PET/CT cameras should dedicate one scanner for patients with suspicious symptoms for Covid-19 and for patients with confirmed Covid-19. Otherwise, schedule those patients late in the afternoon.
- Always review the CT component of PET/CT on lung windows for incidental findings of infection [25]. If it is positive, contact the referring clinician and inform the infectious disease consultant of your hospital unit, to arrange patient's transfer to the designated Covid hospital unit for further examination. Clean and disinfect the operating table, PET/CT scanner and the environment promptly, according to the local infection prevention and control team (IPCT).

PET/CT examinations

- For evaluating fever of unknown origin should not be postponed as in many cases malignancy is the potential cause [26].
- In septic patients should not be postponed [27].
- For evaluating vascular graft infection with a potential need of surgery should not be postponed [28].
- In cardiac conditions [29]:
 - ❖ In cases of suspected prosthetic or device infection PET/CT scan should not be postponed (priority 1). In follow-up evaluation: ^{18}F -FDG PET/CT examination for prosthetic valve infective endocarditis (Priority 2 or 3) should be postponed.
 - ❖ ^{18}F -FDG scan can be used as an alternative to transesophageal echocardiography in suspected endocarditis in a patient with fever and bacteremia, as the latter carries a very high droplet risk exposure for operators.
 - ❖ In cases of heart failure where transthyretin cardiac amyloidosis is suspected perform ^{18}F -FDG PET/CT for sarcoidosis (Priority 1 or priority 2 or 3) in select cases or postpone the exam.
 - ❖ In cases of stable angina (with no urgent revascularization plan) ^{18}F -FDG PET/CT scan for myocardial viability can be postponed (Priority 2 or 3)
- Routine PET/CT scans for evaluating treatment response in stable patients can be postponed.

Conclusion

The world is enmeshed in a significant health crisis which has completely altered our lives and has affected global economy. COVID-19 is spreading rapidly, and as we are in the midst of a storm, concerted efforts and compliance with protective and preventive measures are imperative. Nuclear medicine departments have implemented a variety of procedures in order to reduce the possibility of transmission. The lack of adequate treatment and vaccine, as well as the possibility of a second wave of COVID-19, demands caution and preparedness.

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Recommendations for nuclear neuroimaging of patients with neurological disorders in the COVID-19 era

Varvara Valotassiou¹ MD, PhD, George Angelidis¹ MD, Panagiotis Georgoulas¹ MD, PhD

1. Nuclear Medicine Department, University Hospital of Larissa, Greece

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Corresponding author:

Panagiotis Georgoulas MD, PhD, Nuclear Medicine Department, University Hospital of Larissa, Greece, Email: georgoulas@hotmail.com, Phone: +302413502918, Fax: +302413501851

Abstract

The novel coronavirus disease 2019 (COVID-19) pandemic has changed people's normal lives in a very short time causing extensive infections and mortality, which required the national health systems to be adapted to new situation. Changes in healthcare services included modifications of standard procedures in nuclear medicine departments in order to limit COVID-19 spreading and protect patients and personnel. Here, we recommend management of patients with neurological diseases and especially dementia and movement disorders, who are referred for neuroimaging with nuclear medicine techniques.

Introduction

On March 11, 2020, the World Health Organization stated novel coronavirus disease 2019 (COVID-19) a pandemic due to the rapid worldwide spreading of the disease [1], the first cases of which were recorded in Wuhan, China, on December 2019 [2]. Since then, COVID-19 pandemic raised a great international concern on public health.

COVID-19 is an acute infectious syndrome affecting the lower respiratory system, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which belongs to the beta coronavirus genus and enters the host cells through the angiotensin-converting enzyme 2 (ACE2) receptor [3, 4]. Other organs and systems may also be affected, such as the Central Nervous System (CNS), while in severe cases COVID-19 may lead to death. The spread of the disease occurs mainly through respiratory droplets emitted during coughing or sneezing and avoidance of close contacts, intensive personal hygiene, frequent washing of hands and use of mask and gloves are the most important precautions to limit the disease spread (5,6). COVID-19 diagnosis is based on testing of patients' biological specimens, while treatment includes isolation of patients and manipulation of their clinical status [5, 6].

Patients with movement disorders or dementia are vulnerable to COVID-19 infection due to old age, comorbidities and increased risk of respiratory dysfunction [7-9]. These patients, especially the demented ones, depend on their family or professional caregivers for their survival which may either limit patients' care due to avoiding close contact according to public health recommendations or suffer themselves from COVID-19 infection, increasing the risk of spreading. Moreover, demented patients may be unable to understand and remember public health recommendations, while the limited care may result in omitting treatment and worsening of cognitive function [9, 10]. COVID-19 infection, increased psychological stress and the subsequent reduction of dopaminergic medications efficacy may cause motor deterioration in patients with movement disorders during infection, as well as during the convalescence period [7, 8, 11, 12]. Additionally stress may unmask a subclinical neurodegenerative movement disorder, increasing the new cases during COVID-19 pandemic [8]. On the other hand, the diagnosis of new cases of dementia and Parkinsonism in the COVID-19 pandemic may delay or be disregarded since neurologists are redeployed to manage emergencies, limiting the available time for the investigation of cognitive and movement disorders [13, 14]. However, medical care of patients with dementia and movement disorders should not be neglected or ignored during this challenging period [7, 8].

It has also been reported that neurological symptoms of COVID-19 may share some common features with Parkinson Disease such as olfactory disorders and motor problems, as well as with dementia such as impairment of mental status and executive functions with deterioration of attention and orientation [15-17]. Another emerging issue is the development of parkinsonism after encephalitis due to COVID-19 infection [7, 18].

All the above issues suggest the need for screening and monitoring of these patients and nuclear neuroimaging may be useful in this purpose helping in the diagnosis of new cases, the differential diagnosis between neurological manifestations of COVID-19 and neurodegenerative diseases and the evaluation of disease progression.

COVID-19 pandemic changed significantly the services of nuclear medicine imaging departments [19, 20]. By the time of this manuscript preparation, there is no published literature about adaptations in neurological nuclear imaging of patients with neurological disorders. It should be kept in mind that when these patients are referred for nuclear neuroimaging, a COVID-19 infection, especially in demented ones, may not be known since the underestimation of symptoms by the patients due to cognitive decline and the isolation could impact the diagnosis, while the possibility of caregivers' COVID-19 infection should also be considered. Here we describe modifications and recommendations on nuclear medicine imaging procedures in these patients and mainly in patients with dementia and movement disorders. The purpose was to share our experience on the modifications we made in our department and guide nuclear medicine physicians in their daily routine to best manage these patients with safety, minimizing the risk of infection during the COVID-19 pandemic. The main topics covered are the management of patients with neurological disorders and either with confirmed or suspected COVID-19 or COVID-19 free, who are referred for nuclear medicine neuroimaging, the prevention of COVID-19 spreading in the nuclear medicine personnel or other patients undergoing nuclear medicine studies at the same time, the rescheduling of diagnostic procedures in these patients, and the management after the end of pandemic emergency.

Planning a nuclear medicine neuroimaging study in patients with neurological disorders

[9, 21-26]

- The referring neurology physician should be asked to ensure the necessity and urgency of the nuclear neuroimaging procedure and provide detailed information about patient's symptoms related to probable or possible COVID-19 infection.
- It is recommended to postpone such procedures in patients with neurological disorders and confirmed COVID-19 infection or in suspicious cases at least until the test results of COVID-19 are completed, in order to avoid spreading in personnel and other patients.
- Appointments for nuclear neuroimaging studies should be based on phone communication and an inquiry should be made about the presence of COVID-19 symptoms such as fever, cough, fatigue, breathing difficulties, diarrhea, changes in taste and smell. Information about recent travelling in countries with high COVID-19 infection rates or contact with a positive or suspicious case the last 14 days should also be obtained. The previous questionnaire should be made in patients, as well as in their caregivers and the person who will accompany the patient in the nuclear medicine department, considering the need of demented patients or patients with advanced movement disorders for the presence and care of other people.
- The number of patients scheduled to undergo a nuclear medicine procedure in the daily routine program, should be limited according to the size of the "hot" waiting room to avoid crowding and possible spreading of COVID-19 infection between patients.
- In case there is a change in the timetable, patients and accompanying persons should be informed and suggested to wait at their home or outside the hospital (ie in their car) until the time of their appointment.
- If it is not possible to postpone the nuclear medicine examination in patients with neurological disorders, it would be preferred to make changes in daily program scheduling patients with confirmed or possible COVID-19 infection on the same day or at the same time, while non infected patients on a different day or time.

Upon arrival at the Nuclear Medicine department

[9, 21-26]

- It is recommended that demented patients or unable patients with movement disorders should be accompanied by only one person.
- Patients and accompanying persons should be asked to wear face masks and gloves on their arrival which should be removed and replaced by new ones after cleaning of hands with a sanitizer containing 60-95% alcohol. Face masks and gloves should be put on during the preparation of patient, the staying in the waiting room for the biodistribution of the injected radiopharmaceutical and acquisition. The accompanying persons should guide and help patients.

- Measurement of body temperature in both, patients and the accompanying persons, upon arrival. In cases of fever, nuclear neuroimaging procedure should be canceled and the patient (or the accompanying person) should be transferred to the competent hospital clinic for additional clinical evaluation and COVID-19 testing.
- A distance of at least 1 m should be kept between the reception desk and the patients or the accompanying persons. Alternatively, a barrier placed in front of the reception desk is also desirable.
- Personnel of the Nuclear Medicine department with high risk factors such as cancer, cardiovascular disease, diabetes and chronic respiratory disease are recommended to avoid participating in patients imaging procedures and offer services remotely. Additionally, personnel should monitor themselves for fever and signs of infection and inform the director of the department about their health status.
- Nuclear Medicine physicians obtain a history from patients or the accompanying person, monitoring for COVID-19 related symptoms and asking if there are available results of other pathological and clinical tests. The suspicious cases are directed competently.
- Printed material - brochures may be available in the reception area, as well as in the post administration “hot” waiting room to promote instructions for hygiene.

Preparation of patients

[9, 21-27]

- The personnel of the Nuclear Medicine department, and especially nurses and technologists, who are in the closest contact with patients, are advised to wear the appropriate personal protective equipment (PPE). Level 1 PPE includes disposable surgical mask, latex gloves and gown, and is usually sufficient for Nuclear Medicine personnel. Goggles for eye protection and head and shoe covers are also suggested. Level 2 PPE is suggested in cases of dealing with patients with confirmed or probable COVID-19 infection and the main differences from level 1 PPE are the use of N95 respiratory filtering mask and disposable protective suit.
- All Nuclear Medicine staff should be trained in the correct use and order of wearing and removing PPE, as well as in the decontamination of infected equipment. Hand hygiene with a 60%-95% alcohol -based hand sanitizer or washing with soap and water for at least 20s and then dried with a paper towel, should be performed before and immediately after removing all PPE. Surgical masks should be worn for no more than three hours, while respiratory masks should not be worn for more than eight hours. Respiratory masks can be reused after replacing the filter, while the rest disposable materials should be placed in proper waste receptacles.
- Nuclear Medicine personnel should keep a distance of at least 1m from patients or accompanying persons, when it is possible. During placing intravenous catheters or injecting the

radiopharmaceutical, patients are advised to turn their head to avoid direct and close contact with the personnel's face. In cases of patients unable to cooperate, the accompanying person is asked to keep their heads in the suggested position, trying not to cause anxiety to patients.

“Hot” waiting room

[9, 21-26]

- “Hot” waiting rooms should be well ventilated.
- Patients and accompanying persons should not sit closer than 1m from other patients.
- If it is possible, patients with confirmed or possible COVID-19 infection should be placed in a separate waiting area.
- Asepsis and cleaning of the “Hot” waiting room, toilets and doorknobs should be done regularly.
- Hand washing facilities should be available in “Hot” waiting room.
- Patients and accompanying persons are advised to clean hands frequently. Accompanying persons should encourage patients with hand hygiene, keeping mask in place, not touching their faces, nose, mouth and eyes, covering their mouth and nose when coughing or sneezing and maintain physical distance from other patients, as well as protect them from wandering.
- Patients and accompanying persons are advised to avoid sharing various items (mobile phones, pencils etc) with other patients.

Acquisition phase

[21-26]

- Imaging should start in time, without significant delay.
- In poorly cooperated demented patients or in patients with inability to lie still for the time required for the completion of acquisition protocol, proper adjustments should be made, reducing the scanning time (without decreasing the diagnostic value of the study) to minimize anxiety in patients, as well as the risk of movement and repetition of the acquisition.
- Accompanying persons of demented patients may be present during acquisition in cases the patients are aggressive or unable to understand and comply with the instructions.
- Covering of keyboards, computer mice, and other imaging equipment with a transparent film could prevent contamination of these surfaces.

After the end of examination

[21, 22, 25]

- Cleaning of the wards, toilets, desks, chairs and doorknobs with chlorine containing solutions or disinfectants dedicated for use in hospitals.
- Cleaning camera equipment, including gantries, image monitoring station, computer mouses and keyboards with disinfectant or chlorine solutions, according to the manufacturer's instructions.
- Cleaning should be done regularly, while in cases of confirmed or suspected COVID-19 infection, it should be done immediately after the contact with the patient. In such cases, a level 2 PPE should be used during cleaning.
- The bed covering sheet should be changed after each scan.
- Patients and personnel dispose PPE in certain waste receptacles.
- Patients and accompanying persons are asked to leave the Nuclear Medicine department quickly after the termination of the study to avoid crowding and possible spreading of infection.

Interpretation of data

- Besides the standard interpretation of neuroimaging studies in patients with neurological disorders, nuclear medicine physicians should be aware of incidental findings related to CNS infection from COVID-19, since cases of acute cerebrovascular disease, intracerebral haemorrhage, meningitis and encephalitis in COVID-19 patients have been reported [28-30].

Future perspectives and conclusion

COVID-19 pandemic has affected significantly the standard procedures in Nuclear Medicine departments, leading to modifications in order to face this rapidly changing situation. More specifically, the scheduling of nuclear neuroimaging procedures in patients with neurological disorders, who present cognitive decline or movement disabilities, requires particular manage in order to promote safe studies to these patients, minimizing the risk of possible infection.

After the end of pandemic, hygiene rules including hand cleaning, use of face mask and distancing, as well as reduction of inappropriate or unnecessary examinations should be considered in order to be protected and avoid second waves of COVID-19 infection. Additionally, the postpone of routine scans has created great demands and pressure in rescheduling appointments, however this has to be done carefully and stepwise to avoid crowding in the nuclear medicine departments. Although nuclear neuroimaging of patients with dementia and movement disorders is not considered an urgent case, however it offers significant benefits in patients' management and should be performed on a normal basis after the end of the pandemic, following the suggestive instructions for staff and patients safety.

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COVID-19 and cancer: Revisiting “The comfort zone”

Spyros Retsas MD, FRCP, Retired Consultant Medical Oncologist

*Formerly at Charing Cross Hospital, Department of Medical Oncology, Melanoma Unit
London, U.K.*

Corresponding author:

Spyros Retsas MD, FRCP, Retired Consultant Medical Oncologist, “Parnassus”, 15 Park Hill,
Loughton, ESSEX, IG10 4ES, U.K. Email: sretsas@msn.com

*Καὶ τὸν μὲν καρκίνον ἀρχόμενον ἰασάμεθα εἰς μέγεθος δὲ ἀξιόλογον ἀρθέντα ἄνευ χειρουργίας,
οὐδεὶς ἴασατο*.*

Galen (2nd c. A.D.)

It is estimated that 1.7 billion people, 22% of the global population, have at least one underlying condition increasing their risk of severe COVID-19, if infected; of these, approximately 349 million people (4% of the global population) would require hospital care [1].

Globally, in 2018, cancer accounted for an estimated 18.1 million new cases and 9.6 million cancer deaths worldwide [2].

Patients with cancer, intrinsically or iatrogenically immunosuppressed, are more vulnerable to a serious infection with the SARS-CoV-2 virus, than their peers of the same age.

Given the pressures on health care infrastructures from the highly contagious Sars-CoV-2 virus, priorities for diagnostic and treatment procedures for cancer, have been deferred or severely disrupted, even in countries with the most advanced health care systems [3, 4].

Although cancer emergencies such as superior vena cava syndrome or spinal cord compression, are likely to receive urgent attention as the benefits of treatment outweigh the possible risk of a SARS-CoV-2 infection [3], intuitively, disruption of planned or ongoing treatment for cancer, irrespective of stage, may result in an adverse outcome. Yet, even the opposite has been considered, with the possibility that in a patient with cancer harbouring a COVID-19 infection, anticancer therapy might be protective against the cytokine storm caused by SARS-CoV-2 [5-8].

Liang V Tang and Yu Hu [9], commenting on two studies from China that investigated patients with cancer and COVID-19, report a case fatality rate of up to 20%, much higher than that of 1.8-7.2% of the community [9-11]. Patients with haematological malignancies had poorer

prognoses than did those with solid tumours. Notably, however, cancer stage was not introduced in the multivariate analyses conducted, as this variable was only collected for solid tumours [11].

Lee and colleagues reporting for the UK Coronavirus Cancer Monitoring Project (UKCCMP) analysed 800 patients with a diagnosis of cancer and symptomatic COVID-19. They were unable to identify evidence that cancer patients on cytotoxic chemotherapy or other anticancer treatment were at an increased risk of mortality from COVID-19 disease compared with those not on active treatment and concluded that mortality from COVID-19 in cancer patients appeared to be principally driven by age, gender, and comorbidities [12].

Kuderer and colleagues reporting on 928 patients meeting their inclusion criteria for analysis from the US COVID-19 and Cancer Consortium (CCC19) database, found that among patients with cancer and COVID-19, 30-day all-cause mortality was high and was associated with general risk factors and risk factors unique to patients with cancer. Notably, these researchers did not find any association between recent surgery and 30-day all-cause mortality. As the authors admit, a weakness of this analysis was the inability to compare their studied cohort with patients with cancer without COVID-19 and patients without cancer with COVID-19. The authors emphasised the need of longer follow-up in order to completely understand the effect of SARS-CoV-2 on outcomes in patients with cancer [13].

As of July 1st, 2020, figures from NHS England showed that 840,742 people were waiting for tests, of whom 468,622 had been waiting more than six weeks. Cancer charities in England have raised concerns that “an excess of 18,000 people could die because of delays to diagnosis caused by the pandemic, with late-stage cancers harder to treat than those *caught early*” [14, 15].

An emotionally charged documentary by the British Broadcasting Corporation (BBC1, Panorama on 6th July 2020), made this apparently obvious to the viewers, indicating that the number of anticipated excess cancer-deaths, could be considerably higher.

On balance, an increase in *case fatalities* from certain neoplasms is plausible and perhaps inevitable during the COVID-19 pandemic.

However, will deferred screening procedures for detection of pre-symptomatic cancers or delays in initiating treatment for malignancies uncovered from such screening, alter materially the landscape of cancer in the months and years to come? These are the procedures that *par excellence* “catch the cancer early”!

The prevalence and incidence of various neoplasms in the general population is defined and it is unlikely that this will change substantively during and after the COVID-19 pandemic. Gestational trophoblastic diseases are considerably more common in certain areas of Asia in comparison with western populations; the reverse is true for prostate cancer.

It is uncertain what effect delayed screening will have on uterine cancer or vulnerable groups with hereditary intestinal cancers. It is unlikely, however, that serious consequences, if any, will emerge for prostate or breast cancers, as there is no consensus of benefit from such screening of the general population [16-18].

The cure of *early cancer* has been the “comfort zone” for a lethal disease, ever since Galen of Pergamum (2nd c. A.D), the illustrious physician to the court of the Roman Emperor Marcus Aurelius [19], declared that he had cured the “early” cancer.

“And the early cancer, he wrote*, we have cured, but the one that arose to considerable size without surgery, no one has cured” [20].

The perception of the “curable” *early cancer* appears self-evident in the minds of patients and physicians alike, but its definition is not without certain difficulties!

Does “small” - a dimensional concept - always correlate with “early” - a chronological notion? Is, an incidentally diagnosed small tumour in a kidney, during a radiological procedure for an unrelated condition, an early tumour? Unless a lesion becomes apparent in the interval between two consecutive screenings, how can we be certain for how long this apparently asymptomatic lesion has been present before it came to light? Consequently, is the *early*, a long-standing *low-grade* lesion waiting to be discovered, but posing little threat to the host?

Let us consider malignant melanoma, a tumour developing superficially on the human body whose behaviour can be witnessed by the host and often by those close to the patient.

As an eminent Dermatologist, a dedicated advocate of the early detection of this tumour, once proclaimed, *it has to start, somehow, from somewhere*. Certainly!

Nevertheless, attempts to correlate the size of the primary lesion of a cutaneous melanoma, defined as the Breslow thickness, with the time interval to excision from the patient’s recognition of the lesion, could not establish a congruence for *thin* and *early* lesions [21-23].

The *cure* of the *early cancer* proposed by Galen, ignores the intrinsic biological potential of tumours to grow at different rates and speed, the *grade* of the tumour [24].

This appealing, but so often elusive notion, has prevailed unchallenged to this day!

It should be noted that most curable cancers today, are curable in their advanced stages because they are susceptible to available treatments, rather than because they were discovered early.

Many will argue that such deliberations are of philosophical and semantic value rather than of practical importance in every-day clinical practice. Yet, the COVID-19 pandemic affords the opportunity to understand the profile of neoplastic disease as it really is, rather than as it is perceived to be.

There may be different reasons, however, for a surge in the future of cancer cases as a result of the pandemic. It has been observed, for example, that there is an increase in cases of lung cancer following influenza infections [25].

To these uncertainties, one more can be added; viruses can be oncogenic but also oncolytic!

At this point, these properties, if they exist, are unknown for the newly emerged SARS-COV-2.

Only thorough, accurate, unbiased, *apolitical* and reproducible studies will answer the question whether the COVID-19 pandemic will result in an epidemic of cancer, especially of advanced cases, in the future. Until then, this possibility remains an uncomfortable prediction.

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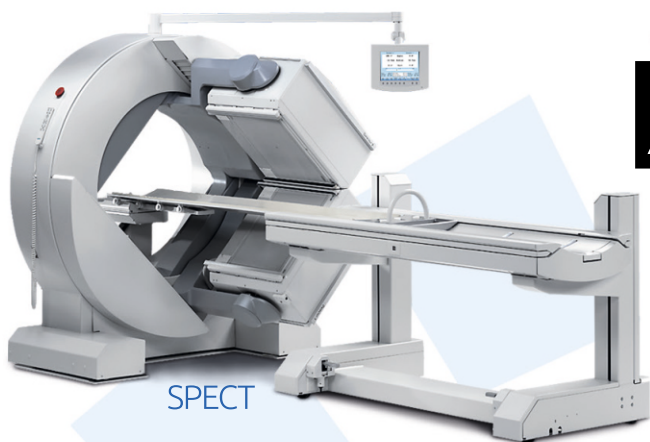
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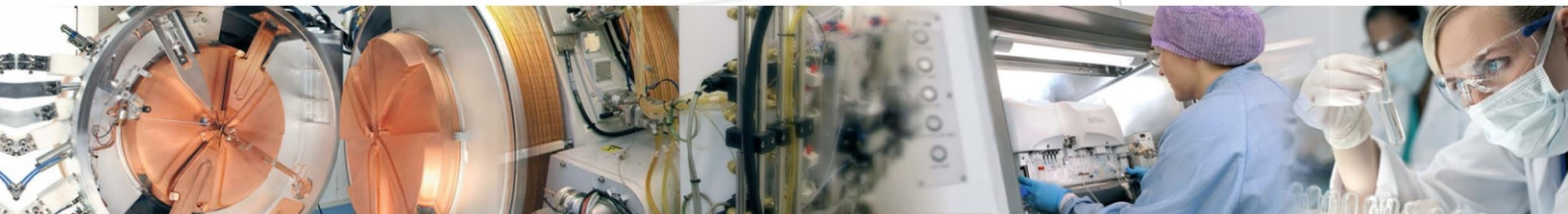
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ΒΙΟΚΟΣΜΟΣ

... Από τον Ιούνιο του 2004 η ΒΙΟΚΟΣΜΟΣ σηματοδότησε την αρχή μιας νέας εποχής για τον ιατρικό κόσμο της Ελλάδος αφού με τη λειτουργία του κυκλοτρονίου της ήταν πλέον δυνατή η εγκατάσταση και λειτουργία PET και PET/CT συστημάτων στην Ελλάδα...

Η ΜΟΝΑΔΙΚΗ ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΕΙΑ ΠΑΡΑΓΩΓΗΣ ΡΑΔΙΟΦΑΡΜΑΚΩΝ

Το 2000 προχωρήσαμε στην υλοποίηση της μεγαλύτερης μέχρι σήμερα επένδυσης υψηλής τεχνολογίας που έχει γίνει στη χώρα μας, στο χώρο της απεικονιστικής ιατρικής, εγκαθιστώντας το πρώτο κυκλοτρόνιο παραγωγής βραχύβιων ραδιοϊσοτόπων. Η επιλογή μας αυτή θεωρήθηκε από την πλειοψηφία του χώρου εξαιρετικά πρόωμη για τα ελληνικά δεδομένα. Για εμάς όμως ήταν ανάγκη της ελληνικής ιατρικής κοινότητας και δικαίωμα της ελληνικής κοινωνίας. Σήμερα η ΒΙΟΚΟΣΜΟΣ καλύπτει πλήρως τις ανάγκες της ελληνικής επικράτειας και συνεχίζει επιτυχημένα την πρωτοπόρο πορεία της με τη δημιουργία νέων μονάδων που θα καλύψουν την Βόρειο Ελλάδα αλλά και τις ευρύτερες περιοχές των Βαλκανίων.



Medical Innovations

ΒΙΟΚΟΣΜΟΣ Α.Ε.

Θέση Πάνορμος
195 00 Λαύριο, Αττική
Τηλ: 22920 63900
Fax: 22920 69235



www.biokosmos.eu
info@biokosmos.eu