“RETROSPECTIVE-PROSPECTIVE OBSERVATIONAL STUDY IN PATIENTS WITH GENITOURINARY TUMORS THAT PRESENT COVID-19 INFECTION (SOGUG-COVID-19).”

Sponsor:

Spanish Genitourinary Oncology Group (SOGUG)

Spanish Agency for Medicines and Health Products Code; AEMPS:

SOG-INM-2020-04

Short title:

Description of the population with genitourinary tumors and COVID-19.

Coordinators:

[redacted]

Protocol version and date:

V1.2 from August 10, 2020

PROTOCOL SIGNATURE PAGE

Protocol title: **"PROSPECTIVE RETROSPECTIVE OBSERVATIONAL STUDY IN PATIENTS WITH GENITOURINARY TUMORS THAT PRESENT COVID-19 INFECTION (SOGUG-COVID-19)."**

Protocol number: SOGUG-COVID-19

Protocol version: 1.2 from August 10, 2020

I have read this protocol and agree to conduct this study in accordance with all provisions of the protocol and in accordance with the Declaration of Helsinki.

REPRESENTATIVE OF THE SPONSOR: [redacted]	Date and signature
COORDINATORS/CHIEF INVESTIGATORS [redacted]	Date and signature
[redacted]	Date and signature
[redacted]	Date and signature
[redacted]	Date and signature
[redacted]	Date and signature

INDEX

1. SUMMARY OF THE PROTOCOL

EPA-AS POST-AUTHORIZATION OBSERVATIONAL STUDY

1.1. Administrative Information

AEMPS study code: **SOG-INM-2020-04**
Sending to the AEMPS: **April 22, 2020**
Study title: **"RETROSPECTIVE-PROSPECTIVE OBSERVATIONAL STUDY IN PATIENTS WITH GENITOURINARY TUMORS THAT PRESENT COVID-19 INFECTION (SOGUG-COVID-19)."**
Abbreviation: **Description of the population with genitourinary tumors and COVID-19.**
Reason for developing the study: **Sponsor initiative**
Sponsor: **Spanish Genitourinary Oncology Group (SOGUG)**
Sponsor contact address: **C/ Velázquez, 7, Planta 3 28001 Madrid**
Clinical monitor: **MFAR Clinical Research S.L.**
Clinical Monitor contact address: **Symphony 28, 2-1, 28054, Madrid.**

1.2. Methodological aspects

medical product of interest **Not applicable**
First ethics committee to evaluate the study: **Autonomous CEIm of Galicia**
Principal Investigators / Coordinators [redacted]

[redacted]

Researcher/Coordinator Centers:
[1] **Valencian Institute of Oncology**
[2] **San Carlos Clinical Hospital of Madrid**
[3] **Puerta del Hierro-Majadahonda University Hospital**
[4] **Lucus Augusti University Hospital, Lugo**

Autonomous Communities of Researchers / Coordinators:
Valencian Community
Autonomous Community of Madrid
Galicia

Territorial scope:
National, Spain

Information source:
Medical records of the patients included after signing informed consent.
RETROSPECTIVE PART ONLY: medical records of patients included after signing informed consent or waiver thereof in the cases contemplated (see 6.3 Informed consent).

Type of study (according to the AEMPS classification):
EPA-AS

Tracking Type::
Ambispective (Prospective and retrospective). A 6-month follow-up is proposed for patients in the prospective part.

Total number of patients expected to include:
They are expected to include **250, sufficient to respond to the objectives set by the study.**

Planned duration of the study:
Data collection **8 months. The estimated duration of the project is 12 to 18 months, depending on the patient inclusion rate.**

Study duration for each participant:
No specific study visits will be carried out, other than obtaining informed consent in cases where it is required.

Main objectives:

a) Main objectives

i) Describe the population infected by COVID-19 with genitourinary tumors (urothelial cancer, prostate cancer, testicular cancer and renal cancer) treated in Spanish hospitals, know the clinical presentation, therapeutic evolution and

prognosis of said intercurrent infectious process, as well as its possible relationship with different clinical and therapeutic factors.

ii) Assess the possible relationship of the different oncological treatments administered to these patients with the clinical evolution of COVID-19 infection, considering both patients who have undergone oncological treatment previously, during or after COVID-19 infection.

iii) To specifically evaluate the impact of COVID-19 infection on the toxicity of immunotherapy treatment (mainly pneumonitis) and the impact of immunotherapy on the evolution of the infectious condition in patients with tumors of genitourinary origin, in three different scenarios: during treatment , after treatment and in patients who are prescribed treatment after the infection has passed.

iv) Analysis of this same relationship in patients with genitourinary tumors and asymptomatic COVID-19 infection with positive Ab serologies (IgM and IgG).

v) To evaluate in patients with Prostate Cancer (PCa) the impact of androgen deprivation therapy (ADT) and new antiandrogen agents (NAH) with or without corticosteroids on infection. COVID-19.

b) Secondary objectives

i) To evaluate the mortality associated with COVID-19 infection in the population with genitourinary tumors. Percentage of patients alive/dead at discharge.

ii) To evaluate the rate (percentage) of complications that have required hospital admission and/or ICU treatment.

iii) Describe the frequency of asymptomatic or minimally symptomatic COVID-19 infections. Percentage of asymptomatic patients or with mild symptoms included in the study.

iv) Evolution of the oncological disease. Impact/influence of COVID-19 infection on the effectiveness of oncological treatment. Data will be collected on delays/modifications in follow-up or oncological treatment regimens. The average delay time and the number of modifications will be evaluated. Likewise, it is expected to obtain data on time to progression and overall survival of cancer patients, which can be compared with the reference values for each type of tumor pathology.

Main variables to evaluate (see section 5 of this protocol for more detail):

1. Epidemiological
2. Medical history
3. Tumor pathology
4. Immunotherapy treatment
5. Current oncological treatment
6. COVID-19 infection

Number of researchers: **32 centers**
Scope of application: **Spain**

2. INTRODUCTION AND JUSTIFICATION OF THE STUDY

2.1. Justification

We are immersed in a very rapidly evolving pandemic that puts patients from vulnerable populations, such as those diagnosed with cancer, at significant risk. Clinical data on COVID-19 in cancer patients is limited and new information is published with each passing day.
Without a doubt, a more accurate understanding of these risks will take us more time and, for now, the only thing we can do is educate the oncology population to minimize the risks of infection and to seek healthcare in case of suspicious symptoms.
Currently available information suggests that cancer patients are at higher risk of infections, serious complications, and more rapid deterioration from COVID-19 than other patients.[(1)]. However, for now we do not have information on the complications associated with COVID-19 infection and the systemic treatments used in these patients.
It is known that chemotherapy causes a state of immunosuppression in cancer patients, associated or not with hematological toxicity secondary to most chemotherapy treatments. The more or less pronounced neutropenia that occurs after the administration of different chemotherapy regimens could be a factor that is related to a greater susceptibility to COVID-19 infection as well as a higher rate of complications. It could also be that the frequency of complications was lower because the immunological storm described during the virus infection did not occur, as the patient did not have a fully competent immune system.
Many patients with prostate cancer receive treatment with low-dose corticosteroids, with the intention of minimizing the toxicity associated with them. Corticosteroids have a hormonal, anti-inflammatory and regulatory role in patients' immunity. We also do not know to what extent these prolonged treatments may be related to a greater predisposition to COVID-19 virus infection, the development of complications or a more aggressive evolution of the disease.
Some organ toxicities secondary to immunotherapy oncology treatments may overlap with COVID-19 complications (e.g. pneumonitis, which causes 35% of toxic deaths caused by immunotherapy), so it may be difficult to distinguish whether They are an adverse effect of immunotherapy, a complication of COVID-19 infection, or a combination of both. Furthermore, a subgroup of patients with severe COVID-19 infection could suffer a “cytokine storm” syndrome, with elevated levels of IL-6, IFN-γ and other cytokines, similar to secondary hemophagocytic lymphohistiocytosis (sHLH), induced, although infrequently, due to viral infections[(2,3)]. In this scenario, the possibility of an immunological hyperreaction due to immunotherapeutic agents and a possible synergy between both mechanisms must also be considered. This could mean a higher rate of patients with complications from the viral infection. On the contrary, immunotherapy treatments could have a modulating effect on the immune response and, to a certain extent, protect against the “cytokine storm” condition, which is the one most closely related to serious complications due to virus infection.
Treatments with antiangiogenic tyrosine kinase inhibitors (TKIs), widely used in patients with kidney cancer, also have a role in regulating immunity, so it is also interesting to know what happens in these patients if they acquire the infection. coronavirus

2.2. Background and current situation

On December 31, 2019, the Wuhan Municipal Health and Sanitation Commission (Hubei Province, China) reported a cluster of 27 cases of pneumonia of unknown etiology, with common exposure to a seafood, fish, and animal wholesale market. alive in Wuhan city, including seven serious cases. The onset of symptoms in the first case was on December 8, 2019. On January 7, 2020, the Chinese

authorities identified a new type of virus from the Coronaviridae family as the causative agent of the outbreak, which has subsequently been named SARS-CoV. 2, whose genetic sequence was shared by the Chinese authorities on January 12. On March 11, the WHO declared a global pandemic.

Coronaviruses are a family of viruses that cause infection in humans and a variety of animals, including birds and mammals such as camels, cats and bats. It is a zoonotic disease, meaning it can be transmitted from animals to humans.[4]. Coronaviruses that affect humans (HCoV) can produce clinical symptoms that range from the common cold with a seasonal pattern in winter to other more serious ones such as those produced by the Severe Acute Respiratory Syndrome (SARS) and of Middle East Respiratory Syndrome (MERS-CoV)[5]. Specifically, SARS in 2003 caused more than 8,000 cases in 27 countries and a fatality rate of 10% and since then it has not been detected in humans again. Since 2012, 2,499 cases of MERS-CoV have been reported in 27 countries (although the majority of cases have been detected in Saudi Arabia), with a fatality rate of 34%.

2.2.1. Epidemiological aspects of the infection

As in other outbreaks caused by coronaviruses, the most likely primary source of the disease caused by SARS-CoV-2 is animal origin. At this time it seems clear that the reservoir of the virus is the bat, while research continues on the intermediate host animal, with controversy between the pangolin and others. How the virus could have been transmitted from the animal source to the first human cases is unknown. Everything points to direct contact with infected animals or their secretions. In studies carried out in animal models with other coronaviruses, tropism has been observed for the cells of different organs and systems, mainly producing respiratory and gastrointestinal symptoms.[6], which could indicate that transmission from the animal to humans could be through respiratory secretions and/or material from the digestive system. The route of transmission between humans is considered similar to that described for other coronaviruses through the secretions of infected people, mainly through direct contact with respiratory droplets of more than 5 microns (capable of being transmitted over distances of up to 2 meters) and hands or fomites contaminated with these secretions followed by contact with the mucosa of the mouth, nose or eyes[7]. SARS-CoV-2 has been detected in nasopharyngeal secretions, including saliva.

2.2.2. Clinic associated with COVID-19 infection

In the longest series published by the China Center for Disease Control, describing the characteristics of all cases detected in mainland China from the beginning of the outbreak to February 11, 2020 (72,314 cases), 1 .2% of cases were asymptomatic[8]. These cases were detected in the context of exhaustive searches in intrafamilial outbreaks [9] and some ended up developing symptoms[10]. In contrast, on the Diamond Princess ship, quarantined in Japan, where diagnostic tests were carried out on 3,700 passengers, 50% of those who had positive results were asymptomatic. [11,12]. Subsequently, after 14 days of observation, the majority developed symptoms, with the percentage of truly asymptomatic being 18% (95% CI: 15.5-20.2). Asymptomatic cases are more frequent in children and it has been observed that some of them present pulmonary radiological alterations, such as multifocal opacities and analytical alterations, such as elevated phosphatase.

The report of the WHO mission to China describes the most common symptoms and signs of 55,924 laboratory-confirmed cases, including: fever (87.9%), dry cough (67.7%), asthenia (38.1%). %), expectoration (33.4%), dyspnea (18.6%), sore throat (13.9%), headache (13.6%), myalgia or

arthralgia (14.8%), chills (11 .4%), nausea or vomiting (5%), nasal congestion (4.8%), diarrhea (3.7%), hemoptysis (0.9%), and conjunctival congestion (0.8%)[13]. In Europe, with 14,011 confirmed cases reported to the European Surveillance System (TESSy) by 13 countries (97% of Germany), the most frequent symptoms were: fever (47%), dry or productive cough (25%), sore throat (16%), asthenia (6%) and pain (5%). In Spain, with 18,609 reported cases, the most frequent

Características clínicas	Yang (n=52) * %	Chen (n=99) %	Wang (n=138) %	Guan (n=1099) %
Signos y síntomas				
Fiebre al ingreso	98,0	83,0	98,6	43,1
Tos	77,0	82,0	59,4	67,8
Astenia/Malestar	35,0	ND	69,6	38,1
Anorexia	ND	ND	39,9	ND
Mialgias	11,5	11,0	34,8	14,9
Disnea	63,5	31,0	31,2	18,7
Expectoración	ND	ND	26,8	33,7
Dolor de garganta	ND	5,0	17,4	13,9
Diarrea	ND	2,0	10,1	3,8
Náuseas/vómito	4,0	2,0	10,1	5,0
Mareo	ND	ND	9,4	ND
Cefalea	6,0	8,0	6,5	13,6
Escalofríos	ND	ND	ND	11,5
Hallazgos Radiológicos				
Infiltrados alveolares unilateral	ND	25,0		ND
Infiltrados alveolares bilaterales	ND	75,0	100	51,8
Infiltrados intersticiales	ND	ND		14,7
Patrón de vidrio esmerilado	ND	14,0		56,4

***Serie de pacientes críticamente enfermos; ** 40% con criterios de ingreso; ND: sin datos**

symptoms were: fever or recent history of fever (68.7%), cough (68.1%), sore throat (24.1%), dyspnea (31%). , chills (27%), vomiting (6%), diarrhea (14%) and other respiratory symptoms (4.5%) (49). Other symptoms related to different organs and systems have also been described:

- Neurological: in a study with 214 patients admitted to a Wuhan hospital, 36% had neurological symptoms: dizziness (17%), altered level of consciousness (7%), stroke (2.8%), ataxia (0 .5%) and epilepsy (0.5%), hypogeusia (5.6%), hyposmia (5%) and neuralgia (2.3%)[14].
- Cardiological: it has been noted that sometimes the disease can present with symptoms related to heart failure or acute myocardial damage, even in the absence of fever and respiratory symptoms. [15].
- Ophthalmological: in a series of 534 patients confirmed in Wuhan, dry eye, 12.7% blurred vision, 11.8% foreign body sensation and 4.7% conjunctival congestion (0.5% presented as the first symptom)[16].

Seven clinical series of hospitalized cases have been published in China, with 5, 41, 52, 99, 138, 1,099 and 72,314 cases respectively. The most frequent symptoms at the time of admission in all series are fever, asthenia and cough. In the series by Wang et al. fever was the most common symptom, while in Guan et al. It is noted that only 43.8% of the patients had fever at the time of admission, although during their stay in the hospital the vast majority develop it.[17,18]. Furthermore, Yang et al. refer to the fact that 11% of critically ill patients did not have fever at the onset of symptoms [19]. The most frequent radiological pattern in all series was alveolar infiltrate (see Table 1).

Table 1. Clinical characteristics of the patient series of Yang et al., Chen et al., Wang et al. and Guan et al.

2.2.3. Data reported in the oncology population

Although so far there is no evidence of the behavior of SARS-CoV-2 in the oncology population, it is possible that patients undergoing immunosuppressive oncology treatment may have a greater susceptibility to it and a higher incidence of associated complications than the general population, such as and as occurs with other respiratory viral infections such as the flu.

There is no evidence that the virus worsens the tumor pathology itself and in many cases it has a mild clinical course. However, in cancer patients it could be associated with a more severe clinical picture, the severity of which could be increased if other factors such as advanced age or the presence of other comorbidities are associated. This increased risk of complications requires strict compliance with prevention protocols and extreme caution. The recommendations made to avoid contagion to the general population must be followed particularly strictly by cancer patients.

Several overview reviews have been published (especially of Chinese and Italian experiences). The most commented article, published in Lancet Oncology a few weeks ago, reveals the possibility that cancer patients have a worse prognosis when suffering from COVID-19 [(1)], but it is also true that this cohort of patients had a higher median age than for those without cancer and the proportion of patients is so small that there may be great heterogeneity in that population (cured vs. metastatic patients, etc.). To this we must add that the risk for cancer patients is also related to a greater inability to receive necessary medical care.

Despite this, recently, a new retrospective review has been published in Annals of Oncology with 28 COVID-19 + oncology patients. [(20)]. The most common tumor in this series was lung cancer (25%), with only 3 patients with genitourinary cancer (2 patients with prostate cancer and 1 patient with testicular cancer). The median age was 65 years. The most common symptoms were fever (82.1%) and cough (78.6%), and the most common laboratory abnormalities were lymphopenia (82.1%) and elevated CRP (82.1%). The risk of severe complications was higher in patients who had received oncological treatment in the 14 days prior to the diagnosis of the infection, with an HR in the multivariate analysis adjusted for age and sex of 4.079 (95% CI 1.086-15.322, p 0.037). However, despite being the largest series collected of COVID-19+ oncology patients, it has its limitations, which are mentioned in the article itself. To begin with, this is a retrospective study of 28 patients. Furthermore, the population is heterogeneous, with different tumors and stages (64.3% are stages I-III), which is not taken into account in multivariate analysis. A more recent article in Cancer Discovery with 69 patients with lung cancer, mainly active or metastatic (80%), determined that previous oncological treatment with Programmed Dead-1 (PD-1) blockers does not have a significant impact on severity of COVID-19 infection [(21)].

23. Working hypothesis

The identification of patients with genitourinary tumors who suffer from infection with the SARS-CoV-2 agent can represent multiple benefits both for themselves and for health professionals and the health system itself. We would be able to know more precisely the clinical evolution of this type of patient, know their prognosis and be able to select the most appropriate treatment modality for future pandemics.

3. OBJECTIVES

3.1. Main objectives

- Describe the population infected by COVID-19 with genitourinary tumors (urothelial cancer, prostate cancer, testicular cancer and renal cancer) treated in Spanish hospitals, know the clinical presentation, therapeutic evolution and prognosis of said intercurrent infectious process, as well as its possible relationship with different clinical and therapeutic factors.
- Assess the possible relationship of the different oncological treatments administered to these patients with the clinical evolution of COVID-19 infection, considering both patients who have undergone oncological treatment previously, during or after COVID-19 infection.
- To specifically evaluate the impact of COVID-19 infection on the toxicity of immunotherapy treatment (mainly pneumonitis) and the impact of immunotherapy on the evolution of the infectious condition in patients with tumors of genitourinary origin, in three different scenarios: during treatment , after treatment and in patients who are prescribed treatment after the infection has passed.
- Analysis of this same relationship in patients with genitourinary tumors and asymptomatic COVID-19 infection with positive Ab serologies (IgM and IgG).
- To evaluate in patients with Prostate Cancer (PCa) the impact of androgen deprivation therapy (ADT) and new antiandrogen agents (NAH) with or without corticosteroids on infection. COVID-19.

3.2. Secondary objectives

- To evaluate the mortality associated with COVID-19 infection in the population with genitourinary tumors. Percentage of patients alive/dead at discharge.
- To evaluate the rate (percentage) of complications that have required hospital admission and/or ICU treatment.
- Describe the frequency of asymptomatic or minimally symptomatic COVID-19 infections. Percentage of asymptomatic patients or with mild symptoms included in the study.
- Evolution of the oncological disease. Impact/influence of COVID-19 infection on the effectiveness of oncological treatment. Data will be collected on delays/modifications in follow-up or oncological treatment regimens. The average delay time and the number of modifications will be evaluated. Likewise, it is expected to obtain data on time to progression and overall survival of cancer patients, which can be compared with the reference values for each type of tumor pathology.

4. STUDY METHODOLOGY

4.1. Study type and design

This is a national multicenter, observational, retrospective and prospective post-licensure (EPA-AS) study that will include patients with genitourinary tumors presenting with COVID-19 infection.

The study will be carried out in Spanish hospital centers, with principal investigators belonging to the medical oncology services of the SOGUG group (Spanish Genitourinary Oncology Group), who will act as sponsor. Once the patients are selected, the variables described in section 5 of this protocol will be collected and studied.

The study will use data obtained from the patient's medical history, with no plans to use other sources.

The assignment of a patient to a specific therapeutic strategy has already been decided in advance by the usual clinical practice of medicine; The decision to prescribe a specific treatment is clearly dissociated from the decision to include a patient in the study. No intervention, whether diagnostic or follow-up, will be applied to patients other than standard clinical practice. Epidemiological methods will be used to analyze the data collected.

4.2. Study population

The inclusion of a total of 250 patients with genitourinary tumors presenting with COVID-19 infection is expected, sufficient to respond to the objectives set by the study.

4.3. Inclusion criteria

- Patients ≥18 years old.
- Diagnosed with genitourinary cancer (urothelial, kidney, prostate and germ cell).
- COVID-19 infection prior to oncological treatment, during treatment or after treatment.
- COVID-19 infection must be confirmed by PCR or serology, regardless of whether or not the patient requires hospitalization due to the infection. Additionally, clinical and/or radiological determination must be available in those patients who present symptoms.

4.4. Exclusion criteria

- Not applicable.

As this study is an EPA-AS, all the researchers' activities are carried out in accordance with the center's usual clinical practice. No withdrawal criteria have been established. Information from the clinical history will be collected as long as it does not exist on the part of the researcher. patient refusal to do so. Therefore, those patients who do not attend the corresponding visits will be declared as lost to follow-up, those patients who withdraw their consent to participate, the data collected up to that point will be used for statistical analysis, being lost to follow-up from which the patient withdraws his consent.

4.5. Study sample size

The inclusion of a total of 250 patients with genitourinary tumors presenting with COVID-19 infection is expected, sufficient to respond to the objectives set by the study.

Given the characteristics of the study, the total number of patients cannot be previously calculated accurately, although the inclusion of approximately 250 patients is expected. The planned analysis is the descriptive one of each of the variables. The qualitative variables will be compared with each other using the Chi-square test. Quantitative and qualitative analysis using Student's T analysis or ANOVA. If necessary, the corresponding non-parametric tests will be applied. Survival will be calculated using Kaplan-Meyer curves and curve comparison using Log-Rank.

The Statistical Package for the Social Sciences (SPSS) will be used for statistical analyses. Additional analyzes could be performed with other statistical analysis packages.

4.6. Sampling and recruitment method

Patients will be included consecutively, in accordance with the inclusion/exclusion criteria previously established in sections 4.3 and 4.4 of this protocol. Inclusion will be carried out competitively without restrictions regarding the number of patients included in each center.

In accordance with the definition of the study population and disease established in this scientific report, patients will be selected from the diagnosed/treated cases of genitourinary tumors presenting with COVID-19 infection treated in the Spanish hospital centers participating in the study.

To prevent two or more doctors participating in the trial from registering the same case, a coordinator is designated, who controls the cases included in his center, in hospital centers with several participating doctors, and preventive measures are implemented in the tool that controls duplications. in the variables (such as age, sex, center or diagnosis).

4.7. Case definition

A "case" is defined as any patient, diagnosed, treated or followed up at the different hospital centers where physicians authorized by the sponsor are informed, who meets the inclusion criteria.

Medical care will be provided following applicable clinical criteria, in the context of routine clinical practice, regardless of the patient's inclusion in the study and following the best judgment of the specialists responsible for the patients.

4.8. Data Logging

Once data collection is possible (when the patient agrees to participate in the study through the informed consent procedure detailed in point 6.3 of this protocol, or after the waiver of consent has been requested and approved (RETROSPECTIVE PART ONLY) , medical history information will be collected to obtain the necessary data and complete the electronic study forms designed for this purpose.

4.9. Study schedule

Study start date (Activation of the first center)	**3Q 2020**
End date of the study (“Last patient last visit” or end of data extraction)	**1T 2021**
Study report completion date	**2T 2021**
Date of first publication	**2Q 2021 (expected)**

5. VARIABLES

5.1. Study variables

A data collection notebook will be prepared in which the following variables will be collected for analysis:

Affiliation of the center:

- Hospital name
- Province
- Investigator's name
- Patient number

Patient characteristics:

- Age
- Sex
- Age
- Hospital center where the patient is recruited (in order to have epidemiological data on the pandemic that may be of interest)

Pathological history:

- Concomitant pathology (cardiac, pulmonary, renal, liver, Diabetes Mellitus, HIV, AI)
- Usual pharmacological treatment
- Smoking and alcohol habit

Tumor pathology:

- Tumor type, histology and stage (initial and at diagnosis of infection)
- Date of cancer diagnosis
- Active cancer treatment or follow-up
- Participation in clinical trial
- Type of treatment most recently received for the infection (Surgery; Radiotherapy; Chemotherapy: Drug, Immunotherapy, TD: Drug, HT: ADT alone or with Abiraterone, Enzalutamide, others)
- Treatment lines
- Start and last dose received of the most recent oncological treatment

For patients with prostate cancer:

- Local treatment and type (Surgery, Radiotherapy)
- Adjuvant ADT or advanced disease (start date)
- NAH (date and line of treatment)
- Associated corticosteroid treatment: Prednisone vs Dexamethasone (dose)

COVID-19 infection data:

- Confirmation date of COVID-19 infection
- PCR diagnostic test
- IgG or IgM serological diagnostic test
- Present symptoms

- Analytical alterations, lymphopenia, elevated CRP, high D-dimer.
- Thrombosis associated with COVID-19 infection
- Date of onset and disappearance of symptoms
- Days duration of fever and cough
- Radiological examination at the moment of greatest severity
- Complications of infection: presence of complications and/or hospital or ICU admission
- Admission date
- Date of most serious complication
- Treatments received for COVID-19
- Discharge status
- Fecha de high / exit
- Negativization of the presence of viruses by PCR
- Negative PCR date

For patients who are receiving or have received immunotherapy treatments, additional information will be collected:

- Immunotherapy treatment line
- Start/end date of immunotherapy treatment
- Date of last dose received prior to COVID-19 infection
- Immunotherapy received as monotherapy or combination
- Type of immunotherapy
- Adverse effects

Prospective follow-up data (6 months from patient inclusion):

- Date of start or restart of oncological treatment after infection
- Negative COVID-19 test prior to starting/restarting treatment
- Change/suspension of oncological treatment after COVID-19
- Surgery date in neoadjuvant patients
- Recurrence of COVID-19
- Best answer obtained
- Date of progression to oncological treatment
- Current status
- Last contact date

6. PROTECTION OF HUMAN SUBJECTS

6.1. Applicable legislation

This is an observational, descriptive, non-interventional study with the main objective of collecting information on patients with genitourinary tumors who present COVID-19 infection, under clinical care and follow-up in the departments of participating centers distributed nationwide.

The study design includes the collection of retrospective and prospective data, promoted by the Spanish Genitourinary Tumors Group (SOGUG) and is considered of public interest. Therefore, in accordance with Order 3470/2009 of Health and Social Affairs (SAS), of December 16, the Sponsor has requested the EPA-AS classification from the AEMPS. This classification has been ratified by the AEMPS on April 23, 2020. In accordance with the same legislation, the participation of any center will be subject to the approval of the Post-authorization Studies Coordination Committee, a favorable opinion from a Clinical Research Ethics Committee accredited in Spain and the approval of the management of each participating center.

Participating in this study does not represent any additional risk for patients because it is a study developed from information recovered from the clinical history and clinical evaluation of patients, all in the context of usual clinical practice and without participation of the patients. patients in any type of intervention or without the modification of the treatment that they would receive if they had not participated in the study.

This protocol will be carried out in accordance with the principles adopted by the 18th World Medical Assembly (Helsinki, 1964) and its subsequent amendments (Fortaleza, 2013), following the rules of good clinical practice and the code of ethics.

6.2. Ethical supervision of clinical research

The study will initially be submitted for evaluation by the **Autonomous CEIm of Galicia**. As detailed in section 6.1, the study will also have the corresponding and applicable authorizations in accordance with the regulations of each center and the guidelines of Order 3470/2009 SAS of December 16.

6.3. Informed consent

All information will be extracted from the medical records of participating patients who have authorized its use by signing the informed consent. All patients included in the prospective part of the study, upon authorization by the competent authorities, must sign an informed consent prior to their inclusion in the study that authorizes the use of the information contained in their medical records.

RETROSPECTIVE PART ONLY: In all cases where it is possible for the patient to sign informed consent, it will be collected. Due to the nature of the study and in order not to generate information bias in those patients with a worse prognosis who have not been able to overcome the disease, exemption from informed consent is contemplated for patients who have died in the retrospective part of the study. study, prior to authorization of the study by the competent authorities.

RETROSPECTIVE PART ONLY: The local Ethics Committee must approve the absence of written authorization by signing the informed consent (as established by local Spanish regulations: SAS

Order 3470/2009). It is possible to dispense with the request for informed consent of patients who have died prior to the authorization of this study by the competent authorities provided that a prior refusal has not been obtained for the signing of the informed consent by of the patient or a revocation thereof. On the other hand, this methodology has been proposed taking into account that:

- There are no studies on the involvement of COVID in patients affected by the disease under study
- The high incidence of fatal cases leads to the need to collect these cases in order not to cause bias in the sample due to relevant loss of patients that generates serious problems of representativeness of the population under study and scientific validity.

For all patients, whether or not they have signed informed consent, the data are included in the study in an anonymized and dissociated form, ensuring that they cannot be associated with any identified or identifiable person. The researcher will assign each patient included in the study a numerical code with which said patient will be identified during the study. The code will not contain personal information and no other data that allows patient identification will be collected during the study. The use of patient data will be subject to a commitment to confidentiality by all personnel participating in the study, including the researcher and his collaborators, data managers, data analysts, and monitors; this should be properly recorded in the patient's medical record, with specific reference to the SOGUG-COVID-19 study. The researchers participating in the study undertake not to identify or carry out re-identification tasks that compromise the anonymity of the patients included in the study.

The data will be recorded using the Electronic Data Capture software owned by MFAR S.L., which is developed and maintained in strict compliance with regulatory standards for electronic digital capture systems for clinical data. All EDC forms are designed according to the eCRF defined by the study protocol.

All database users are uniquely identified by name, all access to the software is over a secure, encrypted connection, and all activities are logged and audited. Only SOGUG (the study sponsor) and MFAR (the CRO with delegated functions) will have access to the data.

6.4. Confidentiality

In accordance with the Organic Law on the Protection of Personal Data (Organic Law 3/2018, of December 5, on the Protection of Personal Data and guarantee of digital rights - LOPD), the sponsor guarantees the adoption of the necessary measures to guarantee confidentiality in the processing of personal data.

Only the reporting physicians (principal investigators participating in the study) will know the full name of their patients. No confidential information unnecessary for the intended purposes of the study is collected.

An electronic platform will be used to record data in the Electronic Case Report Form (eCRF). To access the application, users must identify themselves with a username and password strictly for personal use. Each reporting doctor will only have access to the data he/she submitted that is strictly necessary for the work. Any document containing identification data will remain in the center at all times, without being included in the database.

The data will be collected in a research file under the responsibility of the sponsor and will be processed within the framework of the study, ensuring that the sponsor will adopt the relevant

measures to guarantee compliance with current legislation on data protection in all cases. The encrypted data may be transmitted to third parties and other countries, but in no case will it contain information that can directly identify any patient, such as name and surname, initials, address or social security number, among others. If this transfer occurs, it will be for the same study purposes as those described above or only for scientific publications, but always maintaining patient confidentiality in accordance with current legislation.

The database will be examined exclusively by the scientific and medical staff of the sponsor. No personal data or any information that may be related to patients will be included in this database. The database administrator, data manager and monitor (if applicable) will have access to all data that is not linked to any identifiable person.

In data explorations carried out by researchers authorized by the Scientific Committee and in international data transfers to International Registries, if applicable, patients will be identified by a numerical code assigned automatically and randomly by the computer application at the beginning of the registry. each case to maintain the confidentiality of the patient's personal data, as established in the General Data Protection Regulation 2016/679 of the Parliament and of the Council of the European Union (EU) on April 27, 2016.

Access to the personal information of the study subjects will be restricted to the doctor/study collaborators, the health authorities (Spanish Medicines Agency), the Clinical Research Ethics Committee and the personnel authorized by the sponsor, when they need to evaluate the data. and study procedures, but always maintain patient confidentiality in accordance with current legislation.

This evaluation will be carried out in the presence of the main researcher or collaborators, responsible for guaranteeing the confidentiality of the data in the medical records of the study subjects. Only the data collected for the study will be transmitted to third parties, with at least the level of protection of the current legislation, including the transfer of data outside the area of application of the reference legislation.

6.5. Funding source

The study sponsor funds the study according to the guidelines of this protocol. This funding covers all research materials; the cost of registration and control processes in ethics committees and health authorities; the design, maintenance and management of the database; eventual statistical consultations, if necessary; and publication and reporting costs. The financing will, in any case, be independent of the results of the study.

The board of directors/scientific committee of the sponsor guarantees non-interference in the case selection processes, data analysis or in any other process that may affect the results of the study that involve the exploration and presentation of data.

7. REPORTING OF ADVERSE REACTIONS (AR)

In accordance with the provisions of section 8.3 of Order SAS/3470/2009, of December 16, which publishes the guidelines on observational post-authorization studies for medicines for human use, for studies classified as, EPA- AS they are considered prospective monitoring, suspicions of serious adverse reactions that are detected during the course of the study will be notified to the contact point designated by the competent body in matters of pharmacovigilance of the autonomous community where the health professional who carries out his or her activity. notify the case, within a maximum period of 15 calendar days from when you became aware of the suspected adverse reaction.

In the event that the sponsor is a group of professionals (as is the case of SOGUG), you may choose one of the following two options: 1) yellow card to the corresponding autonomous pharmacovigilance center, indicating in observations the name and code of the study from which it comes; or 2) use the online upload through the SINAEM portal of the AEMPS, following the instructions published by the AEMPS (this second option is the recommended one).

For this study, the research team will make notifications of serious adverse reactions to the Sponsor within 24 hours after having become aware of:

MFAR Clinical Research, S.L. [redacted]

MFAR will act as recipient of the notifications that it will manage with the Sponsor and after receiving approval from the Sponsor, it will notify the competent bodies of each Community in matters of pharmacovigilance, when appropriate.

The accumulated data on safety aspects (serious adverse events and adverse drug reactions) related to medical products subject to study will be recorded in the eCRF and will be included by the sponsor in the clinical study report, since this study is based on the use secondary data, an expedited report to the sponsor is not required.

In addition to the details specified in the previous paragraph, any relevant safety finding detected during the study will be reported to the AEMPS and the competent bodies of the autonomous communities involved, regardless of the design or type of study.

8. QUALITY GUARANTEE

8.1. Data consistency control

The investigator or designated responsible person is responsible for recording and verifying the accuracy of subject data.

The study will use an online data collection notebook (eCRF). Designated CRO staff will review the data collected by research staff for completeness and accuracy, in accordance with the monitoring plan agreed upon with the Sponsor. Electronic data queries indicating the nature of the findings and requesting clarification for discrepancies and missing values will be created and sent to the research center via an electronic data capture (EDC) system. Designated staff at the investigator's site are required to respond promptly to inquiries and make any necessary changes to the data.

Concomitant treatments and all drug information entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemistry classification system.

Medical history/current medical conditions and adverse events will be coded using the NCI CTCAE V 5.0 guidelines and the Medical Dictionary for Regulatory Activities Terminology (MedDRA).

Facility staff designated by the investigator will enter the information required by the protocol into the eCRFs as well as the CRO-designated application form.

8.2. Quality control in the research center

Prior to the start of the study, the protocol and CRFs will be reviewed with the investigators and their staff via a site initiation telephone visit.

During the study, a monitor will contact selected sites through remote monitoring visits to verify the integrity of patient records and the accuracy of entries in the CRFs. Key study personnel should be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, which consist of case and visit notes (medical records from hospitals or clinics) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessment.

All information recorded in the CRFs must be traceable to the source documents in the patient file. The investigator must also retain the original signed informed consent form (a signed copy is given to the patient).

The researcher must give the monitor access to all relevant source documents to confirm their consistency with the entries in the CRF.

8.3. Audits

To ensure data quality, study integrity, and compliance with the protocol and various applicable regulations and guidelines, the sponsor may conduct visits to the institutions participating in the studies.

The investigator, by agreeing to participate in this protocol, agrees to cooperate fully with any quality assurance visits conducted by third parties, including representatives of the sponsor, national regulatory authorities, as well as to allow direct access to documentation related to the clinical trial. (including CRFs, source documents, hospital patient records, and other study files) to such authorized persons.

The investigator must inform the sponsor immediately in case a regulatory authority inspection is scheduled.

9. DISCLOSURE PLAN AND COMMUNICATION OF RESULTS

The study sponsor has the rights to explore the collected data, store and protect it, and acts as a Scientific Committee for the approval of proposals for data exploration and publication of the results carried out by the researchers.

The objective of the study, openly epidemiological, is to collect information on the management of the study disease in different participating hospitals to establish a framework of action (usual practice) and, therefore, study options for the management of the disease beneficial to the patients.

9.1. Commitment and publication standards

The coordinating researchers and the sponsor are responsible for the preparation of manuscripts, abstracts, posters, etc. that summarize the recorded data for publication. The global data will be used in documents sent for publication to conferences and medical journals, mentioning the study and the sponsor.

Regarding the authorship policy of publications, the rules and SOPs of the sponsor (SOGUG) will be followed.

The anonymity of the data source subjects will be maintained at all times.

The results or conclusions of the study will be communicated mainly in scientific publications before being disseminated to the non-health public.

Participating investigators should not publish any patient data that is directly related to the study objectives until the trial report is published.

The sponsor, SOGUG, undertakes to deliver the monitoring reports and the final report to the competent bodies of the CCAA in a timely manner, following current regulations.

10. BIBLIOGRAPHY

1. Liang, W. *et al.* Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *The Lancet Oncology* (2020). doi:10.1016/S1470-2045(20)30096-6
2. Bersanelli, M. Controversies about COVID-19 and anticancer treatment with immune checkpoint inhibitors. *Immunotherapy* (2020). doi:10.2217/imt-2020-0067
3. Mehta, P. *et al.* COVID-19: consider cytokine storm syndromes and immunosuppression. *The Lancet* (2020). doi:10.1016/S0140-6736(20)30628-0
4. WHO. *(Novel Coronavirus (2019-nCoV) situation reports. cited 23 January 2020.* (2020). at <https://www.who.int/emergencies/diseases/novel-coronavirus2019/situation-reports>
5. Paules, C. I., Marston, H. D. & Fauci, A. S. Coronavirus Infections-More Than Just the Common Cold. *JAMA - Journal of the American Medical Association* (2020). doi:10.1001/jama.2020.0757
6. Saif, L. J. Animal coronaviruses: What can they teach us about the severe acute respiratory syndrome? *OIE Scientific and Technical Review* (2004). doi:10.20506/rst.23.2.1513
7. Setti, L. *et al.* Airborne Transmission Route of COVID-19: Why 2 Meters/6 Feet of Inter-Personal Distance Could Not Be Enough. *Int. J. Environ. Res. Public Health* (2020). doi:10.3390/ijerph17082932
8. Team, T. novel coronavirus emergency response epidemiology. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. Vital Surveillances: The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19). *ccdc Wkly.* (2020).
9. Huang, R., Xia, J., Chen, Y., Shan, C. & Wu, C. A family cluster of SARS-CoV-2 infection involving 11 patients in Nanjing, China. *The Lancet Infectious Diseases* (2020). doi:10.1016/S1473-3099(20)30147-X
10. Roback, J. D. & Guarner, J. Convalescent Plasma to Treat COVID-19: Possibilities and Challenges. *JAMA - Journal of the American Medical Association* (2020). doi:10.1001/jama.2020.4940
11. Japan, N. institute of infectious diesease. *Field Briefing: Diamond Princess COVID-19 Cases*.
12. Tabata, St. *et al.* Non-Severe vs Severe Symptomatic COVID-19: 104 Cases from the Outbreak on the Cruise Ship 'Diamond Princess' in Japan. *SSRN Electron. J.* (2020). doi:10.2139/ssrn.3551331
13. WHO. *World health Organization. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19).*
14. Mao, L. *et al.* Neurologic Manifestations of Hospitalized Patients with Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol.* (2020). doi:10.1001/jamaneurol.2020.1127
15. Inciardi, R.M. *et al.* Cardiac Involvement in a Patient with Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol.* (2020). doi:10.1001/jamacardio.2020.1096
16. Chen, L. *et al.* Ocular manifestations and clinical characteristics of 534 cases of COVID-19 in China: A cross-sectional study. *medRxiv* (2020). doi:10.1101/2020.03.12.20034678
17. Wang, Y., Wang, Y., Chen, Y. & Qin, Q. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. *Journal of Medical Virology* (2020). doi:10.1002/jmv.25748
18. Guan, W. J. *et al.* Clinical Characteristics of Coronavirus Disease 2019 in China. *N. Engl. J. Med.* (2020). doi:10.1056/NEJMoa2002032
19. Yang, X. *et al.* Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir. With.* (2020). doi:10.1016/S2213-2600(20)30079-5
20. Zhang,L.*et al.* Clinical characteristics of COVID-19-infected cancer patients: A retrospective case study in three hospitals within Wuhan, China. *Ann. Oncol.* (2020). doi:10.1016/j.annonc.2020.03.296
21. Lou J. *et al.* Impact of PD-1 blockade on severity of COVID-19 in patients with lung cancers. *Cancer Discovery* (2020). two: 10.1158/2159-8290.CD-20-0596