Institut de Cancérologie de l'Ouest
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Titre court: **PAPESCO-19**
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SYNOPSIS
PROTOCOLE PAPESCO-19

A) IDENTIFICATION OF THE CLINICAL TRIAL			
TITLE OF THE TRIAL:	**PA**tients et **PE**rsonnel de **S**anté des Centres de Lutte Contre le Cancer pendant la pandémie de **Co**vid-**19**: constitution d'une collection biologique adossée à une étude de cohorte, prospective, multicentrique.		
SHORT TITLE:	**PAPESCO-19**		
COORDINATOR:	Dr Frédéric BIGOT Medical Oncologist		
CO-COORDINATOR:	Dr Michèle BOISDRON-CELLE Department of Cancer Biopathology		
METHODOLOGISTS:	Dr Audrey BLANC-LAPIERRE and Dr Valérie SEEGERS Biometry Department		
ESTIMATED NUMBER OF CENTERS:	4	**NUMBER OF SUBJECTS:**	15 000 - Patients: 12 000 - Healthcare personnel: 3 000

B) IDENTIFICATION OF THE SPONSOR	
SPONSOR:	ICO Institut de Cancérologie de l'Ouest (ICO) Direction de la Recherche Clinique Cellule de Promotion
CONTACT:	**Délégation à la Recherche Clinique et à l'Innovation (DRCI)** **15, rue André Boquel - 49 055 Angers cedex 02** Contact: Marine TIGREAT 15, rue André Boquel - 49 055 Angers cedex 02 Tel: 02 40 67 99 08 Email: marine.tigreat@ico.unicancer.fr

C) RATIONALE

Covid-19 pandemic

Coronavirus disease 2019, or Covid-19 (an English acronym meaning coronavirus disease 2019), is an emerging infectious disease caused by a coronavirus strain called SARS-CoV-2. This disease appeared in November 2019 in Wuhan, in central China. The World Health Organization (WHO) declared the outbreak a Public Health Emergency of International Concern (PHEIC) on January 30, 2020, and a pandemic on March 11, 2020. As of April 20, 2020, 166,000 deaths were estimated to be linked to Covid-19, of which around 80% occurred in Europe and the USA.

Among the main consequences, strict national lockdown measures were implemented — first in China in January 2020, then in many other countries in March (Italy, Spain, France, Switzerland, Belgium, Canada, etc.). These measures led to mass cancellations of public events, border closures, a sudden slowdown in the global economy, and unprecedented individual and social adjustments.

Early descriptive studies

The first descriptive studies of the disease originated from China and will likely need to be revised in light of the European and American data. The incubation period is estimated at 5 days (range: 2–12 days). When symptoms occur, they develop progressively: headache, muscle pain, fatigue, followed by fever and respiratory signs 2–3 days after initial symptoms.

In a number of cases, the situation continues to worsen, with chest pain, respiratory discomfort, and a radiological pattern of viral pneumonia. Signs related to involvement of other organs have been described (neurological, dermatological, etc.).

This clinical picture may be severe enough to justify hospitalization in nearly 20% of symptomatic patients and admission to intensive care in 5% of these cases. These severe forms predominantly affect certain high-risk groups, particularly older and more fragile individuals, who represent the main cause of Covid-19–related deaths.

Clinical presentation and challenges

Initial descriptive studies came from China, but European and American data suggest differences. Incubation lasts about 5 days (range 2–12). Symptoms, when present, develop progressively: headache, muscle pain, fatigue, then fever and respiratory signs 2–3 days later. Some cases worsen with chest pain, dyspnea, and viral pneumonia. Multisystemic manifestations have been reported. Around 20% of symptomatic cases require hospitalization; 5% require ICU admission—mainly affecting elderly and fragile patients.

The main diagnostic test aims to detect viral RNA in nasal secretions or sputum, quantified by RT-PCR. This PCR test, which is rather uncomfortable, appears to have a substantial false-negative rate (~30%).

Screening for minimally symptomatic or asymptomatic forms — which are likely no less contagious — is essential to slow the pandemic and prevent overwhelming the healthcare system. At present, no systematic screening strategy has been implemented in France.

Numerous serological tests detecting IgG and IgM antibodies are emerging. They are much simpler and faster than RT-PCR.

While antibody production (IgM and/or IgG) is known to be detectable from the second week after symptom onset in the general population, recent studies report the appearance of IgM and IgG antibodies as early as the 4th day after onset of clinical signs.

However, the kinetics of IgM/IgG antibody production are poorly characterized in asymptomatic or mildly symptomatic individuals, and even less so in patients with pre-existing conditions (cancer or other causes of immunosuppression).

Finally, high IgG and IgM antibody titers appear to be independently associated with disease severity.

Covid and cancer

Patients with cancer may be more susceptible to viral infections and especially more vulnerable to such infections. According to the French High Council for Public Health (HCSP), it is estimated that, for patients with cancer, the risk of hospitalization is multiplied by 4 and the risk of death by 10 compared with the general population. This excess risk is particularly pronounced in individuals presenting with lymphopenia or neutropenia — conditions frequently observed in patients receiving chemotherapy or those who have undergone multiple lines of treatment.

A higher rate of Covid-19 infection among cancer patients than in the general population may be explained by pre-existing respiratory comorbidities (e.g., lung cancer), greater medical surveillance, but also by immune fragility related to cancer treatments and shared risk factors for both cancer development and Covid-19 complications (particularly age).

However, diagnosis in these more fragile patients is currently based only on clinical symptoms (fever, cough, chest pain, dyspnea), which leads to immediate exclusion or isolation of the patient. The lack of simple diagnostic tools, the high frequency of asymptomatic forms, and the anxiety caused by this new threat have resulted in major reorganization of healthcare services: cancellations or postponements of chemotherapy sessions, imaging procedures, and surgeries. For healthcare workers, the lack of reliable testing generates anxiety and fear of contaminating patients and their families.

Impact on oncology care in France

In France, the classification of cancer patients as a "high-risk population" has led to increased vigilance and specific recommendations within oncology departments. These departments must reorganize to optimize decision-making regarding patient management schedules. Some non-urgent consultations or procedures have been postponed, and teleconsultations have been implemented. Physicians sometimes face the difficult task of weighing the consequences of delaying treatment against the risks associated with Covid-19 infection.

Strong preventive measures have been put in place. Furthermore, quarantining certain healthcare personnel can result in shortages in human resources.

Main hypothesis and objectives

Overall, patients with solid tumors, especially those recently treated with surgery or chemotherapy, appear to be at higher risk than the general population of developing severe or even fatal forms of the viral infection. However, very little data are available regarding:

- the humoral immune response to Covid-19 in cancer patients,
- the risk of respiratory complications,
- comparisons with the general population,
- differences according to systemic treatments received.

In addition, Covid-19 infections are suspected to be more severe in cancer patients due to immunosuppression, but this immunosuppression is highly heterogeneous and poorly assessed in treated or monitored cancer patients.

To date, within the network of French Comprehensive Cancer Centers (CLCC), no study has examined the extent and consequences of the Covid-19 epidemic on service reorganization. Yet this represents an important learning opportunity that could facilitate adaptation during future crises, ensuring optimal management of cancer patients.

Purpose of the study

The aim of this study is to describe the impact of Covid-19 in:

- patients undergoing treatment,
- patients who completed treatment more than one year ago,
- healthcare personnel working in CLCCs,

within a longitudinal study covering several interrelated domains ("Work Packages", WP):

- serological evolution and immune response
- clinical presentation
- epidemiology
- health economics
- psychology

Expected outcomes

We aim to:

- study the evolution of immune response in cancer patients during treatment, compare it with long-term survivors and healthcare workers
- document clinical presentations and determine whether disease course and risk factors depend on specific conditions (e.g., treatment type)
- quantify economic and organizational impacts on care, healthcare personnel, and mobilized health resources
- examine infection modes (epidemiology), despite the challenge created by interactions between the three study populations
- observe the psychological impact of this "period" on healthcare personnel by measuring their anxiety and stress levels

D) GENERAL INFORMATION ABOUT THE TRIAL

POPULATION:	Population consisting of patients and healthcare personnel from the CLCCs who fall into one of the following 3 categories during the pandemic (between March 2020 and the end of the pandemic): • Patients undergoing treatment, • Patients in follow-up (having completed their treatment more than one year before inclusion), • Healthcare personnel (clinical, medical-technical, and administrative staff) of the institutions.

METHODOLOGY:	This is a prospective, multicenter cohort study with the creation of a clinico-biological database, falling within the framework of a category 2 interventional research study (RIPH 2). This research will include: • The recruitment of patients receiving care in participating centers who attend within the context of their treatment or follow-up during the inclusion period, and the recruitment of healthcare personnel working within these same institutions. • A collection of blood samples (biobank). • Biological and clinical data collected from patient medical records. • Psychometric questionnaires (STAI state, STAI trait, PTGI, HADS) (ANNEXES 8 to 11) and the "Healthcare Personnel" questionnaire (ANNEXE 7) completed by staff. • Sociodemographic, lifestyle, and Covid-19 clinical-symptom questionnaires completed by both personnel and patients (ANNEXES 4 to 6). • PMSI data. • Focus groups with healthcare personnel to explore different behaviors in response to changes. A semiannual extraction of data may be considered for exploratory analyses.
NUMBER OF SUBJECTS:	As this is a cohort study involving the creation of a clinico-biological database, the number of subjects directly depends on the recruitment potential of each center. Based on the information provided by the 4 participating CLCCs, the cohort size has been estimated at 15,000 subjects distributed as follows: • Number of patients (in treatment and follow-up): 12,000 • Number of healthcare personnel: 3,000
MAIN OBJECTIVE:	Creation of a clinico-biological database to describe Covid-19 infections (incidence and severity) among CLCC patients and personnel.
SECONDARY OBJECTIVE:	***WP 1: SEROLOGY*** ***MANDATORY*** Evaluate the humoral response to a Covid-19 infection in the following subgroups: a. In patients with cancer who are symptomatic with a probable Covid-19 infection b. In patients whose treatment has been suspended c. In patients with treatment currently ongoing: ○ Patients receiving immunotherapy ○ Patients receiving chemotherapy: ▪ Patients with neutropenia-inducing chemotherapy ▪ Patients with lymphopenia-inducing chemotherapy d. In healthcare personnel of the CLCCs Describe the diagnostic performance of serological tests (IgM rapid test and IgM serological test). Describe long-term IgG persistence and quantification (Month 12) in populations from the CLCCs. Among individuals who developed IgG: a. describe the frequency of reinfections in each study population. b. describe the protective IgG threshold in each study population. Evaluate the influence of polymorphisms in low-affinity Fc gamma receptors for IgG (FcγRIIa, FcγRIIIa) on the humoral response. Evaluate the appearance of IgG and their evolution during study follow-up after vaccination. Evaluate the number of individuals presenting antibodies after vaccination.

	Evaluate the neutralizing capacity of IgG (neutralization assays) after vaccination over the duration of the study. ***WP 2: CLINICAL*** ***MANDATORY*** Describe severity (asymptomatic, symptomatic, prolonged, severe, fatal) by age group: a. In healthcare personnel b. In cancer patients c. In patients in follow-up d. In patients undergoing treatment: ○ Receiving chemotherapy and according to whether the chemotherapy induces grade 3–4 neutropenia or lymphopenia (as defined in the primary literature) ○ Receiving immunotherapy Determine the frequency of Covid-19 reinfection (recurrence of clinically suggestive symptoms with positive viral PCR and/or positive IgM serology) during follow-up in the different groups. Identify risk factors (clinical and therapeutic) for developing severe forms of Covid-19 infection among patients. ***WP 3: ECONOMIC ANALYSIS OPTIONAL FOR CENTERS*** Describe the consequences of Covid-19 in terms of organizational changes and care practices, from the start of the epidemic until the end of systematic screening for patients and healthcare personnel. Identify changes in healthcare personnel practices regarding: Coordination between healthcare workers a. Communication b. Patient management Identify resources associated with organizational changes at the level of: a. Modification of treatment regimens for patients (e.g., chemotherapy, radiotherapy, surgery) b. Organization of teleconsultations c. Diagnostic investigations for new cancers Analyze the impact of changes on patient health status. Evaluate resources allocated to: a. The organizational changes described above b. Systematic screening of patients and healthcare personnel c. Work stoppages. ***WP 4: PUBLIC HEALTH / EPIDEMIOLOGY OPTIONAL FOR CENTERS*** Identify risk factors for SARS-CoV-2 infection among patients, including: a. Sociodemographic factors (age, socio-professional category, housing, cohabitation) b. Lifestyle (work modalities, mobility, protective measures, etc.) c. Contact with infected individuals at work or at home d. Care pathway in CLCCs (number and duration of visits, number of care units visited, etc.), use of community care Estimate SARS-CoV-2 infection prevalence at the end of the lockdown: a. among patients b. among healthcare personnel who continued onsite work c. among healthcare personnel who were confined Identify risk factors for Covid-19 infection among healthcare personnel, including: a. Sociodemographic factors (age, socio-professional category, housing, cohabitation) b. Lifestyle (work modalities, mobility, protective measures, etc.)

	c. Contact with infected individuals at work or at home d. Use of community care Describe the incidence of Covid-19 infections among patients and healthcare personnel. Compare the distribution of contamination risk factors among patients and those of the general population (Constances cohort). Describe adherence to SARS-CoV-2 vaccination among personnel and patients. ***WP 5 : PSYCHOLOGY OPTIONAL FOR CENTERS*** Examine the evolution of state anxiety over time and determine whether perceptions of anxiety evolve, indicating a possible adaptation process. Examine associations between post-traumatic growth, trait anxiety, sociodemographic variables, and the evolution of state anxiety over time. Examine the evolution of depression over time and determine whether perceptions of depression evolve, indicating a possible adaptation process. Examine associations between post-traumatic growth, trait anxiety, sociodemographic variables, and the evolution of depression over time.
INCLUSION CRITERIA:	1) Age ≥ 18 years; 2) Population from a CLCC meeting one of the following three definitions: ○ patients undergoing treatment, ○ patients in follow-up (having completed their treatment more than one year prior to inclusion), ○ healthcare personnel; 3) Subjects having had or not had an infection compatible with, or confirmed as, Covid-19; 4) Subjects informed and having signed the informed consent form; 5) Subject affiliated with a social security system.
NON-INCLUSION CRITERIA:	1) Refusal to provide consent; 2) Patients unable to give consent or presenting psychiatric history; 3) Inability to comply with medical follow-up for geographical, social, or psychological reasons; 4) Individuals under legal protection (guardianship or curatorship); 5) Individuals deprived of liberty by judicial or administrative decision.
PRIMARY EVALUATION CRITERION:	**Biological data:** Serological status (rapid immunochromatographic test) and IgM and IgG titers (enzyme immunoassay, ELISA type), performed at M0, M3, M6, M9, and M12. Collection via questionnaire of results from tests detecting SARS-CoV-2 viral genome (RT-PCR molecular test) performed in community settings **Clinical data:** Follow-up questionnaire on clinical signs suggestive of Covid-19.
COMPLETION EVALUATION CRITERION:	***WP 1: SEROLOGY MANDATORY*** Time to appearance and titers of anti–SARS-CoV-2 IgM and IgG at the different measurement timepoints in each subgroup. Specificity, sensitivity, PPV (Positive Predictive Value), and NPV (Negative Predictive Value) from the different tests, with quantitative serology (ELISA) considered the gold standard. IgG levels at M12. Number of reinfections or viral reactivations (appearance of clinical signs confirmed by RNA tests — RT-PCR positive — and serology) in the subgroup of patients who developed IgG. Anti-SARS-CoV-2 IgG titers according to the occurrence or absence of reinfection during follow-up.

	Time to appearance and titers of anti-SARS-CoV-2 antibodies according to FCGR2A and FCGR3A genotypes. IgG-positive results on rapid TROD tests and semi-quantitative ELISA IgG titers in vaccinated individuals. Number of vaccinated individuals in whom anti-Spike protein IgG titration is feasible. Number of vaccinated individuals with positive neutralization test results. ***WP 2: CLINICAL MANDATORY*** Number of Covid-19-related deaths, severe infections (requiring oxygen therapy), prolonged symptomatic infections, moderate infections, and asymptomatic infections, relative to all subjects in the population with seropositivity and/or a positive RT-PCR test, as well as duration of the symptomatic phase. Reinfection cases are defined as recurrence of clinical symptoms and/or positive viral PCR and/or positive IgM serology after a symptom-free interval. Frequency is defined as the number of reinfection cases relative to all subjects in the population with seropositivity and/or a positive RT-PCR test. Among subjects in the population with seropositivity and/or a positive RT-PCR test, factors significantly associated with severe forms / mortality among the following: ○ Ongoing or recent anticancer treatment: - Immunotherapy - Chemotherapy, according to frequency of grade 3/4 neutropenia and/or lymphopenia - Radiotherapy - Surgery ○ Concomitant treatments ○ Comorbidities ○ Cancer (cancer type, stage, etc.) ○ Cancer-related medical history (number of treatment lines, surgical and medical history) ○ Biological markers (CRP, etc.) ***WP 3: ECONOMIC ANALYSIS OPTIONAL FOR CENTERS*** Type of organizational and practice changes implemented and their frequency according to specialties/services. Total number of patients affected and number of patients per type of change. Positive or negative effects on patient morbidity or mortality. Monetary value of resources mobilized (increased or decreased) depending on observed changes. Number and duration of healthcare personnel sick leave. Benefits of organizational changes for healthcare personnel. Costs of systematic screening of patients and healthcare personnel.. ***WP 4 : PUBLIC HEALTH / EPIDEMIOLOGY OPTIONAL FOR CENTERS*** Number of SARS-CoV-2 infections among all monitored patients. Prevalence of SARS-CoV-2 infection/immunization during the 3 weeks following the end of lockdown among patients, healthcare personnel working onsite, and healthcare personnel who were confined, by age group, by region (center), and according to comorbidities. Number of SARS-CoV-2 infections among all monitored healthcare personnel. Quarterly incidence rates among patients and healthcare personnel by age group, by region (center), and according to comorbidities. Percentages (qualitative variables) / means or medians (quantitative variables).

	Percentage of personnel and patients refusing vaccination, and distribution according to reasons for refusal. ***WP 5 : PSYCHOLOGY OPTIONAL FOR CENTERS*** a. and b. State anxiety score at 3, 6, 9, and 12 months. c. and d. Depression score at 3, 6, 9, and 12 months. <u>Variables assessed at T0 (before screening)</u> State anxiety (STAI-State questionnaire, Spielberger, Gorsuch, Lushene, Vagg & Jacobs, 1983; 20 items) Post-traumatic growth (PTGI, Tedeschi & Calhoun, 1996; 21 items; induction instruction: "since the lockdown"). The PTGI evaluates perceived positive changes such as shifting life priorities, closer relationships with others, developing new interests, etc. Trait anxiety (STAI-Trait questionnaire, Spielberger et al., 1983; 20 items) Sociodemographic variables (related to the Epidemiology WP) Depression (HADS questionnaire, Zigmond & Snaith, 1983; 14 items) <u>At 3, 6, 9, and 12 months (within the week following screening)</u> State anxiety (STAI-State, 20 items) Depression (HADS, 14 items)

E) DESCRIPTION OF THE STUDY INTERVENTIONS

In this study, screening of patients and healthcare personnel will be performed using two or even three techniques depending on the result:

- **Repeated blood sampling, performed at inclusion (M0), Month 3 (M3), Month 6 (M6), Month 9 (M9), Month 12 (M12), plus on demand in the event of Covid-19 symptoms:**

  a) Rapid serological test (TDR) — qualitative

  - Performed immediately on site.
  - Technique: immunochromatography strip detecting IgM / IgG.

  b) Serology by ELISA — quantitative

  - Performed later on frozen samples.

  c) Genotyping of FCGR2A and FCGR3A genes

  - Performed only at M0.

- **Nasopharyngeal swab (RT-PCR)**
  Detection of viral RNA.

  This examination is performed with immediate result exclusively in the event of symptoms, irrespective of the rapid test result, for patients hospitalized in a Covid unit when such a unit exists within the center.
  Results of RT-PCR tests performed in community settings (outside the hospital) will be collected via questionnaires.

- **Questionnaires** (Linked to the Work Packages — some are therefore optional)
  - <u>Patients</u> **:** Q1, Q2, Q3
  - <u>Healthcare personnel</u> **:** Q1, Q2, Q3, Q4, STAI (ETAT & TRAI), PTGI, HADS

TRIAL SCHEDULE

INCLUSION PERIOD:	12 months
DURATION OF PARTICIPATION PER SUBJECT:	12 months
MINIMUM PARTICIPATION TIME PER PATIENT:	12 months
OVERALL STUDY DURATION:	24 months
START OF THE CLINICAL TRIAL:	June 2020
END OF THE CLINICAL TRIAL:	Last follow-up of the last patient included: May 2022