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Determination of central pain modulation biomarkers to characterize and profile cancer patients with refractory pain

Submission date
19/05/2023

Recruitment status
Recruiting

Registration date
30/05/2023

Overall study status
Ongoing

Last Edited
27/02/2026

Condition category
Signs and Symptoms

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims

The mechanisms of cancer pain are not fully understood. Although quantifying the function of descending pain modulatory pathways using quantitative sensory testing (QST) would improve our understanding of cancer pain, the available evidence is limited. Most of the existing research has focused on the study of peripheral mechanisms. Some studies have used QST, but they only included patients with chemotherapy-induced peripheral neuropathy and evidenced abnormal responses (mostly thresholds) to a variety of stimuli. Nevertheless, few studies have considered dynamic indices, such as conditioned pain modulation (CPM) and reduced temporal summation of pain (TSP) or osteoarthritis (OA), which are more closely linked to the underlying neurobiological mechanism of pain. In this line, it has been found that women who experienced chronic pain after breast cancer surgery, as compared with women without pain after that surgery, displayed enhanced TSP of mechanical pain (i.e., increased painful sensations with repeated stimulation) and deficits in CPM. The study suggested that persistent postoperative pain may be associated with alterations in endogenous pain inhibition at the central nervous system (CNS) and that treatment strategies should target those pain-modulatory systems. A recent systematic review also highlights that QST indices may improve knowledge of the mechanisms involved in cancer pain. According to this, we aim to characterize and profile patients with cancer pain (using the central pain biomarkers and moderator variables) and select the more sensitive variables of classification to study the response to treatment. A novel methodological approach will be used for data analysis to select the best biomarkers classifiers and profile patients, using supervised machine learning algorithms, including the latest Deep Learning approaches. Finally, we intend to create a Cancer Pain Biomarkers Database with normative data on the central biomarkers used (it could be helpful for clinicians in the field of oncology and to manage other chronic pain diseases).

Who can participate?

Adult (≥ 18 years old) non-hospitalized patients with cancer affecting the lung, breast, pancreas, or colon (with metastasis or not) who have cancer pain (cases) and those who have no pain (controls)

What does the study involve?
In this study, the same evaluation will be carried out on both groups (cases and controls) at a single time point (cross-sectional study). In this study, an interview will be conducted (sociodemographic and clinical data), and questionnaires will be administered to patients (to measure different variables such as pain, fatigue, quality of life, sleep, mood, etc.). In addition, data will be collected from their clinical history. Also, we will use quantitative sensory testing (QST) procedures and electroencephalography (EEG) to assess how participants perceive and modulate pain.

What are the possible benefits and risks of participating?
Participation will not give participants direct benefits. The research aims to discover unknown or unclear aspects of chronic pain in cancer patients. This information may be useful to other patients in the future. All procedures used in the study are completely safe. QST is a set of tests in which an experienced researcher applies thermal/painful stimuli to participants' arms and hands. All the stimuli are designed to assess the sensation of pain without burns risk and are adapted to participants' pain threshold. This pain sensation will remit within a few minutes. EEG is a harmless procedure (it is painless and with no risk). It consists of placing a cap with electrodes on your head and recording your brain activity. All the procedures we use are safe and do not involve a health risk, except for minor discomforts arising from the use of painful stimuli, which will disappear in a few minutes. Participating in this study will involve spending time answering the questionnaires.

Where is the study run from?
This is a multicenter study, in which different clinical units participate:
1. SERGAS (Galician Service of Health) with two units (FIDIS - Santiago de Compostela Health Institute Foundation) and (FBGS Galicia Sur Biomedical Foundation)
2. University of Santiago de Compostela (USC)
3. Technion (Israel Institute of Technology)
4. University Medicine Gottingen (UMG)
5. Ente Ospedaliero Cantonale (EOC); HOSPICE Casa Speranţei (HCS)
6. Institutul Oncologic Bucuresti Prof. Dr. Alexandru Trestioreanu (IOB)

When is the study starting and how long is it expected to run for?
June 2022 November 2027

Who is funding the study?
HORIZON EUROPE research and innovation program under the GA 101057367

Who is the main contact?
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Additional identifiers

Protocol serial number
WP2

Study information

Scientific Title
Determination of central pain modulation biomarkers to characterize and profile cancer patients with refractory pain

Acronym
PAINLESS

Study objectives
1. The study of diagnostic biomarkers derived from quantitative sensory testing and brain electrical activity will help to stratify the patients according to those mechanisms.
2. The central pain modulation mechanisms will be more dysfunctional in older patients and for females than males.
3. The Cancer Pain Biomarkers Database will provide a standard simple protocol, guidelines, normative data, and valuable AI algorithms to characterize patients with cancer pain.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 21/09/2022, Research Ethics Committee of Santiago-Lugo (Comité Territorial de Santiago y Lugo. Xerencia Do Servizo Galego De Saúde. Complexo Administrativo de San Lázaro. 15781 Santiago de Compostela, Spain; +34 881 546425; ceic@sergas.gal), ref: 2022/324

Study design
Cross-sectional case-control multi-centric study

Primary study design
Observational

Study type(s)
Screening

Health condition(s) or problem(s) studied
Assessment of cancer pain in patients with breast, pancreatic, lung, colon or prostate cancer.

Interventions

This study will measure different variables (pain biomarkers and moderating variables) at a single time point (baseline; cross-sectional study) to compare cancer patients with cancer pain and those without pain and characterize and profile cancer patients with refractory pain (case versus control).

This study attempts to improve the knowledge of cancer pain mechanisms by using central modulation biomarkers (quantitative sensory testing and EEG indices) to characterize and profile the patients. The research proposal is:
1. To assess the central pain biomarkers of cancer pain: select the best ones to classify the patients who experience pain in relation to those who do not, and analyze the role of other moderator variables.
2. To create a database of pain modulation biomarkers in cancer pain.

The study will use quantitative sensory evaluation equipment (thermal contact stimulator (TCS II) and cold plate) to measure the quantitative sensory testing biomarkers and a portable recording system of 32 electrodes adapted for clinical use to measure EEG indices. In addition, the team will conduct a face-to-face interview session, use different questionnaires (both on paper and via an online platform) and collect data from the patient's medical records to assess the different variables.

The staff involved in the study are oncologists and neuroscience researchers. All staff have received specific training in data collection (quantitative sensory evaluation and EEG).

The study will be carried out in hospitals, research institutes and universities.

The study team will make a single assessment at a single point in time, which will consist of a face-to-face assessment (estimated duration 2h) and the completion of several questionnaires through an online platform, from home (estimated duration 1h).

Intervention Type
Other

Primary outcome(s)
Cancer pain measured using a Numeric Rating Scale (NRS) at one timepoint

Key secondary outcome(s))
The study team aim to assess a number of variables to characterize patients with cancer pain, comparing patients with and without pain (cases versus controls). All variables are assessed at one time point (cross-sectional study):
1. Sociodemographic and clinical variables measured using an interview
2. Clinical variables measured using data from the clinical history of the patients
3. Mood (anxiety and depression), pain, sleep quality, fatigue, pain catastrophizing, cognitive functioning (subjective complaints) and quality of life, etc. measured using questionnaires
4. Quantitative Sensory Testing biomarkers measured using a thermal contact stimulator (TCS II) and a cold plate
5. Electroencephalogram (EEG) indices measured using a portable recording system of 32 electrodes adapted for clinical use

Completion date
30/11/2027

Eligibility

Key inclusion criteria
Cancer patients with pain:
1. Adult subjects ≥ 18 years old
2. Able to provide informed consent to participate in the study
3. Able to self-report pain
4. To have a diagnosis of cancer affecting the lung, breast, pancreas, colon or prostate (with metastases or not)
5. The life expectancy of at least six months
6. Cancer pain persisting despite best-tolerated pharmacological treatment
7. Pain rated ≥5 on a 0-10 Numeric Rating Scales (NRS) persisting for over 1 month prior to enrolment
8. Ability to use the internet and WhatsApp or have a person (relative, caregiver) to help them

Cancer patients with no pain:
1. Adult subjects ≥ 18 years old
2. Able to provide informed consent to participate in the study
3. Able to self-report pain
4. To have a diagnosis of cancer affecting the lung, breast, pancreas, colon or prostate (with metastases or not)
5. The life expectancy of at least six months
6. No chronic pain after cancer disease or treatment
7. Ability to use the internet and WhatsApp or have a person (relative, caregiver) to help them

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
110 years

Sex
All

Total final enrolment
0

Key exclusion criteria
Current key exclusion criteria as of 27/02/2026:
Cancer patients with pain:
1. Pregnant women or women of fertile age who did not have efficacious contraception during

the whole period of the study
2. Neurological or psychiatric diseases (except anxiety or depression)
3. Unstable medical conditions (e.g., uncontrolled diabetes, uncompensated cardiac issues, heart failure or chronic obstructive pulmonary disease)
4. History of neurosurgery, traumatic brain injury with loss of consciousness, and/or cortical lesions
5. Present risk factors for receiving tES (e.g., history of epilepsy, metal devices in the brain, etc.)

Cancer patients with no pain:
1. Pregnant women or women of fertile age who did not have efficacious contraception during the entire period of the study.
2. Neurological or psychiatric diseases (except anxiety or depression).
3. Unstable medical conditions (e.g., uncontrolled diabetes, uncompensated cardiac issues, heart failure or chronic obstructive pulmonary disease).
4. History of neurosurgery, traumatic brain injury with loss of consciousness, and/or cortical lesions.
5. History of non-malignant chronic pain.

Previous key exclusion criteria:
Cancer patients with pain:
1. Pregnant women or women of fertile age who did not have efficacious contraception during the whole period of the study
2. Neurological or psychiatric diseases (except anxiety or depression)
3. Unstable medical conditions (e.g., uncontrolled diabetes, uncompensated cardiac issues, heart failure or chronic obstructive pulmonary disease)
4. History of neurosurgery, traumatic brain injury with loss of consciousness, and/or cortical lesions
5. Present risk factors for receiving tES (e.g., history of epilepsy, metal devices in the brain, etc.)
6. History of non-malignant chronic pain

Cancer patients with no pain:
1. Pregnant women or women of fertile age who did not have efficacious contraception during the entire period of the study.
2. Neurological or psychiatric diseases (except anxiety or depression).
3. Unstable medical conditions (e.g., uncontrolled diabetes, uncompensated cardiac issues, heart failure or chronic obstructive pulmonary disease).
4. History of neurosurgery, traumatic brain injury with loss of consciousness, and/or cortical lesions.
5. History of non-malignant chronic pain.

Date of first enrolment
20/02/2024

Date of final enrolment
30/11/2026

Locations

Countries of recruitment
Germany

Israel

Romania

Spain

Switzerland

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Sponsor information

Organisation
University of Santiago de Compostela

ROR
https://ror.org/030eybx10

Funder(s)

Funder type
Government

Funder Name
HORIZON EUROPE Framework Programme

Alternative Name(s)
Horizon Europe, Horizon Europe Programme, Framework Programme, Horizon Europe, EU Framework Programme, Horizon, Horizonte Europa

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

Results and Publications

Individual participant data (IPD) sharing plan
1. Types of information:
Personal and contact data (name, email address, telephone number) will be collected and stored separately from the remaining data. We will detail later how this sensitive information will be handled. All remaining data will be coded.
Clinical data will be collected by two ways: from the clinical history of patients diagnosed with cancer; and project-generated information on symptoms related with pain, comorbidities, and the general condition of participants.
QST and EEG data will be collected. We will obtain data on detection and pain thresholds using single or repeated noxious stimuli (hot and cold), with concomitant painful stimuli being applied to the other side of the body. We will record EEGs in a resting-state phase and during the presentation of heat stimuli.
Personal and contact data will be generated and stored physically in the clinical unit where they were obtained with access control. Only the email, will be stored digitally in .xls and similar formats (also with access control). The clinical, central pain mechanisms will be generated and stored only digitally in .xls and similar formats. The electrophysiological data will be generated and stored also digitally in .csv and Matlab (https://www.mathworks.com/) compatible formats.

2. Informed consent:
This information will be collected in a pseudonymized form. Permission for access to this information will be included in the informed consent. The consent will include assurance that patient data sets used in training and machine learning processes will be anonymized before being consumed by these processes. In this context, just the clinical info is relevant and not any personally identifiable information.

3. Data security:
Concerning sensitive data protection, we will comply with the directives of the General Data Protection Regulation (GDPR), approved by the European Commission on April 27, 2016 (UE 2016 /679), on the protection of individuals regarding the processing of personal data. Privacy concerns any data, which relate to an identifiable individual. Prior to collecting, storing & processing sensitive health data the consortium will seek the consent of the applicable local /national data protection authorities and work within the processes recommended in the e-

Health Task Force Report “Redesigning Health in Europe for 2020”. The coordinator (USC) will follow the guides and guidelines on the application of the rules published by the Spanish Agency of Data Protection, under the advisement of the Data Protection Officer of the institution. We assure the confidentiality of all the data generated from the project.

4. Repository:
Data repository will not contain personal-identifiable data. So, the mapping between personal identification and respective clinical data will not be possible.
The data repository will be composed by the next three repositories:
Identification Management, which will be a database server service and a backend dedicated persistence service, for storing the personal identification and session data, but not clinical information. Before storing it in database, the sensitive data will be encrypted, using Advanced Encryption Standard (AES) – a symmetric encryption algorithm. Also, some info (such as password) will be encrypted without decrypting possibility. The Identity Management component will be an internal and private component inside cloud, and not opened to outside Domain Name System (DNS); the data inside id can be accessed just through intermediate interoperability and orchestrator services.
Structured Data management, which will be a database server and a dedicated persistence service, is used for storing clinical data, in a structured content, and linked information. The component will apply the pseudonymization and de pseudonymization procedures for data securing, in order to apply the health secure data standards as GDPR and HL7 data protection. The Structured Data Management component will be an internal and private component inside cloud, and not opened to outside DNS; the data inside it can be accessed just through intermediate interoperability and orchestrator services.
Unstructured Data Management, which will be composed by a Secure File Transfer Protocol (SFTP) server and a backend access server, intended to store files with clinical contents, of different formats, like PDF, CSV, EXCEL, PNG, etc, with no limitation, except some case that will be eventually impounded by the pilot. The files will be stored using an encryption mechanism. The Unstructured Data Management component will be an internal and private component inside cloud, and not opened to outside DNS. The data inside it can be accessed just through intermediate interoperability and orchestrator services.
The data of the PAINLESS project will be digital and will be stored in the Supercomputing Centre of Galicia (CESGA; www.cesga.es). CESGA infrastructure offers a trusted repository where custody arrangements will be deployed. It is a non-profit Singular Scientific Technological Infrastructure that offers a service for storing and treating high performance information, with distinct massive data storage solutions, and ensures high availability and access from any computer connected to the Internet. CESGA participates in the main initiatives building the EOSC (European Open Science Cloud), like the EOSC-hub and the EOSC-synergy, as well as the supercomputing initiatives like PRACE-5IP, and thus it will allow us to connect and use these infrastructures to process and store the data in the evolving EOSC.
The repository will guarantee the assignment of a digital identifier to control the access to the data but will not provide the assignment of the identifier to a digital object (e.g. DOI). If this service is necessary, we will consider other options for the data repository (e.g. Zenodo; https://zenodo.org/).

5. Data access:
Access to PAINLESS data will be offered via the project web platform. SIMAVI (PAINLESS partner responsible for the creation of the web platform -WP4) will provide this service.
During the project and for one year thereafter the data will have restricted access to the public, only authorised PAINLESS members will have access to the data. This access will be controlled and standardised through the PAINLESS platform. During the PAINLESS project, if unauthorised consortium members need to access the database, they should request access from the PIs of

each data collection unit and the coordinator of the project. Both PIs and the coordinator must agree to consent to access. After the project, the parties with rights over the data will study the best conditions to make the anonymised datasets accessible beyond PAINLESS.
Given the international nature of the project, it is expected that participant data could be shared with consortium members via email or Sharepoint. This information sharing will be done using an anonymized data set in accordance with the European General Data Protection Regulation (GDPR, Article 5).
Within PAINLESS, three different possibilities for data dissemination will be considered:
Open Access Publications and Data-sharing: For the publication of the results (articles, poster, conference, etc.), a meaningful selection of generated results will be made open access to the scientific community and to the public, possibly restricted by embargo periods and/or respecting restrictions from editors of scientific journals and organizers of conferences. The publications during the PAINLESS project and one year thereafter must be validated by all consortium parties with rights over the data and by the project's coordinator. Regarding transparency of the data and results of the project, the preparation of tailor-made dataset packages to be shared with the scientific community will be considered. A package will contain a compilation of the metadata of the published results and the metadata of the relevant datasets needed to verify the results, provided that these can be made available. The PAINLESS consortium will discuss whether digital object identifiers (DOIs), which could easily be included in publications as references, will be used for these dataset packages.
Commercial exploitation: One year after the end of the PAINLESS project, the parties with rights over the data and over the PAINLESS web platform will study how to make the anonymised datasets accessible beyond PAINLESS. This study will consider the possibility of creating licenses and/or patents. We intend to implement a registration procedure for all those interested in such datasets. This includes the opportunity to differentiate the conditions for access depending on the type of inquirer or planned re-usage (e. g. dataset could be free of charge for public scientific institutions for scientific work but with charge in case of commercial re-use by a company). After registration of the request of a dataset, a time-limited download link will be provided via e-mail to the registered contact together with the terms of usage. The requisition will be implemented in the metadata.
Indirect dissemination: Parts of the PAINLESS' generated data could be disseminated based on post-analysis of results

IPD sharing plan summary

Stored in non-publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Study website	Study website	11/11/2025	11/11/2025	No	Yes