Characterization of Central Pain Syndrome in Survivors of Head and Neck Cancer

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1.0 Background:

Over the past three decades, the survival rate of patients diagnosed with cancer has steadily increased as a result of advancements in cancer screening tools, multidisciplinary treatment plans, and the development of targeted therapies. By the year 2026, it is estimated that 20.3 million people in the United States will be defined as a cancer survivor - one who carries or has carried the diagnosis of cancer (*1*). But it is becoming increasingly clear that fighting cancer is only half the battle. As patient outcomes have improved and lifespans extended, long-term toxicities associated with therapy significantly impact quality of life after cancer.

A particularly challenging morbidity in this patient population is the development of persistent, chronic pain. Interestingly, as many as 28% of survivors continue to have moderate pain six months after treatment completion (*2*). Not only is this distressing for the patient, but the continued use of opioids months or years after curative treatment further contributes to the burden of the ongoing national opioid epidemic (*3*). Opioid use is associated with its own deleterious side effects which include difficult access to medication, risk of overdose, addiction, gastrointestinal dysmotility, and obtundation. In addition, these chronic pain states are closely associated with the development of depression, anxiety, cognitive dysfunction, and sleep disturbances which are further detrimental to quality of life (*4, 5*).

Head and neck (H&N) cancer patients often undergo rigorous treatments which involve chemotherapy, radiation, and surgery. As a result, these patients are highly susceptible to the development of acute and chronic pain. Initially, pain in this population can manifest as acute, well-localized nociceptive pain or neuropathic pain from direct nerve injury. In most cases, these types of pain can be treated with NSAIDs, acetaminophen, and/or opioids during treatment. However, some patients will gradually develop an increasing sensitivity to pain that extends beyond the course of treatment. In extreme cases, patients experience exaggerated pain responses to noxious stimuli (hyperalgesia), painful responses to innocuous stimuli (allodynia), pain in areas unaffected by cancer or its related treatments, and other systemic symptoms of neurological impairment such as fatigue, cognitive dysfunction, and mood disturbances. In this particular subset of patients, the pathogenesis of this exaggerated pain phenotype is highly reminiscent of an amplified pain state also known as central sensitization. In the presence of a repetitive noxious stimulus, the threshold for pain in nociceptive receptors is lowered as a protective mechanism (primary hyperalgesia) (*6*). The exaggerated response to pain eventually returns to baseline after removal of the stimulus. However, in chronic pain states, overamplification of the nociceptive pathway and dysfunction of inhibitory pathways in the central nervous system leads to permanent pathological pain amplification, known as central sensitization. This manifests clinically as secondary hyperalgesia (pain outside of the site of injury), allodynia, and/or widespread pain (*7*).

The literature regarding pain in cancer survivors is still in its infancy given the increasing number of curative therapies leading to longer rates of survival after treatment. What we are just now starting to realize is that specific pain phenotypes are unique to specific types of cancers and consequently require different types of pain regimens. However, lack of education and consensus definitions in the classification of pain have resulted in continued opioid use long after commencement of cancer treatment, leading to increased tolerance and escalating doses in the cancer survivor population. Perhaps the most well documented cancer pain syndrome is post-mastectomy pain syndrome (PMPS). The incidence of pain after breast surgery has been reported to

be around 20-50% (*8-11*). This variability can be attributed to the lack of a consensus definition to describe PMPS (*12*). In addition, different types of pain are encompassed within the single definition of PMPS. Patients may suffer from pain overlying scar tissue, direct nerve injury, phantom breast pain, pain from impaired lympathic drainage, and/or musculoskeletal pain just to name a few (*13*). To complicate matters further, each of these pain phenotypes have differing underlying mechanisms which include pain induced by local inflammation and destruction sensed by nociceptors, neuropathic pain due direct injury to the peripheral and central somatosensory system, central sensitization from abnormal ascending and descending pain processing mechanisms, or mixed pain (*14, 15*). As one can image, the underlying pathogenesis of pain strongly determines the response to specific medications and account for treatment failure. In fact, trials that examine treatment effect in a population of patients without proper pain classifications may lead to negative results (*16*). Thus, cancer type specific classifications of pain and their underlying pathogenesis must be carefully studied in order to establish effective clinical trials for the prevention and treatment of pain in cancer survivors.

Classically, central sensitization is a feature of several chronic pain states such as fibromyalgia, irritable bowel syndrome, and temporomandibular disorder (*17*). Although these conditions are seemingly heterogenous in nature with varying anatomical focal points of amplified pain, the syndromes themselves encompass many of the same systemic symptoms as described above. These central sensitivity syndromes are often difficult to treat because an identifiable cause or trigger remains to be elucidated. It has been speculated that genetic predisposition, neuro-inflammation involving both the innate and adaptive immune systems, and rewiring of the pain circuitry in the central nervous system are all involved (*17-20*). However, the natural progression of these disease states is difficult to follow because patients often present after the disease process is already well underway.

Recently, imaging modalities have garnered much interest in identifying structural and functional changes in the brains of patients with central sensitivity states. In fibromyalgia patients, there is both decreased and increased grey matter volume and increased connectivity in brain areas responsible for the anticipation of, attention to, and emotional processing of pain (*21-23*). Resting state functional magnetic resonance imaging (fMRI) scans measure basal metabolic signatures during periods of “rest” that can reveal underlying connectivity of different areas of the brain and have been shown to be amplified in patients with central sensitization syndromes such as fibromyalgia, chronic fatigue, irritable bowel syndrome, temporomandibular joint disorder patients (*24*). Structural alterations such as grey matter volume can also be measured using structural MRI measurements in areas of the brain that are associated with stress, pain, emotional processing, and memory development. A combination approach of quantitative sensory testing (*25*) along with fMRI imaging has been used to correlate pain thresholds with brain activity in the fibromyalgia patients (*23*). In these studies, a stimulus of increasing intensity (vibratory, thermal, or pressure) is administered in a step-wise fashion and changes in blood flow (and therefore activity) to specific brain regions are assessed. These types of studies have shown that lower pain thresholds correlate well with earlier activation of pain centers in patients with fibromyalgia when compared to negative controls. Although these studies have made great strides in unveiling the dynamic processes involved in central sensitization, the sequential events leading to the development of the central sensitivity syndromes are still unknown. This is because the existing literature only provides a snapshot of ongoing pathological pain processes since these patients present only after

disease onset. This is supported by the conflicting structural and functional MRI data in the literature which is likely due to a heterogeneous patient population who may be in distinct stages of disease progression.

Upon initial diagnosis, most H&N cancer patients present with localized nociceptive pain but the combination of surgical resection and radiation therapy commonly causes acute and chronic pain localized to the involved area of the head and neck region. What is less well recognized is that 23% of H&N cancer survivors report persistent moderate to severe widespread pain that may last indefinitely (*21, 26*). In addition, H&N cancer patients often present with other systemic symptoms such as depression, anxiety, and cognitive dysfunction that can severely affect their quality of life. Given the relatively high occurrence of what resembles a central sensitivity state in this patient population and the potentially trackable development of this state during the course of cancer treatment, the H&N cancer population provides an exceptional model system for studying the pathogenesis of central sensitization in real-time.

We hypothesize that central sensitization is a key pathological process that occurs in a subset of H&N cancer patients who experience chronic pain beyond treatment completion. In our pilot study, we propose to conduct a cross-sectional study of H&N cancer survivors who have completed multimodal treatment to assess and characterize the presence of distinct pain phenotypes: localized, nociceptive pain versus centralized pain. Using structural and functional MRI, we will determine if a distinct brain signature similar to other central sensitivity syndromes is present and if we can distinguish central from non-central (normal, nociceptive) pain in this specific population. We will also document the presence of other systemic symptoms such as fatigue, mood disturbances, neurocognitive changes, and sleep disturbances to see if the culmination of specific symptoms correlates to the presence of distinct MRI signals to predict and diagnose central sensitization in these patients. This study will aim to answer several important questions. 1) Does central sensitization play a role in the pathogenesis of chronic pain in H&N cancer survivors? 2) Can we objectively and reliably measure nociceptive versus centralized pain in this population? 3) Does this objective brain signature correlate to the presence of specific subjective symptoms?

The answers to these questions will provide us with the foundation for future studies in which we hope to characterize the evolution and progression of central sensitization in this unique patient population. This will allow us to eventually guide personalized treatment regimens for treating and preventing central pain in the cancer population using multimodal, non-opioid based regimens. It will also provide us with a rare opportunity to expand our knowledge in the pathogenesis of central sensitization that will be globally applicable to other centralized pain syndromes.

2.0 Study Summary and Specific Aims:

Summary: We propose to conduct a cross-sectional pilot study of H&N cancer survivors who have completed multimodal treatment to assess and characterize the presence of distinct pain syndromes. We plan to screen patients who have completed head and neck cancer therapy using a battery of patient reported outcome measures (PRO's). Based on the PRO responses, patients will be characterized as follows: 1) no pain, 2) central pain, and 3) nociceptive pain. Patients will then undergo structural and functional magnetic resonance imaging

(MRI). We will correlate clinical presentation with MRI signatures to determine if distinct signatures can be identified for each cohort. In addition, we propose to correlate the clinical and MRI signatures for central pain with the presence of other systemic symptoms. Participants will be asked to fill out several questionnaires that capture systemic symptoms commonly associated with other central sensitivity syndromes.

Aim 1: To correlate structural and functional MRI signature with one of three pain phenotypes in H&N cancer survivors: 1) no pain, 2) central pain, and 3) nociceptive pain.

Hypothesis 1: Structural and functional MRI can identify unique signatures that correspond with pain phenotype.

Aim 2: To correlate the presence of chronic systemic symptoms with pain phenotype.

Hypothesis 2: Patients with central pain will have an increased frequency of other systemic symptoms (fatigue, neurocognitive dysfunction, depression, etc.) as measures on the General Symptom Survey.

Exploratory Aim: DNA, RNA, and plasma will be collected for genomic, transcriptomic, and proteomic studies. Results will be vertically integrated along with the results of clinical studies described within this protocol to identify targets for future correlative studies.

3.0 Methods:

Patient Eligibility:
Inclusion Criteria:
- Patients with histologically proven head and neck cancer
- Patients without a diagnosis of head and neck cancer (up to 10 patients, see below)
- Completed multi-modality therapy a minimum of 6 weeks prior to study entry.
- Willing and able to provide informed consent
- All participants must be at least 21 years of age
- Able to speak English

We anticipate enrolling a total of 75 patients with a history of head and neck cancer who will complete all questionnaires and MRI scanning. We will also recruit up to 10 patients WITHOUT a diagnosis of head and neck cancer to facilitate optimization of the MRI scanning processes. This will allow us to address logistical issues, such as pressure stimulator setup and timing of each scan to be performed.

Exclusion Criteria:
- Patients who are pregnant. See below under “Study Procedures” section on pregnancy testing.
- Patients who are unable to lie still.
- Patients who are unable tolerate pressure stimulator.
- Non-MRI compatible devices such as aneurysm clips, cardiac pacemakers or defibrillators, cochlear implants, hardware, or any other implants
- Iron-based tattoos, pieces of metal (bullet, BB, shrapnel) close to or in an important organ (such as the eye), or other non-MRI compatible metal in the body.

Study Procedures:

Recruitment

The attending physicians, nurse practitioner or nurses in the Oncology Clinic routinely review the list of patients presenting to clinic for follow-up visits. All patients who are a minimum of 6 weeks post treatment will be provided with information about the study and asked if they are interested in study participation. If patients express interest, trained study staff will be notified. Study staff will meet with all interested patients to discuss the study in more detail and answer questions.

Informed Consent Process

Research staff will obtain informed consent from the study participants before initiation of data collection. This process will take place in a quiet, private location at Vanderbilt Medical Center to ensure confidentiality. During the informed consent process, a copy of the IRB-approved consent from will be provided to prospective study participants. Research staff will review the study risks, potential benefits, and procedures to assess confidentiality and data de-identification. Prospective study participants will be assured that their participation in the study is voluntary, and that they can withdraw at any point in the study by notifying research staff. Participants will be provided with research staff contact information. Prospective study participants will be informed that refusal to participate in the study or withdrawal from the study will not affect their care. After verbally reviewing the informed consent documents, prospective participants will be allotted ample time to read the consent form or have the consent form read to them aloud. Research staff will verify comprehension of the informed consent process, and then ask the prospective participant if they wish to enroll on the study. If so, prospective study participants will be instructed to sign the IRB-approved consent form. In addition, research staff obtaining informed consent will sign the form. The study participant will then be provided with a copy of the signed consent form. The research staff will have received training in obtaining informed consent.

The original signed IRB-approved consent form will be stored in a locked file drawer in the study office or stored in the password protected REDCap database if applicable. The informed consent document will be scanned into the study participant's electronic medical record. Alternatively, we will use an electronic consent form that will be completed on the REDCap database.

Pressure Stimulator Testing

At the time of enrollment and after the informed consent has been signed, the study staff can demonstrate the use of the pressure stimulator (IPC-1000 (*27*)) in the clinic if requested by the patient. These systems are computer-controlled, MRI-compatible pressure stimulators that allow for remote delivery of a stimulus that can be used in synchronization with imaging sequences if needed. Patient pain responses can be recorded in real time to varying degrees of pressure inside or outside the MRI machine. The pressure stimulus is delivered to the thumbnail via a thumbnail pressure stimulator. Those who are unable to tolerate the pressure stimulator will not proceed with the study.

On the day of the MRI scans, we will conduct two separate tests. First, we will measure the pain threshold (when pain is >0) and tolerance (when pain is unbearable) to a pressure stimulus as previously described in the literature (*28*). This information will be used to calculate an individualized pressure intensity for the next test (*29, 30*). Next, we will test for central sensitization using the slowly repeated evoked pain protocol. This

test consists of delivering a five-second pressure stimulus with a 30 second rest period repeated for a total of 9 times. The sequence of events is anticipated to be as follows:

Pain Threshold and Tolerance Testing

1. Delivery of 0.5 kgf/cm^2 pressure stimulus to dominant thumbnail for 5-10 seconds using the automated system.
2. Patient rates pain intensity of stimulus from a scale of 0-100.
3. 20 second rest period (patient will not be told how long to prevent anticipation).
4. Repeat steps 1-3 with increasing levels of pressure in 0.5 kgf/cm^2 increments until participant asks to stop, pain intensity is >80/100, or maximum pressure of 10 kgf/cm^2.

5-10 minute rest period

Slowly Repeated Evoked Pain Testing

1. The intensity of the stimulus will be determined by using the following equation: Individualized SREP intensity = Threshold + 1.25*(DF/4), where DF = Tolerance-Threshold (ref)
2. Delivery of individualized SREP intensity pressure stimulus to non-dominant thumbnail for 5 seconds using automated system.
3. After 5 seconds, patient rates pain intensity of stimulus from a scale of 0-100.
4. 20-30 second rest period (patient will not be told how long to prevent anticipation).
5. Repeat steps 2-4 eight more times.

The average time to test completion is less than 12 min based on the literature. We believe that most patients will be able to tolerate this stimulus. In a recent study by Harte *et. al.* (*28*), tolerability of the pressure stimulus was high and only 10 out of 298 patients opted out. They were able to obtain data for 62 patients with urologic chronic pelvic pain syndrome at the initial visit and 52 measurements at a 6 month follow-up visit. In fact, the pressure pain stimulus protocol has been adapted from this article. However, those who are unable to tolerate the stimulus will not be included in the anticipated accrual goal count.

Since the initiation of study, we have recruited and tested 3 subjects. For those who have already completed the study, we will attempt to repeat the pain threshold and tolerance testing along with the slowly repeated evoked pain testing during a future clinic appointment. All other enrolled subjects who have not completed the study will undergo the entirety of the protocol on the day of MRI scanning.

Exclusion of Pregnant Women

Although MRI has not shown to affect pregnancy, those who are pregnant will be excluded from the study. Women of reproductive age will be asked to take a pregnancy test after informed consent has been obtained. The pregnancy test will be conducted on the day of the MRI scan. Those who have had bilateral oophorectomies, hysterectomy, and/or tubal ligations will be excluded from pregnancy testing. If pregnancy test is declined, the patient will be excluded from the study.

PRO Data Collection

Disease and treatment data (e.g. type and stage of cancer, date of cancer diagnosis) will be obtained from the participant's medical record review by study staff at Vanderbilt.

After patients have signed informed consent, they will be scheduled for study related activities at a time that is convenient to them. All patients will complete the Sociodemographic Data Collection Form, the Vanderbilt Head and Neck Symptom Survey plus General Symptom Survey Version 2.0, Profile of Mood States-Short Form, Neurotoxicity Rating Scale, the Quality of Life Assessment, Central Sensitivity Inventory, the Fibromyalgia Diagnostic Tool, and the Head and Neck Pain Inventory.

Blood Draw:

About 20% of the H&N cancer population develop long-term pain and systemic symptoms after treatment. However, the risk factors associated with the presumable development of central sensitization in this specific patient population have not been identified. To better understand the molecular basis of this treatment complications, patients will undergo phlebotomy for future molecular analyses. DNA, RNA, and plasma will be collected for genomic, transcriptomic, and proteomic studies. Results will be vertically integrated along with the results of clinical studies described within this protocol to identify targets for future correlative studies.

At the time of MRI, blood will be drawn from each patient. Up to 20 ml of blood will be divided for RNA, DNA, and plasma extraction. A portion of the blood will be divided into PAXgene tubes for RNA extraction. The remainder of the blood will be separated into plasma for proteomic analysis and cells for DNA extraction. Samples will be stored at -80C until ready for processing.

Phenotype Designation:

Following completion of the questionnaires, the patient's responses will be reviewed by the principle investigator. Patients will complete the Central Sensitivity Inventory questionnaire, the Fibromyalgia Diagnostic Tool, and the Head and Neck Pain Inventory to determine inclusion into each cohort. Using criteria established in the non-oncologic patient population, patients will be assigned to one of three cohorts by thre independent reviewers (Dianne Lou, Barbara Murphy, and Nancy Wells): those with 1) no pain, 2) central pain and 3) nociceptive pain. At least two out of three reviewers much agree with each assignment. 25 patients from each of the principle cohorts will proceed to structural and functional MRI testing. Recruitment will continue until all three cohorts are filled. The patient's participation will be concluded.

Structural and Functional MRI Testing:

The study staff will schedule MRI testing at a time that is convenient for the patient. The procedure will take approximately 1.5-2 hours.

Compensation:

Upon completion of the MRI, patients will be provided with a $50.00 gift card to compensate them for their time and effort.

4.0 Measures:

Questionnaires:

Demographic Data Form: Patients will be asked to report their birthdate, gender, race, ethnic category, highest educational level, marital status, employment status, area of residence, insurance coverage, and annual household income.

Vanderbilt Head and Neck Symptom Survey plus General Symptom Survey version 2.0 (VHNSS v2.0 plus GSS): The VHNSS v2.0 (*31*) assesses the prevalence and severity of treatment-related symptoms and their functional impact in patients with head and neck cancer. The VHNSS v.2.0 consists of 50-items within 13 domains including nutrition, swallowing, xerostomia, mucositis, excess mucus, speech, hearing, taste change, smell, dental health, mucosal sensitivity, range of motion, and pain. Items are scored on a numeric scale rating the severity of the symptom from 0 (none) to 10 (severe). The VHNSS v.2.0 takes approximately 10 minutes to complete. VHNSS v2.0 plus GSS includes 12 additional items directed at the systemic effects of therapy.

Profile of Mood States-Short Form (POMS-SF): The POMS-SF is a 37-item scale is composed of six subscales: depression, vigor, confusion, tension, anger and fatigue. Cronbach's alphas ranged from 0.78 to 0.91. It correlates will with other measures of mood and physical function, yet is has the benefit of a short administration time.

Neurotoxicity Rating Scale (NRS): The NRS is a 37 item instrument whose items reflect symptoms associated with neurotoxicity of medical treatment (*32*). Participants rate the severity of all of the 37 item, 5 point Likert-like scale that rates neuropsychiatric symptoms on a scale of "not present" to "extremely severe."

Quality of Life: QOL will be measured using Cantril's Ladder, a single item self-anchoring scale (*33, 34*). The measure asks patients to rate their current quality of life on a scale ranging from 0 to 10, with higher scores indicating better overall quality of life. Discriminant validity has been supported by significantly lower scores in patients with rheumatoid arthritis than in healthy controls (*35*). Construct validity has been supported by a positive relationship between scores on to social role retention in survivors of bone marrow transplantation (*36*). A 5 item domain-specific QOL questionnaire will also be used.

Central Sensitivity Inventory (CSI): The CSI is a two-part survey consisting of 35 questions (*37*). Part A asks patients to identify systemic symptoms as being present "never", "rarely", "sometimes", "often", or "always". Part B determines whether patients have been previously diagnosed with central sensitivity syndromes or other related disorders. Only Part A is used for scoring.

Fibromyalgia Diagnostic Tool (FDT): The FDT is a questionnaire developed based on the revised American College of Rheumatology's diagnostic criteria for fibromyalgia from 2016 (*38*). It combines the widespread pain index and the symptom severity scale to aid in the diagnosis of fibromyalgia and the severity of the disease. We will adapt the use of this diagnostic tool for the H&N cancer patient population to detect the presence of a central sensitivity phenotype.

Head and Neck Pain Inventory (HNPI): The HNPI is a diagram in which patients can document specific areas of pain with an emphasis on the head and neck region. The patients are also asked to rate their pain on a scale

of 1-10 in the past week, describe the type of pain they are experiencing, and document any treatments for their pain.

Opioid Risk Took (ORT): The ORT is a self-reporting screening tool for adults to assess the risk for potential opioid abuse in patients with chronic pain. A score of <3 indicates low risk, 4-7 moderate risk, and >8 high risk (*39*).

MRI protocol:
Standardized protocols developed by investigators in the Imaging Center will be used for the structural and fMRI sessions. The scans will be acquired in order of importance. The study PI and/or appropriately trained key study personnel will be present at the time of imaging. The anticipated time to complete all of the following is estimated to be about 60 to 90 minutes. Physiologic data, such as heart rate and respiratory rate, will be collected using a pulse-oximeter on the non-dominant hand and a chest plethysmograph around the subject's abdomen. These physiologic parameters have been shown to influence fMRI data acquisition and analysis. The following MRI scans will be acquired:

- Baseline structural and resting state fMRI:
  Patients will be placed in scanner and acquisition of structural and resting state fMRI will be performed. Imaging will occur for a period of about 10-20 minutes while the patient is "resting" but not asleep.

- fMRI in the presence of noxious stimulus:
  The pressure stimulus will be delivered via the IPC-1000 as described above. These systems are computer-controlled and MRI-compatible so that a pressure stimulus can be administered in synchronization with imaging sequences. They allow for participant feedback during image collection so that patient pain responses can be recorded in real time. A pressure stimulus of XX will be delivered in a block design to the dominant thumbnail using the IPC-1000 for 5-30 second intervals with 5-30 second intervals of rest at an intensity that produces a pain score of 50 (characterized as "moderate pain") as determined by previous testing in the clinic OR a pre-specified intensity of 2-4 kg/m2. This range produces an elicits an average pain score of 4-5/10, considered a "moderate" intensity, in fibromyalgia patients and has been used frequently in the literature (*27, 40, 41*). The scan is expected to take no longer than 10-20 minutes.

- Diffusion Tensor Imaging:
  Following the completion of the stimulus scans, patients will undergo Diffusion Tensor Imaging in the resting state. This will take on average about 10-20 minutes.

Blood Draws:
Blood will be drawn before or after the above studies by staff trained in phlebotomy. Blood will be appropriately labeled, processed, and stored in a -80 degree freezer.

5.0 Risks

The risks associated with this study are minimal. Participants may be inconvenienced due to the time required to complete the study instruments. It is possible that participants may experience psychological or emotional distress when they think about or talk about their illness and treatment experiences. The completion of self-report questionnaires is anticipated to take less than thirty minutes. We will make every attempt to minimize any inconvenience.

Interviews/surveys will be scheduled at a time that is convenient for participants. The interviews will take place in a quiet, private location and are estimated to last approximately 30 minutes. Participants will be allowed to take breaks as needed. Participants also will be allowed to refuse to answer any questions they do not wish to answer. Likewise, participants may discontinue answering questions at any time. If participants become emotionally upset or distressed, the research team member will provide an opportunity for them to discuss their concerns and will provide support. Participants also will be offered the opportunity for counseling with an oncology social worker at Vanderbilt-Ingram Cancer Center (VICC).

The risks for MRI are as follows: There are no known major risks with an MRI scan. But, it is possible that harmful effects could be found out in the future. Even though the tunnel is open, it may bother you to be placed in a tight space (claustrophobia), and to hear the noise made by the magnet during the scan. You will be given earplugs to reduce the noise. You may also feel the table vibrate and/or move slightly during the scan. It may be hard to lie on the table during the scan. If you have any metal pieces in your body, they could move during the scan and damage nearby tissues or organs.

If you use a transdermal patch (medicated patches applied to the skin), you may need to take it off during the MRI scan. Transdermal patches slowly deliver medicines through the skin. Some patches have metal in the layer of the patch that is not in contact with the skin (the backing). You may not be able to see the metal in the backing of these patches. Patches that contain metal can overheat during an MRI scan and cause skin burns in the immediate area of the patch. Tell the study doctor that you are using a patch and why you are using it (such as, for pain, smoking cessation, hormones). Ask your doctor for guidance about removing and disposing of the patch before having an MRI scan and replacing it after the procedure. Tell the MRI facility that you are using a patch. You should do this when making your appointment and during the health history questions you are asked when you arrive for your appointment.

The MRI used in this study has been used in human research for several years and no risks have been identified. However some people may experience discomforts such as nausea, dizziness, flashing lights in the eyes, and a metal taste in the mouth. These discomforts are most likely to occur as a result of rapid head movement in or near the MRI machine. For this reason, you should try not to move, especially your head, while you are inside the MRI.

6.0 Reporting of Adverse Events

The PI will oversee the safety of study. Any study-related adverse events will be reported to the IRB within 3 business days depending on severity. The PI will check the REDCap database weekly to ensure improper access and handling of the data does not occur. All logs will be checked to ensure that any information downloaded from the REDCap database is performed by authorized personnel and for research purposes only.

The PI will attend the weekly Head and Neck Research Team Meeting at which time she will review the study status with the study staff and her primary mentor, Dr. Murphy. Screening logs will be reviewed to make sure that there is appropriate capture of patients who are eligible for study. The status of patients who have consented will be reviewed to ensure timely completion of questionnaires, cohort assignment, and scheduling of MRIs. Issues with recruitment and completion of study related activities will be discussed at this meeting. There is no plan for a DSM because no intervention is involved. No interim analysis is planned due to the pilot nature of the study.

There are no interventions in this study, therefore we do not anticipate adverse events. However, any adverse events will be presented at the weekly Head and Neck research Team meeting and reported to the IRB per requirements.

7.0 Study Withdrawal/Discontinuation

Participants will be informed that their participation in the study is completely voluntary. At the time of enrollment into the study, participants will be instructed that they may withdraw from the study at any point without penalty. To withdraw from the study, participants will be instructed to notify a research team member either by phone or in person. Participants will be assured that withdrawal from the study will not affect their care, services, or benefits in any way. If participants choose to withdraw from the study, the data collected prior to their withdrawal may still be used for research purposes.

8.0 Privacy/Confidentiality

All reasonable efforts will be made to protect the confidentially of study participants. Informed consent and data collection will take place in a quiet, private location. All participants will be assigned a unique study identification number (ID). This unique ID will be the sole identifier on all study data collection forms and other portable electronic media (CD's). No names will appear on data collection forms or other media. The names, addresses, and telephone numbers that correspond to study identification numbers will be kept in a secure file in the study offices or on the REDCAP database. All data on paper forms or portable electronic media will be secured in a locked file drawer in the study office. All electronic data will be kept in password-protected files on a secure network. Only the Co-PIs and appropriate study personnel will have access to the data. Findings from the study will be presented in aggregate form.

9.0 Records and Samples to be kept:

Data Monitoring: All data forms (PRO's, demographic data, disease and treatment data, etc.) and the consent form will be entered directly into electronic REDCap database, which is a secure, password-protected database. MRI imaging data (not part of standard of care) will be saved on the study password-protected database on a secure sever. Only the PI's and research team have access to the electronic database. All data will be coded without any identifiable information. The study PI's will maintain a key that links participants to ID number in a password-protected database on a secure server at close of study. Once the study results have been reported, the database will no longer be accessed, and all hard copies will be destroyed.

Blood sample storage: Blood samples will be aliquoted into three vials. Each of the samples will be labeled with a unique study identification number and no names will appear on the vials. The samples will be stored at -80 degrees Celsius until ready for DNA, RNA, or protein processing. Processed samples will again be labeled with the unique study identification number assigned to each subject and stored at the appropriate temperature in Cardiovascular Translational and Clinical Research Core Facility.

10.0 Statistics and Sample Size:

In this pilot study, patients will be categorized as having either no pain, peripheral pain or central pain according to responses given in the Fibromyalgia Diagnostic Tool, Central Sensitivity Index, and/or Head and Neck Pain Inventory. In the second aim of this study, we hypothesize that general symptom information, as measured using PRO measures, will be associated with these pain categories. Subscale information will be calculated from patient responses to the VHNSS v.2 + GSS, POMS, and the NRS for each patient. The resulting information will be stratified by pain group. The groups subscale scores will be compared using an analysis of variance to determine if there is a significant difference. A difference in the 0-10 subscale score of 0.35 would require approximately 25 patients per group to achieve 80% power.

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