

The influence of stochastic modulated vibrations on the autonomic nervous system of breast cancer patients during radiation therapy: A randomised clinical trial.

Protocol of the VUB chair 'Andullation Care Research'

November 2018

Chair promotor: Prof. Dr. N. Adriaenssens
Chair coordinator: Prof. Em. Dr. P. Lievens
Chair researcher: Ellen Vandyck

1) Title of the project:

The influence of stochastic modulated vibrations on the autonomic nervous system of breast cancer patients during radiation therapy.

2) Objective of the study:

The aim of this research is to study the influence of stochastic modulated vibrations (Andullation® technology) on the autonomic nervous system of breast cancer patients during radiation therapy.

Since it is well known that breast cancer patients experience an important load of stress from diagnosis through treatment and throughout cancer survivorship (fear of cancer recurrence), this study focusses on activating the parasympathetic nervous system and making patients as comfortable as possible during treatment. The scope of this study is based on previous research, that has shown that controlling physical and psychological complications during treatment, may have a positive (preventive) effect on late term and long-term quality of life and survival outcomes. (Basch E et al., 2017)

Our choice for the intervention, the application of Andullation® technology, is twofold. First and foremost, this technique has shown positive effects on the use of analgesics and an increase of the pain threshold in chronic pain patients. Furthermore, an increase of the lymphatic and arterio-venous flow was found following the application of this technique, which makes it promising in the frame of this study. (www.iaat.eu/science) Based on these results, our hypothesis is that Andullation® technology has an influence on the autonomic nervous system and thereby may influence commonly experienced complications of breast cancer (treatment) that are related to the autonomic nervous system.

The primary outcome measure of the autonomic nervous system is vagal nerve activity, a modulator of the parasympathetic nervous system. Vagal nerve activity plays an important role in subjective (patient reported) sensations of pain, (di)stress and edema (Koenig J et al., 2016; De Couck et al., 2014; Adriaenssens et al., *article in progress*) (secondary outcome measures), three common complications of breast cancer and its treatment. These three negative side effects may be risk factors for sleeping disorders in this population. Our hypothesis is that vagal nerve activity may directly influence sleeping disorders in this population without the presence of stress, pain and/or edema as well. (Werner et al., 2015) The relations between the parameters are shown in Figure 1.

The second reason for choosing this intervention, the application of Andullation® technology, is socio-economically. The whole western world is searching for self management strategies to help this big growing population of chronic patients, that can no longer be followed up close in the long run in standard hospital care.

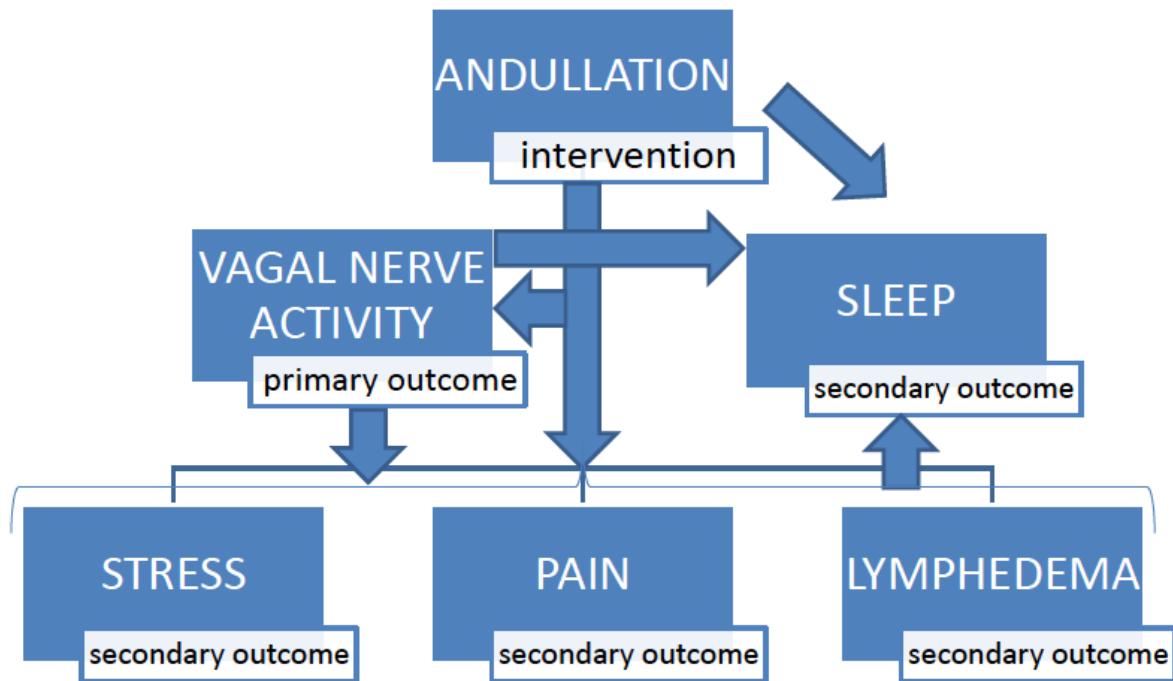


Figure 1: Hypothesis of the relations between the intervention and the outcome measures.

3) Investigator(s):

Promotor: Prof. Dr. N. Adriaenssens

Universitair Ziekenhuis Brussel; Laarbeeklaan 101, 1090 Jette

- Oncologisch centrum: coördinator Oncological Rehabilitation and responsible for Cancer Survivorship at the UZ B
- Lymfekliniek: responsible of conservative treatment, consultant

Vrije Universiteit Brussel; Laarbeeklaan 103, 1090 Jette – Faculteit Lichamelijke Opvoeding en Kinesitherapie

- vakgroep KIMA, unit KINE – docent Revalidatiewetenschappen en Kinesitherapie
- research group Rehabilitation Research – Head of research line 'vascular pathology and oncology'
- President of the Postgraduate course 'Vascular Pathology and Oncology' at VUB
- General Secretary of the Belgian Society of Lymphology

Coordinator: Prof. Em. Dr. P. Lievens

Vrije Universiteit Brussel; Laarbeeklaan 103, 1090 Jette – Faculteit Lichamelijke Opvoeding en Kinesitherapie

- vakgroep KIMA, unit KINE – Gewoon Hoogleraar emeritus Revalidatiewetenschappen en Kinesitherapie
- co-founder of the European Society of Lymphology

- winner of the Europa Donna award by Queen Mathilde of Belgium
- winner of the Hilde Breurs award by the Vrije Universiteit Brussel

Research collaborator (Master of Science - Rehabilitation Sciences and Physical Therapy):
Ellen Vandyck

Vrije Universiteit Brussel; Laarbeeklaan 103, 1090 Jette – Faculteit Lichamelijke Opvoeding en Kinesitherapie.

4) Sponsor:

This research is financed by the VUB Chair ‘Andullation Care Research’, represented by the investigators (cfr. point 3) and

- International Association of Andullation Technology (IAAT) - Avenue Louise 65 Box 11, 1050 Brussel (president dr. Guy Declerck)
- Home Health Product bvba (HHP) – Ambachtstraat 1, 9700 Oudenaarde (CEO Bruno Nuyttens)

5) Departments/laboratories involved in the study:

Universitair Ziekenhuis Brussel; Laarbeeklaan 101, 1090 Jette

- Medical Oncology (Prof. Dr. Jacques De Grève)
- Radiotherapy (Prof. dr. Mark De Ridder)
- Breast Clinic (Prof. dr. Jan Lamote)

6) Introduction:

The (breast) cancer population in Belgium is growing due to increasing prevalence and decreased mortality, thanks to evolutions in diagnostics and treatment of cancer. More breast cancer patients survive and live with the complications of cancer and its treatment. That is why quality of life of this big group of chronic patients has become more important in the past decade(s). Bio-psychosocially as well as economically and financially, the whole Western World is struggling with a lack of options to monitor these patients with long-term effects and late effects of breast cancer and its treatment. Therefore, there is an active search for ways to prevent complications and facilitate self-management for these cancer survivors with negative side effects.

With this study, we address the breast cancer patient and not the breast cancer survivor in the first place. Our hypothesis is that a lot of complications can be prevented when acting proactively at the start of treatment. From recent research, we know that monitoring complications during chemotherapy results in higher survival rates for example. (Basch E. et al., 2017) The comfort of the patient during treatment will result in a more positive outcome, for example because there is a better therapy adherence and compliance. This will lead to faster rehabilitation and reintegration, less work absenteeism and other psycho-socio-economical disadvantages.

Physical and mental comfort of the patient during treatment is co-determined by (di)stress of diagnosis and treatment with its consequences like f.e. pain. From previous research, we know that the autonomic nervous system and more specifically the vagal nerve plays an important role in

(di)stress and pain. These two symptoms can be mediated by vagal nerve activity. The vagus nerve is the tenth of twelve cranial nerves and the main nerve of the parasympathetic nervous system. Several hypotheses emerged and theorized that vagal nerve activity may moderate and inhibit the pathophysiological mechanism and risk factors in predicting cancer. (Gidron et al., 2005; De Couck et al., 2012) Three mechanisms might play an important role in tumorigenesis: oxidative stress, inflammation and excessive sympathetic nervous system activity, all of which are inhibited by vagal nerve activity. (De Couck et al., 2012) These mechanisms can also be found in the pathophysiology of pain and stress.

When the patient has a lot of discomfort, mentally (due to stress) or physically (due to pain), vagal nerve activity decreases and melatonin concentration decreases (while adrenaline levels are elevated). Melatonin is necessary for a good sleep-awake cycle (circadian rhythm) (Werner et al., 2015) and therefore, sleep deprivation is also a frequently registered complication during cancer treatment. Besides stress, pain and sleeping disorders, lymphedema (and/or vascular edema) is also a common complication of breast cancer treatment. (Lymph)edema may develop due to damage of the lymphatic (and/or vascular) system, but can be triggered by a disbalance of its innervation (by the autonomic nervous system) as well. (Yulan et al., 2018; Földi M)

Vagal nerve activity can be stimulated by f.e. relaxation therapy and biofeedback of heart rate variability (HRV). (van Dixhoorn et al., 2005) Since the application of Andullation® technology has shown positive effects on the use of analgesics and an increase of the pain threshold in chronic pain patients, as well as an increase of the lymphatic and arterio-venous flow, (www.iaat.eu/science) N our hypothesis is that Andullation® technology has an influence on the autonomic nervous system and thereby may influence commonly experienced complications of breast cancer (treatment) that are related to the autonomic nervous system.

7) Study design:

The design of the study is a randomised clinical trial (that will be registered at clinicaltrials.gov). Breast cancer patients will be randomised into two groups (group 1: intervention or group 2: control). The patients will be randomized using the Efron's biased coin design. (Efron, 1971) Patients are stratified by duration of radiation therapy/intervention (3 weeks vs. 5 weeks), type of surgery (mastectomy vs. breast conserving surgery and axillary lymph node dissection vs. sentinel node biopsy), and chemotherapy sequence (none vs. sequential vs. concomitant chemotherapy). Randomisation occurs when the informed consent is signed by the patient. Patients need to be referred as eligible candidates by an MD and can give consent only following an intake conversation, giving all information concerning the trial by going through the informed consent with the patient. This design is shown in figure 2.

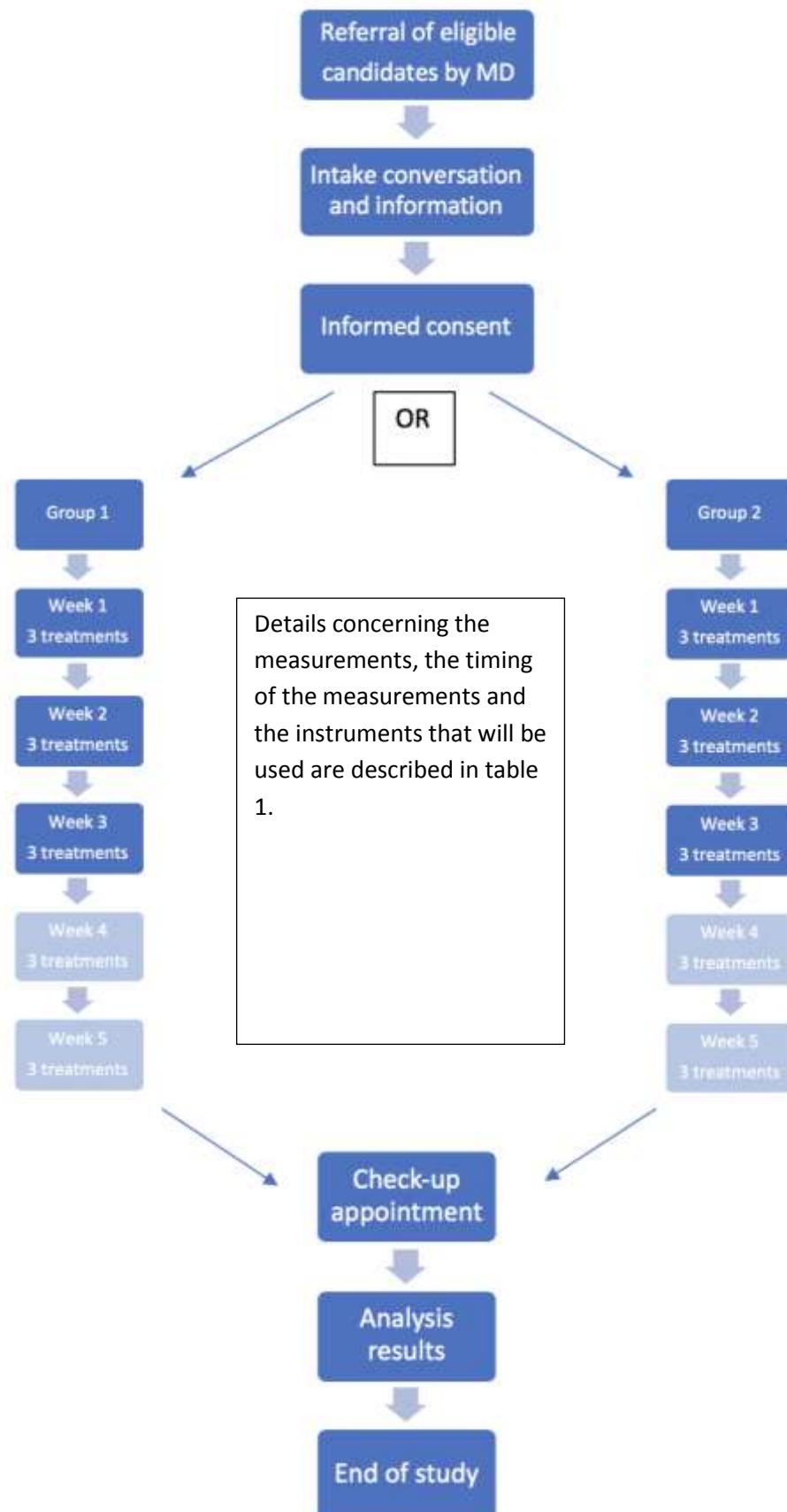


Figure 2: Design of the study.

8) Medical device

Andullation® technology is a horizontal vibration technique, with stochastically modulated vibrations. Lievens (2007) described Andullation® as “a new vibration therapy introduced for medical application approved by the TÜV Rheinland Belgium N.V. and FDA massage mattress VM9100RM”. The technology is build-in in a massage mattress. Several studies show that vibration (Prisby et al., 2008) and horizontal position (Nepal et al., 2012) in general have a positive influence on relaxation, without side effects. References concerning the technology can be found at <http://www.iaat.eu/science/>

The medical device has a CE-mark in classification Pc IIa, type bf with certificate number Z-18-051-P and identification No. 0633.

Composition and dosing

Group 1 (intervention group): 3 to 5-week Andullation® intervention* (depending on and as long as the duration of the radiation therapy) will be performed, 3 times a week for 20 minutes. Patients wear comfortable clothing. The position of the medical device is adapted to the body contours of the patient for an ergonomic position. The patient is lying in a relaxed position with hands posed next to the body on the lateral side of the mattress.

* <https://www.hhp.be/nl/producten/andumedic-3-professional>

Medical device: Andumedic® 3 Professional

Settings of the medical device: a combination of program 3, 8 and 18 (standardized)

Group 2 (control group) will follow the same intervention protocol as group 1, but without the application of the Andullation® technology. Environmental parameters will be equal to those of group 1.

Producer/distributor

Producer:

International Association of Andullation® Technology (IAAT) - Avenue Louise 65 Box 11, 1050 Brussel (president dr. Guy Declerck) www.iaat.eu

Official dealer:

Home Health Product bvba (HHP) – Ambachtstraat 1, 9700 Oudenaarde (CEO Bruno Nuyttens) www.hhp.be

Packaging/storage conditions

Normal packaging, transport and storage conditions.

Known side effects

Up to now, there are no negative side effects reported about 20 minutes of Andullation® technology in literature or clinical experience. The Andullation® application is approved as a medical device by TÜV Rheinland Belgium N.V. and FDA massage mattress VM9100RM.

Pregnancy, epilepsy and a recent orthopaedic implant are contra indications reported by the producer and dealer.

Side effects will be registered during the trial.

9) The subjects:

Number of subjects

At the Department of Radiation Therapy of the UZ Brussel, an average of 8 breast cancer patients starts radiation therapy for about 3 to 5 weeks every week. Taking into account the sample size estimation/calculation, the duration of the project (Chair ‘Andullation Care Research’ of the VUB) and the availability of the medical device(s), we have constructed the inclusion schedule below (table 1).

The schedule is based on a 5-week intervention (and control) over a duration of 14 months to include 118 patients for the two study arms. If patients who have only 3 weeks of intervention are included, even more patients can be included. Therefore, insurance is based on the inclusion of maximum 130 patients, taking into account extra (3-week intervention) patients and a drop-out of 10%.

	M1/M2									start/2M	N = (op M14)
	W1	W2	W3	W4	W5	W6	W7	W8	W9		
1st week intervention	2	2	2	2	2	2	2	2	2	18	118
2nd week intervention		2	2	2	2	2	2	2	2		
3rd week intervention			2	2	2	2	2	2	2		
4th week intervention				2	2	2	2	2	2		
5th week intervention					2	2	2	2	2		
interventions/day	2	4	6	8	10	10	10	10	10		
	M13/M14										
	W53	W54	W55	W56	W57	W58	W59	W60	W61		
1st week intervention	2	2	2	2	2						
2nd week intervention	2	2	2	2	2	2					
3rd week intervention	2	2	2	2	2	2	2				
4th week intervention	2	2	2	2	2	2	2	2			
5th week intervention	2	2	2	2	2	2	2	2	2		
interventions/day	10	10	10	10	10	8	6	4	2		

Table 1: Inclusion schedule of the study.

Inclusion criteria

- Histological proven breast cancer, following breast cancer surgery
- Starting with adjuvant radiation therapy (with or without concomitant chemotherapy) for 3 to 5 weeks
- Age: older than 18 years
- Medical report (possibly for another hospital) is required with:
diagnosis: tumor type and time of 1st biopsy (if relevant)
proposed therapy (start and end dates of each treatment and treatment type)
- Patients have to be able to perform the intervention (laying supine on the mattress for 30', of which 20' intervention)
- A written informed consent has to be signed in the spoken language of the patient. (French, Dutch or English as well as the questionnaires)

Exclusion criteria

- Severe neurological, orthopaedic or rheumatic disorders of the lower or upper limbs which makes it impossible to lay on the mattress in supine position
- Cardiac disorders

- Early or synchronous malignancy
- Pregnancy or lactation
- Persons suffering from depression or illnesses who influence the mental health or wellbeing

Replacement of subjects

A drop-out of 10% was taken into account in the sample size calculation and inclusion schedule. Since we can prolong the intervention with a few weeks (the Chair is assigned for 24 months), we can have an extra medical device of the distributor during the study, we can include more than two patients a week at the UZ Brussel, because there are on average 8 patients starting radiation therapy every week, ... we will be able to anticipate for a bigger drop out.

Restrictions and prohibitions for the subjects

Provocation of vagal nerve activity minimal 24 hours before intervention will be registered prior to every intervention. The use of medication that influences pain sensation, fluid homeostasis, sleep hygiene and stress will be registered.

10) Procedures:

The measurements will be obtained and results will be analysed at the PR4 building of the Universitair Ziekenhuis Brussel, Laarbeeklaan 101, 1090 Jette.

	Autonomic nervous system	Stress	Pain	Edema	Sleep	Quality of life
Outcome measure	Primary	Secondary	Secondary	Secondary	Secondary	Secondary
Measurement	Heart rate variability through skin sensor (ANSWatch®)			Volume measurement of the arms (Perometer®) for the evaluation of lymphedema Body composition (bioimpedance) for the evaluation of vascular edema		
Questionnaire		- Distress Thermometer	- Brief Pain Inventory (BPI) - Numeric Pain Rating Scale (NRS)		- Pittsburgh Sleep Quality Index (PSQI) - Insomnia Severity Index (ISI)	- EORTC QLQ BR23

Measurement moment	Before, during and after each intervention	Baseline After each 3 rd intervention Follow-up	NRS: Before and after each intervention, Follow-up BPI: baseline, after each 3 rd intervention and follow-up	Baseline After 3 weeks After 5 weeks (if radiation lasts 5 weeks) Follow-up	Baseline After 3 weeks After 5 weeks (if radiation lasts 5 weeks) Follow-up	Baseline After 3 weeks After 5 weeks (if radiation lasts 5 weeks) Follow-up
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Table 2: Procedures of the study.

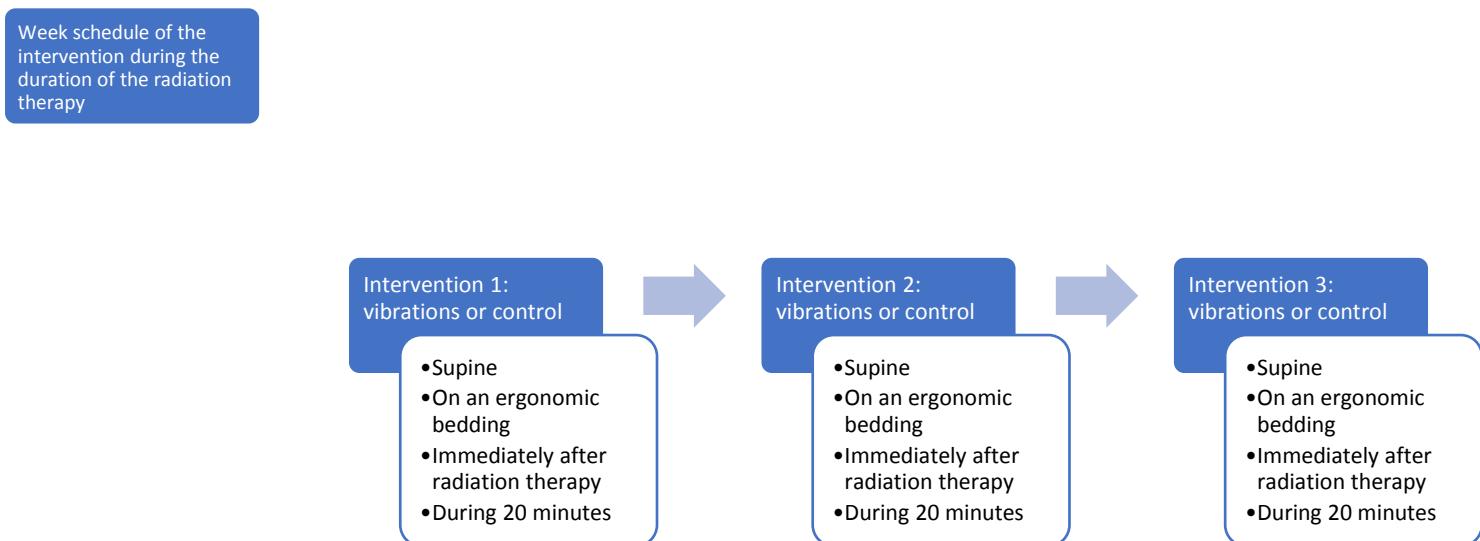


Figure 1: These measurements will be repeated in week 3 and if your radiation therapy has a duration of more than 3 weeks, these measurements will also be repeated in week 5.

Questionnaires

- Distress Thermometer
A questionnaire to evaluate in what extent the patient experiences complaints like distress and anxiety, on a visual thermometer. (Mitchell et al., 2007)

- EORTC QLQ BR23
A questionnaire designed to investigate the quality of life in breast cancer patients. (Michels et al., 2013)
- Brief Pain Inventory
This questionnaire was designed to investigate the extent of pain and the influence of it on quality of life. (Abahussin et al., 2018)
- Pittsburgh Sleep Quality Index (PSQI)
This questionnaire was designed to assess sleep quality, quantity and disturbance. (Beck et al., 2004)
- Insomnia Severity Index (ISI)
This questionnaire was designed to assess the severity, nature and impact of insomnia over the past two to four weeks. (Morin et al., 2011)

Body parameters

- ANSWatch®
A device measuring heart rate through skin sensors. With the information withdrawn, the device calculates heart rate variability. (Sun et al., 2011)
- Perometer®
A device measuring arm contours with the use of infrared light. It is an efficient, safe, painless and reliable method to examine arm volumes. (Adriaenssens et al., 2013)
- Bioimpedance
By using bioimpedance, body composition will be estimated. Patients have to stand on scale and hold on to a handgrip that is connected with the scale. A small current will determine the body composition and especially extracellular fluid. This is a painless and innocuous examination. (Seward et al., 2016)

11) Flowchart

Inclusion (and intervention) will start from the moment we receive a positive advice of the Medical Ethical Comité and will last for 14 months. The project (VUB Chair) is assigned for 24 months in total. An MD will refer patients as potential candidates for the trial after screening of the inclusion criteria and during the intervention, there will always be at least one MD in the PR4 building. (cfr table 1 and figure 2)

12) Randomisation/blinding:

The patients will be randomized using the Efron's biased coin design. (Efron, 1971) Patients are stratified by duration of radiation therapy (3 weeks vs. 5 weeks), type of surgery (mastectomy vs.

breast conserving surgery and axillary lymph node dissection vs. sentinel node biopsy), and chemotherapy sequence (none vs. sequential vs. concomitant chemotherapy).

Blinding is not possible.

13) Prior and concomitant therapy:

The patients are allowed to use every medication needed for their treatment before, during and after the intervention.

Any medication that has an influence on HRV activity, sleep, stress, edema and pain are reported before intake in the trial and monitored throughout the study.

14) Study analysis:

Sample size calculation

Based on our calculation in G*Power (with a medium effect size of 0.5 and with a power = 0.8), the total sample size is 128.

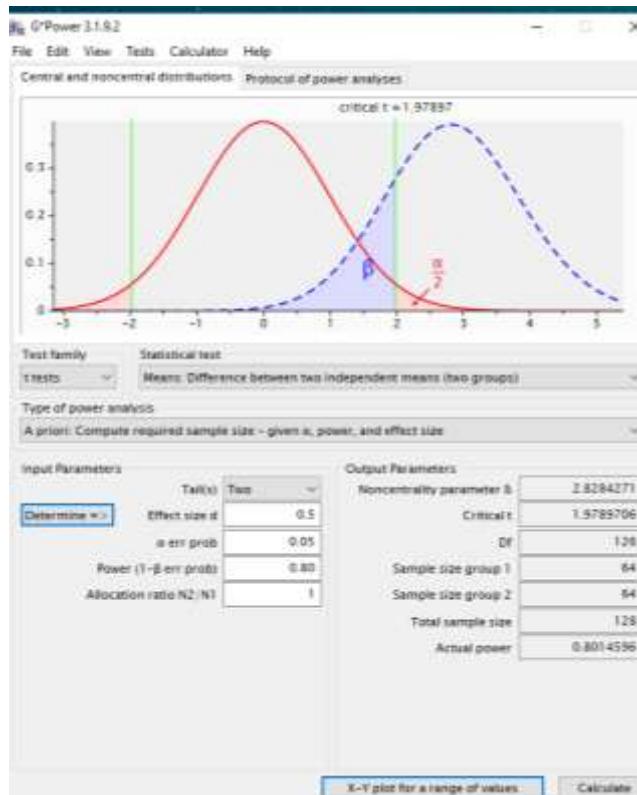


Figure 5: Sample size calculation

Analysis of the samples and statistical analysis

The promotor and researcher of the VUB Chair will analyze the samples and do the statistical analysis.

For all statistical analyses, superiority will be based on a two-sided p-value < .05. All statistical computations use SPSS v. 20.0 (IBM Corporation, Somers, NY, 10589, USA). Descriptive statistics will be used to describe medical and demographic characteristics of the population. Normality and homogeneity for both groups will be calculated. The repeated measures ANOVA design will be used to evaluate the changes over time and between groups. Correlations between outcome measures will be calculated as well.

15) Quality control and quality assurance:

The researcher will be present when the intervention is given to install the patient, to start the intervention and to make sure that everything runs according to plan.

The researcher will also make sure that all settings are properly programmed and placed as indicated in the protocol prior to welcoming the patient. The researcher will use the same checklist before starting each intervention.

Related to the quality control and assurance of the outcome measures:

- Each participant will have a form fill to list every data.
- All measurements are conducted by the same investigator and the same validated measurement instruments.
- All interventions are performed with the same medical device.

16) Publication policy:

Scientific and marginal publications will be possible within the academic freedom of the researchers and there are no restrictions concerning the other (industrial) partners of the VUB Chair.

A signed agreement of the Chair can be obtained at VUB TechTransfer (Sophie Cammaerts) Contracts Administration Building M - Room 409 Pleinlaan 2, 1050 Brussels.

17) All documents are confidential. These documents are only accessible to the treating doctor and to the persons concerned in the execution and control of this clinical study. The name and every information that could reveal patients' identity will not be used in publications arising from this study and will not be shared with third parties. The data will be processed according the principles imposed by the new European General Data Protection Regulation (GDPR), that is operative since May 25th 2018. In the context of the study certain personal data will be collected. We, Adriaenssens Nele and Vandyck Ellen, are responsible for the correct processing and the information duty that is required.

Of course, we are only allowed to use personal data for the scientific purposes described in the information consent document. It is possible that the data are seen by persons in countries that do not use the same norms in the field of legal protection of data as in the EU. In that case, we commit to ensure that the requirements of the European and Belgian legislation about the protection of personal data are respected.

Thereafter we would like to announce that, conform the relevant legislation, the data obtained in this study will be saved during at least 4 years. According to the GDPR there are

certain rights in the processing of the data. The data protection officer of the VUB can be contacted: dpo@vub.be

References:

All references related to Andullation® technology: <http://www.iaat.eu/science/>

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