# MICROWAVE ABLATION OF SOLITARY BREAST CANCER FOR ELDERLY WOMEN & NEUROSTIMULATION OF THE PLEXUS COELIACUS AS A TREATMENT FOR OVERWEIGHT AND OBESITY

# DHABIA AL SAMARRAI



An exploration of the steps needed for a clinical study Master thesis – Medical Imaging & Interventions Dhabia al Samarrai: *Microwave ablation of solitary breast cancer for elderly women & Neurostimulation of the plexus coeliacus as a treatment for overweight and obesity,* An exploration of the steps needed for a clinical study © May 2016

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University of Twente

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# COLLIQULUM COMMITTEE:

Prof. dr. ir. C.H. Slump

Dr. M.J.C.M. Rutten, MD

Drs. A.G. Lovink

Dr. E.J.F.M ten Berge, MD

إهداء إلى أمي، أبي، راويه، جمانه، مينه، وسا

Dedicated to my mother, my father, Rawia, Jomana, Miena, Wassa

#### FOREWORD

This thesis is comprised of two different parts. Part I is about an ex vivo study on microwave ablation of small, solitary breast tumours as a minimal invasive treatment for elderly women, in whom surgery is not an option or not preferable.

This study is currently an being conducted at the department of Radiology in the Jeroen Bosch Hospital. Part I contains an elaboration of a test set-up and one resection specimen of a patient. The MWA have been conducted on one lump and a second is planned.

Part II is a proposal for a clinical study about the treatment of overweight and obesity with neurostimulation.

The common ground of the different parts is that both are written as proposals. Both proposals contain an exploration of the steps needed for a clinical study in a first phase and clinical implementation for an advanced phase. In both proposals, the investigator is exploring ideas which are underpinned by the current literature. Regarding to part II, the present proposal has been used in negotiation with the industry to fund this study and help conduct the research. We found two companies interested, the negotiation is ongoing.

# ABSTRACT

Breast cancer is the most common type of cancer in women. Based on current incidence rates, the chance is one in eight for Dutch women to develop breast cancer at some time during their lives.[1, 2]

Current standard of care treatments for breast cancer include: surgery, radiation therapy, chemotherapy and hormonal therapy depending on the stage of the cancer at clinical presentation.[2] Breast surgery can involve either breast conservation therapy, which can be performed as a lumpectomy, or it can involve a mastectomy.

Recent studies show no difference in the overall survival between lumpectomy and mastectomy.[3–7] Since this discovery, there is a growing tendency to use minimal invasive approaches for the local treatment of tumours. MWA is an interesting recent minimal invasive technique for the treatment of breast cancer.[8] MWA has selective properties for breast tissue. The dielectric properties, conductivity and permittivity, in malignant tissue is higher than in the host tissue which contains fatty and glandular tissue.[9–11]

Surgery is the golden standard, however, there is a group of patients who is not eligible for conventional therapy. Elderly women with a solitary, small breast tumour could be treated successfully with percutaneous MWA.

The focus of this study is on the following research questions:

1. What is the technical efficacy of MWA for solitary, small primary breast tumours in an ex vivo setting?

2. How accurate and predictable is the target zone created during MWA?

To the best of our knowledge, is this the first study where the Emprint ablation system is used to treat breast cancer. Small breast cancer, less than 1.5 cm in diameter are included in the study. Our purpose is to perform ten valid MWA measurements in breast specimen resectioned from women who had surgery. MWA was conducted on bovine liver and one resection specimen to determine the appropriate settings of the system. Generator settings of 100 Watt for the duration of at least 3 minutes are expected to be effective for the next specimen, dependent on the tumour size and the margin. This work discusses the results, the potential application of MWA as a local treatment for breast cancer and the preconditions for clinical implementation.

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# ACRONYMS AND DEFINITIONS

- ABLATION Medical term for surgical removal of body tissue or a science term for destroying the tissue by melting or evaporation
- BCT Breast-conserving therapy is comprised of breast-conserving surgery combined with radiation therapy.
- BIOPSY MATERIAL the biopsy or puncture material is breast tissue taken from the tumour to be examined on tumour characteristics.
- **CEM** Cumulative Equivalent Minutes
- ск8 Cytokeratin 8
- CNB Core needle biopsy
- DCIS Ductal carcinoma in situ
- EXCISION TISSUE the tissue which the surgeons remove during operation.
- не Hematoxylin-eosin

HIFU High intensity focused ultrasound

ICD Immunogenic cell death

- IDC Invasive Ductal Carcinoma
- IRE Irreversible Electroporation
- LCIS Lobular carcinoma in situ

LUMPECTOMY an operation where the tumour is removed.

MASTECTOMY an operation where the whole breast is removed.

мwа Microwave ablation

PMWA Percutaneous Microwave Ablation

**RFA** Radio frequency ablation

**RT** Radiation Therapy

SOLITARY TUMOUR a single centric tumour, there are no other tumours.

us Ultrasound

UNIFOCAL TUMOUR a tumour concentrated in one spot.

Part I

# MICROWAVE ABLATION OF SOLITARY BREAST CANCER

# 1

# CLINICAL BACKGROUND

Worldwide, breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in women.[1] In the last decades, the implementation of nationwide screening programs and the increased awareness about the disease have led to a growth in the rate of breast cancer diagnoses in general and small tumours in particular.[12]

There are various ways to detect breast cancer. One of them is for the patient to feel it by self-examination. The majority of carcinomas are being detected at the screening for breast cancer.

See figure 1 for the anatomy of the female breast. Invasive ductal carcinoma (IDC), is the most common type of breast cancer. About 80 % of all breast cancers are invasive ductal carcinomas. IDCs are solitary tumours.

Breast cancer cells are most likely to spread first to lymph nodes located in the axilla, or armpit area, next to the affected breast.[13] Before treatment of the tumour, it is important to examine if and which axilla lymph nodes are affected. Therefore a sentinel node biopsy (SNB) is performed. A sentinel lymph node, is the first lymph node to which cancer cells are most likely to spread from a primary tumour. During an SNB procedure the sentinel lymph node is identified, removed and examined to determine whether cancer cells are present.

The removed specimen with tumour gets pathologically examined to determine the size, margin and the tumour characteristics. The most important are: the Bloom-Richardson classification, hormones receptor and Her2-neu expression<sup>1</sup>. The outcomes of the surgery and pathological evaluation are used to develop an appropriate treatment plan.

For the diagnosis of the disease, a mammogram is conducted first to detect suspicious lesions. After a mammogram, an echo graphic exam follows to investigate the existence of suspicious lesions. A suspicious echographic result is followed by a core needle biopsy (CNB)

<sup>1</sup> Her2-neu receptor expression is a measure for how aggressive the tumour is.



Figure 1: The breast is the tissue overlying the pectoral muscles. Female breasts are made of glandular tissue and ducts embedded in connective tissue. The milk-producing part of the breast is organised into 15 to 20 sections, called lobes. Within each lobe are smaller structures, called lobules, where milk is produced. The milk travels through a network of tiny tubes called ducts. The ducts connect and come together into larger ducts, which eventually exit the skin in the nipple. The dark area of skin surrounding the nipple is called the areola.

to confirm or to exclude the diagnose of breast cancer.

Breast cancer is multidisciplinary treated with radiotherapy, chemotherapy and or hormonal therapy. A combination of these therapies is also an option. The treatment plan depends on the stage and spread of the disease at clinical presentation.

In the last two decades a growing interest is observed for minimal invasive therapies for the local treatment of breast cancer. This interest is arising from results of randomised trails, showing no difference in overall surviving rates between mastectomy and breast conservation treatment.[3–7]

The oncological principle, by which the primary tumour is completely removed including a margin of healthy tissue to minimise the chance of local recidivism, is followed by an aesthetic purpose. The aesthetic purpose is the conversation of an adequate amount of healthy breast tissue for preservation of a normal breast contour.

#### 1.1 MINIMAL INVASIVE TREATMENTS

The trend toward less aggressive, local treatment of both benign and malignant tumours have led to research of a number of minimally invasive techniques including: irreversible electroporation (IRE), cryo-ablation, laser ablation, high intensity focused ultrasound (HIFU)[14] and radiofrequency ablation (RFA)[15]. Irreversible electroporation

is a non thermal ablative modality whose role in the management of cancer is being studied.[16, 17] During the IRE procedure, high electric-field and ultra-short pulses are given to destroy lipid bilayer structure of cancer cell membrane and form numerous irreversible nano-sized pores in the cell membrane. Cell membrane permeability will be changed to allow molecules of different sizes free access to cells, which will lead to cell death.

Cryoablation is an ultrasound guided technique, where a probe filled with liquid nitrogen is inserted in the tumour to destroy tumour cells by using freezing the tissue to about -40 °C.[18] The other mentioned techniques are thermal ablative applications, where heat is used to destroy or damage diseased cells.

The thermal dose is used to measure the amount of energy deposition in, in vivo thermal studies. It is defined as cumulative equivalent minutes (CEM).

Earlier research has shown that tumour cell death is induced at a temperature of 43 °C for 60 minutes. The needed time for complete tumour cell death is reduced with a factor 50 % for every degree temperature increase. It suffice to raise the temperature within a tissue above a lethal threshold (> 50 - 60 °C) to ensure cellular death within seconds in the target tissue through coagulation.

During ablation, the active heating zone occurs around the tip of the needle, within the tissue where the intensity of energy is high and its absorption by tissue is fast. In this case, the energy absorption is much higher than the tissue environment's ability to compensate.[19] See figure 3. The passive zone occurs outside the active zone, further from the ablation device where the intensity of energy is lower. Passive zone extension beyond the active zone is determined by local physiology and its inherent ability to circumvent thermally damaging temperatures.

In laser ablation, an optic fiber with a diffuser tip is inserted in the tumour and the infrared laser raises the temperature around the diffuser. HIFU uses a transducer, located outside the patient body. The transducer focuses the ultrasound at a focal point central in te tumour to raise the temperature and destroy the tumour.

#### 1.2 THE CONCEPT AND APPLICATION OF RFA

RFA has proven to be one of the most adaptable technologies. The technique is based on current energy. The alternating current flow



Figure 2: The RFA principle is the same as that of the stove oven, based on alternating current flow.[19]

between the tip of the needle and the grounding pad creates a charged electromagnetic field. This field forces the water molecules of the cell membranes to oscillate back and forth between the charges in the field. The oscillation of the water molecules results in frictional heat and thus a raise in temperature above the lethal threshold. This results in destruction of the cell membrane structure of the target zone. The cell membrane is destroyed and the rest of the cell is eliminated by the immune response of the body in an in vivo setting.

Current-based technologies work the same as an electric stove top, where electrical current passes through a resistive heating element. With an electric stove, the physics are simple. The resistive heating element, see figure 2 left image, has a uniform impedance and unchanging cross sectional size across its length. This leads to a consistent flow of electrons and uniform heating across the element.

In contrast, with current-based ablation the cross sectional size of the tissue is very small in close proximity to the device and very large a short distance away. As a result, the flowing electrons can spread out as they move away toward the return pad, resulting in a heating effect which dramatically drops off just millimeters from the device figure 2 right image.

The applicator of RFA is a needle, which is inserted central in the tumour with ultrasound guidance during treatment. The needle is connected to a radio frequency current generator and a grounding



Figure 3: This is a needle of a thermal ablative technique. Thermally ablative devices regardless of a technology, coagulate and necrose tissue with two distinct heating zones. An active heating zone and a passive heating zone. The active ablation zone is shown in red and the passive in yellow.[19]

pad in a closed circuit.

#### 1.3 CONCEPT AND APPLICATION OF MWA

Microwave ablation is a newer, less available technique compared with RFA. Microwave energy is being studied for a while as a possible technique to characterise parameters for breast imaging .[20, 21] After the introduction of percutaneous RFA for solid tumours and the challenges of the heat sink phenomenon<sup>2</sup> adjacent to vessels, percutaneous MWA has been developed and introduced to give the same results without the drawbacks of the heat sink in RFA.

MWA is a field based technique. The microwave energy is used to create an electro magnetic field. This field forces the dipole of a water molecule to continuously reorient itself, oscillation, resulting in heat production. The MWA concept uses the same waves that a microwave oven use. There are two differences. See figure 5 The microwave oven uses heating from outside on the food while the MWA heating is introduced inside the tissue by needle placement. The other difference is the focus of the field. The electromagnetic field is generated only in the green part of the needle which creates a spherical zone ablation. The heat generation is limited to this zone.

Percutaneous MWA has proven to be effective and safe for the treatment of liver[22][23], lung[24] and renal[25] tumours. Earlier studies[9–11] measuring the electric properties of malignant

<sup>2</sup> The phenomenon that liver tumours adjacent to large blood vessels are inadequately ablated because of heat loss that is the result of convection by tissue from the blood flow, which acts as a heat sink.



Figure 4: This figure shows a tumour in light green. The green part of the needle is where the RF energy is generated. The active ablation zone is shown in red and the passive in yellow. This is an illustration of the drawbacks of the RFA technique. The shape of the ablation zone is influenced by the conductive properties of the adjacent tissue. If there is a vessel in the neighbourhood, this will lead to heat sink in this zone and less predictable ablation shape.[19]

and normal breast tissue, found that conductivity and permittivity are higher in the malignant tissue than in the host, normal tissue. These electrical properties where also measured in the liver, renal and lung tissue. The difference in electrical properties between normal and diseased tissue was the highest for the breasts. The difference in water concentration is higher between the diseased and normal tissue in the breasts. Malignant tissue contains more water compared to the glandular and fatty tissue. This results in higher electric properties, conductivity and permittivity, in the malignant tissue and makes it more vulnerable to damage of the microwave energy.

The difference between concentration in water is the highest in the breasts compared to the other measured tissues (liver, lung and renal). This suggest that the microwave energy should give better results in application for breast tumours than for the other types of tissue, where they are already being used in clinical practise. The focus of this thesis is on the application of ultrasound-guided percutaneous MWA.

#### 1.4 ADVANTAGES OF MINIMAL INVASIVE TREATMENTS

Treatments with a percutaneous application method have a short duration compared to surgery. MWA of liver tumours has a total ablation time of approximately 16 minutes[26, 27]. The average treatment procedure for breast cancer patients will be reduced to 10 - 30 minutes. A reduction in procedure time will also result in less costs.

Another advantage is the cosmetic effect. In breast surgery, the more healthy, host tissue is left behind the better the cosmetic results.



Figure 5: Left the concept of microwave oven heating of food. The electromagnetic field is shown by the green stripes. The red dots represent the heat. Right illustration shows the MWA needle with a sphere representing the shape of ablation zone.[19]

During an in vivo MWA ablation, the cell membranes of the tumour will be destroyed and the host tissue will eliminate the dead cells.

The most exciting future possibility associated with local treatment is the harnessing of a specific tumour immune response to improve results in the treated patients. Based on clinical data from previous RFA in vivo research, see section 1.5, locoregional relapse does not occur as frequently as we would expect, so another mechanism of killing of tumour cells may be occurring. Preclinical studies in various tumour models have shown that exposing tumour cells to lethal doses of radiation can elicit cell death while inducing strong antitumour immunity, a process termed "immunogenic cell death" (ICD).[28–30]

At this stage, surgery is still the golden standard for breast cancer. It can be omitted in a select patient group. This group consists of elderly women, who are not eligible or not willing to choose for conventional treatment options because of the risks and collateral damage. For this select group, percutaneous MWA could offer a curative treatment option.



Figure 6: The MWA needle creating a spherical ablation zone and encapsulating the tumour inclusive vessels.[19]

#### 1.5 PREVIOUS EXPERIENCE

Previous research[31] carried out by the department of Radiology at the Jeroen Bosch Hospital, focused on RFA of small breast tumours in elderly women. The study was carried out in an ex vivo setting. The outcomes in percentage tumour cell death were promising. The feasibility and effectiveness of RFA were assessed using histopathologic staining, methods to evaluate tissue viability. In 20 patients with unifocal small ( $\leq 1.5$  cm) invasive ductal carcinoma, ultrasoundguided RFA was performed immediately after surgery. Cell viability was assessed using cytokeratin 8 (CK8) and nicotinamide adenine dinucleotide diaphorase (NADHD) in addition to hematoxylin-eosin (HE). At histopathological examination, ex vivo RFA resulted in complete cell death of the target lesion in 17 out of the 20 patients. In two cases viable ductal carcinoma in situ (DCIS) was found just outside the completely ablated lesion with complete destruction of the target lesion. In one case pathological evaluation revealed viable cells lining the needle tract. The following was a clinical study to asses the effectiveness and safety of the treatment with a treat and resect design. The last study performed in this research-line was an in vivo study which included five patients with small<sup>3</sup>, solitary tumours. The patients were treated with RFA and came back for follow-up with contrast enhanced MRI.

The microwave as an energy source has been studied earlier. It is referred to as microwave therapy. There are three main research contributions about the effect of microwave therapy as a treatment for breast cancer, see chapter 2. The objectives and the rationale are mentioned in chapter 3. The methodology for the test set-up and ex-

<sup>3</sup> Small tumours in the study were defined as less than 1.5 cm in diameter.

cision specimen is described in 4. Chapter 5 includes the results of the bovine liver ablation and the first specimen of this study. The results are discussed in chapter 6 and the conclusion is mentions in chapter 7.

# LITERATURE EXPLORATION

So far, there are a limited number of in vivo studies conducted with microwave thermotherapy in a small group of women with breast cancer. These studies show that the microwave technique is a feasible treatment option for breast cancer patients.[32–34]

Gardner et al. were the first to conduct a study about the use of microwave therapy as a treatment for breast cancer. They used the same set-up to conduct the consecutive two studies. Gardner et al.[34] carried out a phase I study. The patients included in the study were first treated with microwave thermotherapy and received later a mastectomy. After the excision, the breast tissue including tumour was pathologically examined.

#### 2.1 METHODOLOGY GARDNER ET AL.

Ten patients were included in the study. All breast tumours were confirmed by CNB. The tumour characteristics were: T1-T3 breast tumours with a variable size of 1 to 8 cm, (mean: 4.3 cm). The microwave thermotherapy treatment consisted of one session of microwave therapy. First, the patients underwent the microwave thermotherapy and 5-7 days later the mastectomy.

For the thermotherapy treatment set-up, see figure 7. This thermotherapy system is first described by Gardner et al. and later used in the thermal dose escalation study by Vargas et al.[32]. The patient was lying in a prone position with compression of the breasts; like regularly used during stereo-tactical punctures. Two compression plates with a hole on a certain depth, d, were used to compress the breasts. The d could be set in previously. Echographic examination was performed at this, d, through the hole to locate the tumour. First the tumour had to be positioned central in the hole. Then, two probes were placed in the same hole. One probe was used to focus the microwaves energy central in the tumour and the other to measure the temperature. The breasts compression was used to minimize the needed penetration depth to cause tissue heating. In addition, to reduce the blood



Figure 7: Block diagram for the plates microwave thermotherapy system for treating breast cancer like used by Gardner and Vargas et al. The breast-compression plates are made of an acrylic material transparent to microwaves. Air cooling through the rectangular waveguide applicators is used to reduce the skin temperatures. The applicators generate a focused E-field radiation pattern that will illuminate a large volume of breast tissue. High-water content breast carcinomas may heat more rapidly than the surrounding normal breast tissues when exposed to the microwave field.[34] flow in the breasts resulting in fast tissue heating. Another advantage of the compression device is that it pushed the tumour away from the chest wall. Plastic material was used to flatten (press the breasts flat) the breasts and improve the transfer of the microwaves from the plates to the breasts.

Five non-invasive temperature sensors were placed on the breast skin and one on the nipple. The needed surface temperature was not allowed to increase above the 41 to 42 °C. The thermal dose was calculated by the computer during the treatment. The treatment ended if the needed thermal dose was given or if the pre-set maximal treatment time, respectively 40 minutes, was reached.

The breast compression varied per patient from 4.5 to 6.5 cm. Effectiveness of the treatment was determined by echographic examination of the breast and pathological evaluation before and after the microwave thermotherapy treatment. All the excision tissue of the 10 patients were pathologically examined with HE dye, on tumour necrosis. Eight out of ten patient received the M<sub>3</sub>0 dye too, the dye to examine the excision tissue on apoptosis.

The total treatment time varied from 12 to 40 minutes. The mean treatment time was 34.7 minutes per session. The calculated thermal dose varied from 25 to 103 minutes, (mean: 52 minutes). The tumour peak temperature varied from 43.3 to 47.7 °C, (mean: 44.9 °C). The peak surface temperature for all sensors varied from 37.2 to 42.1 °C. Echographic examination showed a reduction in tumour measurements, in 6 out of the 10 patients, which varied from 29 % to 60 %, (mean: 41 %), in 5 to 18 days after the microwave thermotherapy. 4 (40 %) out of the ten patients showed 40 % to 60 % with a mean of 48 % tumour cell death of the total tumour volume, examined using the HE dye. Two patients did not receive the M30 dye. Based on the apoptosis examination, 6 out of 8 patients showed tumour cell death of 82 % to 97 %, (mean: 89.7 %) out of the total tumour volume. Based on pathological examination, non of the 10 patients showed total tumour cell death, as in 100 % tumour cell death.

#### 2.2 METHODOLOGY VARGAS ET AL.

Vargas et al. (2004) carried out a study following Gardner et al. A prospective, non-randomized, dose escalation study.[32] Purpose of the study was to determine the minimal needed effective thermal dose, which was sufficient for a safe and complete ablation (100 % tumour cell death) of primary breast cancer tumours. The set-up of the microwave thermotherapy was the same as described in the study of Gardner et al.

25 patients were included in this study. The patients had invasive T1 or T2 breast tumours with an average size of 1.8 cm. They made three

cohort groups for the treatment with a thermal dose of respectively 80 CEM (5 patients), 100 CEM (5 patients) and 120 CEM (15 patients). The patients underwent microwave thermotherapy and then on average 17 days later (varied from 6 to 38 days) lumpectomy. Thereafter, all the excision breasts were histopathologically examined.

24 (96 %) of the 25 patients tolerated the treatment. The treatment was aborted in one patient, in the group who received a thermal dose of 120 CEM. Tumouricidal temperatures (equal to or higher than 43 °C) were achieved in 23 patients (92 %). Tumour size was unchanged after the microwave thermotherapy. The breast compression thickness varied per patient from 3.5 to 6.5 cm.

17 patients (68 %) showed tumour necrosis at histopathological examination of the excision breasts. 2 patients (8 %) showed complete (100 %) cell death of the invasive component, however, both patients had residual in situ breast cancer. There was an other patient with a cluster residual tumour cells, in this patient tumour necrosis was estimated at respectively 99.9 %. In the other patients who responded on the treatment, the tumour necrosis varied from 25 % to 90 % per patient of the total tumour volume. The other 7 patients showed (0 %) no tumour necrosis.

Vargas et al.(2004) analysed the relation between the thermal dose in CEM, the tumour peak temperature and tumour response to the treatment. Results of the analysis concluded that a CEM of 140 predictable is for 50 % tumour response and a CEM of 210 for 100 % tumour response. Univariate analysis regression predicted that tumour peak temperatures of 47.4 and 49.7 °C result in respectively 50 % and 100 % tumour response.

Based on the results of former research contributions, we conclude that a temperature of equal or higher than 50 °C is essential te generate in the tumour to induce 100 % tumour cell death.

#### 2.3 DIFFERENCE IN APPLICATION

Microwave thermotherapy in the studies of Gardner and Vargas et al. are carried out with two plates, which generate the microwave energy, as well as a probe to focus the microwaves. The histopathological results of these studies in percentage tumour necrosis of the total tumour volume are not convincing, however, the microwave energy have had improved since these studies were conducted.

The microwave thermotherapy device that Gardner and Vargas et al. used is quite complicated, patient unfriendly and gives little possibilities for application during treatment.

In the study of Gardner et al. the temperature measured central in the

tumour, was on average 4.2 °C higher than the surface temperature of the breast. The described temperature difference of 4.2 °C and the breast surface could be improved with the percutaneous MWA technique proposed in the present study. The needle technique is more patient friendly and more selective during application.

For this study, a percutaneous MWA antenna or needle is used. Because of the percutaneous application, we postulate to achieve better results, due to the range of freedom provided by the needle.

#### 2.4 CLINICAL STUDIES EVALUATING THE MWA SYSTEM

Berber[26] was the first to report about the Emprint ablation system used in this study. Berber conducted a study evaluating the safety and efficacy of the Emprint MWA system in the laparoscopically treatment of malignant liver tumours. The study included 18 patients with malignant liver tumours treated with MWA within a 3-month time period. Tumour sizes and response to MWA were obtained from triphasic liver CT scans done before and after MWA. The ablation zones were assessed for complete tumour response and spherical geometry. There were a total of 18 patients included, with an average of three tumours measuring 1.4 cm (range 0.2-4). Ablations were performed laparoscopically in all, but three patients who underwent combined liver resection. A single ablation was created in 72 % and overlapping ablations in 28 % of lesions. Total ablation time per patient was  $15.6 \pm 1.9$  minutes. There was no morbidity or mortality. At 2-week CT scans, there was 100 % tumour destruction, with no residual lesions. Roundness indices confirmed the spherical nature of the ablation zones.

Ierardi et el.[27] conducted another clinical study to assess the feasibility of the percutaneous application and to identify its advantages. The focus of the study was on the spherical ablation zone obtained and its usefulness in terms of effectiveness. Ten liver nodules, 8 hepatocellular carcinomas and 2 metastasis, were percutaneously treated. The mean diameter was 24.9 mm with a range of 16–35 mm. To define the shape of the ablation zone, multiplanar reformatting (MPR) was performed. Roundness index transverse was calculated: a value near 1 represents a more spherical ablation zone shape, and a value distant from 1 implies an oval configuration. Technical success was 100 %. Mean ablation time was 3.85 minutes with a range of 3–5 minutes, mean overall procedure time was 30.5 minutes with a range of 25–40 minutes. No major complications were recorded. Roundness index transverse presented a mean value of 0.94, meaning that a spherical shape of ablation zone was achieved. The investigators conclude that the spherical shape of the ablation volume one of the most promising innovations of this new microwave technology is, improving the effectiveness and safety of the treatment.



#### OBJECTIVES

#### 3.1 HYPOTHESIS AND SET-UP

The aim of this ex vivo study is to assess the technical efficacy of MWA for breast tumours. Freshly excised specimen of small breast cancer are ablated immediately after surgery. We postulate that MWA is capable of inducing 100 % cell death in the target ablation zone. The following research questions are formulated:

1. What is the technical efficacy of MWA for solitary, small primary breast tumours in an ex vivo setting?

2. How accurate and predictable is the target zone created during MWA?

The evaluation is done by histopathological staining after the MWA. The pathology results will be in percentage tumour cell death out of the total tumour volume and the viable cells in the host, normal, tissue. The goal is to treat at least ten resection specimens.

#### 3.2 RATIONALE

MWA has selective properties for breast tissue. The dielectric properties, conductivity and permittivity, in malignant tissue is higher than in the host tissue which contains fatty and glandular tissue.[9–11] For breast tumours, the microwave technique deposits more heat and thus damage into the tumours containing higher water ions relatively, compared with the heat deposit in the host breast tissue. In addition, MWA causes consistent higher intramural temperatures, bigger ablation volumes, shorter ablation time and a better convection profile than RFA.[35–38] As well as, MWA is less sensitive for local shrivelling and coaling of the tissue.[39]

Studies conducted earlier with microwave thermotherapy, the same energy source but different application method[32–34, 40] conclude that the microwave thermotherapy is technical feasibly and safe. Nev-

ertheless, the results of these studies using the application with plates shown in figure 7 are not convincing for clinical implementation. To date, the application technique has been improved to a more easier applicable needle technique. MWA has potential to be an effective treatment option. The percutaneous application goes with less burden and collateral damage compared to surgery, is more plausible with a better cosmetic effect and is also cheaper.

MWA is a potential curative treatment option for elderly women. Patients who are not eligible for the conventional surgery or the patients who does not want the burden of conventional treatment.



Figure 8: The Emprint ablation system used in this study. The generator is 2.45 GHz. The system uses saline circulation to cool off the antenna. There are three different lengths possible for the antenna: 15, 20 and 30 cm.

The patient population consists of women aged 65 years and older, diagnosed with invasive ductal carcinoma with a maximal diameter of 1.5 cm. Only patients with solitary and unifocal invasive ductal breast carcinoma were included. All the patients were scheduled to have a lumpectomy or mastectomy.

Patients were excluded from participation if they had DCIS, Lobular carcinoma, or LCIS. Because these types of tumours do not appear



Figure 9: A closer look at the needle. The microwave antenna looks like a knitting needle. The needle is 13 Gauge, 2.413 mm in diameter and available in the length of 15, 20 and 30 cm. The green part at the tip measures 3 cm, this is the only part where the microwave energy is generated.

as one lesion but rather spread in different lesions. Furthermore, patients were excluded if they had negative hormone receptors at the biopsy material examination. The reason for this, is that patient with negative hormone receptors are eligible for chemotherapy. The excision tissue of patients who receive chemotherapy has to be kept in the Biobank. More exclusion reasons were: tumours which are not visible on echographic examination, multiple tumours in one breast and ipsilateral breast surgery or radiotherapy in the history.

The equipment, Emprint ablation system, was provided by Covidien. The new system is composed of: a 2450 MHz generator that delivers a maximum power of 100 Watt, a fiberglass antenna, a pump for internally cooled antenna and a temperature probe. See figure 8 for an overview and figure 9 for a closer look of the needle. The MWA needle measures 2.4 mm in diameter and the length of the one used was 15 cm.

The system is commercially available for the treatment of liver, lung and renal cancers. In other words, it is already being used for application in clinical practice. The equipment was used as supplied by Covidien. Firstly, a test was performed on bovine liver because that is the regular test set up Covidien uses to test their equipment. All the experiments, including the test, were performed in the interventional radiology room.

The overall procedure of percutaneous MWA is as follows: firstly, the target zone ('imaginary tumour') is located on echographic examination. Subsequently the tip of the needle is inserted in the centre of the target zone. The needle is connected to the generator and the procedure is started. During the procedure the temperature probe is used to measure the temperature real-time. During the test set up, the temperature was measured at the centre of the created ablation zone and at the peripheral part of the ablation zone. The procedure ended if the temperature central in the tumour reached above the 50 degrees Celsius. Subsequently, the ablated zone was sectioned to evaluate the effect of the MWA on the bovine tissue, measure the dimensions and evaluate the shape of ablation zone. The same procedure for the test set up, was performed on excision tissue.

#### 4.1 MWA PROCEDURE OF THE RESECTION SPECIMEN

After localisation of the tumour by US, the needle was placed in the centre of the tumour. Then the power of the generator was set to 100 Watt and the duration to 1 minute. These settings were chosen based on the results of the bovine test set-up and the available phone application of the Emprint system. See figure 11 for an example. The MWA generator was turned on, after 20 seconds the real-time measured temperature in the periphery of the tumour was 90 °C. After another 20 seconds the temperature was > 100 °C<sup>1</sup> and the MWA procedure was ended. The total MWA duration of the specimen was 40 seconds.

After the procedure the specimen was stained with HE and CK8 to assess percentage cell death and viability respectively. HE is the golden standard in histopathological staining for diagnose purposes in medical practice. HE is used in this study to evaluate the percentage cell death in the examined tissue.

<sup>1</sup> If the temperature exceeds the 100 °C, the MWA device shows 'high'. The temperature probe measures between 0 - 100 °C



Figure 10: This is the main menu of the 'Emprint App', the phone application available in iTunes for the system. The experience of in vivo and ex vivo studies to date are processed in this application. This could be used as a reference to plan the size of the ablation zone.

# 5

# RESULTS

#### BOVINE TEST SET-UP

The combination of a low power, 15 Watt, and a short duration, 2.2 minutes, showed no visible change in the colour of the tissue. See figure 15. The maximum power of the device, 100 Watt, induced remarkable tissue charring as the tissue started to colour black and smelled like charred meat after 55 seconds. This power applied for 1 minute gave an ablation zone with a circumscribed and spherical



Figure 11: a. The planning of target zone size in the Emprint application. The ablation zone shown is the size in an ex vivo setting for human liver tissue ablation. When the power is set at 100 Watt and the duration at 1 minute. b. The ablation zone becomes bigger when the chosen duration is set at 3 minutes.

zone, approximately 1 cm in diameter. Real-time temperature measured in the centre was 92 °C and the periphery of target zone was 80 °C.

Settings of 100 Watt for the duration of 40 seconds resulted in an oval shaped ablation zone of 1.6 cm by 1.8 cm. Settings of 75 Watt and 1 minute showed a comparable homogeneous, spherical and circumscribed ablation zone.

Power of 100 Watt for the duration of 6 minutes resulted in a large ablation zone with tissue charring. See figure 16

#### PERCUTANEOUS MWA OF RESECTION SPECIMEN BREAST TISSUE

The whole specimen was approximately 3 cm by 6 cm. See figure 17. The US axial view of the specimen gave the best visualisation, see figure 18, however, this was not the largest dimension of the tumour. The tumour diameter in axial view was 6.9 mm and the largest tumour diameter was 12 mm. So the ablation zone coverage of the needle was not guaranteed. Thus the needle has to be placed in the longitudinal view like can be seen in figure 20.



Figure 12: This picture shows the test set-up on bovine liver. The needle is inserted in a chosen ablation zone under ultrasound guidance.



Figure 13: The generator and the cooling pomp can be seen. Firstly the cooling system is used to prevent the needle from heating.



Figure 14: An ablation zone created with the Emprint MWA system in bovine liver. An incision was made to evaluate the shape of the ablation zone and measure the dimensions. The ablation zone is circumscribed and spherical. The diameter was 3 cm.



Figure 15: This is the result of an ablation procedure with low power (15 Watt) and a short duration (2.2 minutes). The spherical ablation zone is small and the tissue is probably heated a little. Yellow arrows mark the little change.



Figure 16: This is the result of an ablation procedure with high power (100) and a long duration (6 min). The tissue charred, can be seen as a black spherical zone in the centre.



Figure 17: a. The specimen, the green part of the needle is 3 cm. The specimen measured 3 by 6 cm. The tumour largest diameter was 12 mm. b. X-ray cranial view showing the whole specimen and the position of the MWA antenna and the temperature probe. The temperature probe is placed to measure the temperature in the periphery of the tumour. c. The same X-ray cranial view rotated. d. Visualisation of the US imaging views of the specimen.



Figure 18: a. US axial view of the tumour zoomed in before needle insertion. Tumour diameter measured: 6.9 mm. The largest tumour diameter was 12 mm. b. Same US view, tumour is marked by the red circle.



Figure 19: US axial view of the tumour zoomed in, after needle insertion. The tumour (red arrows), the needle tip (blue arrow) and the localisation marker (yellow arrow) placed for the operation.

# HISTOPATHOLOGICAL EVALUATION

The tumour margins were very small. Pathological evaluation concluded that there was no influence of the MWA on the routine resection margin evaluation

The pathological evaluation with HE and CK8 staining revealed a vital tumour. Tumour cell death in percentage of total tumour volume: o %. Percentage cell coagulation of the tumour volume: 30 %.



Figure 20: US longitudinal view showing the tumour (red arrows), the needle (blue arrow) and the marker (yellow arrows) during localisation.

# DISCUSSION

The present work is a pilot study to assess the technical efficacy and predictability of percutaneous MWA in an ex vivo set-up. The study has just started, one resection specimen is treated with MWA. The second is scheduled for ablation. The goal is to treat at least ten resection specimens.

The objective of the bovine test set-up was to know how to use the device. Generator settings of 100 Watt applied for the duration of 1 minute resulted in a circumscribed and spherical ablation zone with a diameter of 1 - 2 cm. Settings with 100 Watt for 40 seconds and 75 Watt for 1 minute gave a comparable result. Based on these findings, we expect settings of 100 Watt for the duration of at least 3 minutes to be effective for the tumour ablation in specimen. The tumour is maximal 1.5 cm in diameter + a range 0.5 cm margin.

The purpose of the first resection specimen ablation was to prove that the MWA ablation has no influence on the resection margin of the operation. This is important in order to be able to include women scheduled to have a lumpectomy, otherwise we could include only the patients scheduled for a mastectomy which is a smaller group.

Histopathological evaluation with HE and CK8 showed a vital tumour. The duration of 40 seconds was too short for ablation. Actually this was expected. There were some other issues during needle insertion. The needle could not be placed in the centre of the tumour in the US axial view. One obstacle was the localisation marker, see figure 19 and the other issue is that this was not the largest dimension of the tumour. The tumour was also difficult to visualise in the US longitudinal view, figure 20, in which the ablation was conducted. Even with these needle insertion problems, if the ablation had been longer, for example, for more than 2 minutes the ablation results would probably had been better in terms of percentage tumour cell death. We chose for this duration because of the small specimen. The margins were small.

#### 6.1 EX VIVO STUDY SET-UP

Although we tried to simulate an in vivo setting in the test set-up, there are some factors that differ from the in vivo setting. Firstly, the most important difference is that there is no blood flow in the excision specimen. Secondly, there are more degrees of freedom in the way the needle can be placed. The application of the needle is easier, because there is no patient. Finally, skin burns are less likely to occur. There is no danger of placing the needle in such a way that the skin of the patients gets damaged. These issues have to be kept in mind before continuing into an in vivo study.

#### 6.2 PATIENT SELECTION

Patient selection is very important in the study design of assessing the efficacy of a new treatment. Women of an age of 45 years or younger are often diagnosed with multifocal and multicentric cancers, higher rate of recurrence after breast conserving therapy[3] and thus not suitable for local approaches and minimal invasive techniques like RFA or MWA.

The patient inclusion in this study is limited to the group who is not eligible for chemotherapy. This is a group of elderly women of an age of 60 years or older who are often diagnosed with unifocal, solitary and small tumours.

The advantage of this precondition, is that the patients to be included in this study will be a representative group for the patients to whom this technique offers a valuable alternative treatment option.

#### 6.3 MONITORING ABLATION PROCEDURE

Imaging for monitoring the ablation procedure is done by ultrasound. Ultrasound is a good choice because of the availability and utility of the technique. The other method used during the MWA procedure is real-time temperature measure at chosen moment(s) and point(s) in the specimen. We chose to measure at the periphery of the tumour after 20 seconds and after 40 seconds. The rationale behind is that if the periphery is > 50 - 60 °C, then the centre of the tumour must also be higher than the lethal threshold. These measurements were two separated observation moments in time. It would be helpful for monitoring of the treatment to have a technique to measure or visualise the temperature rise in time. An infra-red camera, could visualise the temperature development inside and outside the target zone. Another available technique to measure the temperature is MRI. The drawback of the MRI temperature measurements is the limited availability. Another drawback is that the MWA system is not MRI compatible.

Temperature measurements in time would improve the MWA procedure by giving more monitoring and thereby control about the procedure. To implement this procedure in the clinic, the physician must be able to measure the temperature in the periphery of the target zone and of the skin, in time. The duration of how long the tissue is at a certain temperature, is as important as the temperature value for monitoring the ablation.

#### 6.4 MOST EXCITING ADVANTAGE OF MWA

Every patient and biological profile is unique, therefore, treatments should anticipate with local approaches that react based on the molecular profile. MWA has proven to induce anti tumour response effects during treatment of osteosarcoma.[41] Long term in vivo studies are needed to investigate this effect.

#### 6.5 WHY IS MWA STILL NEW FOR BREAST CANCER TUMOURS?

Although from a theoretical point of view, MWA should be the most effective in breast cancer[9–11], it is currently being used to treat other type of cancers: liver, lung, renal and osteosarcoma.[22–25, 41] The cause is multifactorial: firstly, it is a new and therefore unknown technique. Secondly, the type of patient population; Breast cancer patients have relatively better overall survival rates compared to other types of cancer where MWA is already being used for experimental treatments. Thirdly, the limited availability of MWA devices. The present study is the first study where the Emprint ablation system is applied to assess the feasibility of MWA for the treatment of breast cancer. Because of the limited availability it is a less known treatment option compared with other minimal invasive treatments.

# CONCLUSION

The results of the specimen evaluation could be considered as a preliminary experience with the MWA system. The specimen was small and the margins were limited. The ablation duration of 40 seconds was too short and the tumour was vital at pathological evaluation. Settings of 100 Watt and a duration of 3 minutes is advised for the next specimen ablations.

In order to be able to introduce the MWA as a treatment option for breast cancer in the clinic: we should address accurate patient selection, monitoring and evaluation of the ablation procedure.

MWA is one of the many technologies that are being investigated at the moment for local treatment of tumours. Time will tell the utility of each. Studies like the present, resulting in clinical studies for a long term are needed to prove safety and effectiveness.

# Part II

# NEUROSTIMULATION OF THE PLEXUS COELIACUS AS A TREATMENT FOR OVERWEIGHT AND OBESITY

Proposal for a clinical study

# NEUROSTIMULATION OF THE PLEXUS COELIACUS

#### 8.1 BACKGROUND AND RATIONALE

So far, medical intervention strategies could not decrease the prevalence of overweight and obesity. Obesity is associated with the disappearance of the satiety response. Over time, with increasing weight, patients become obsessed with food. Although conventional bariatric surgery results in weight loss, it does so with short-term and longterm morbidity. Bariatric surgery for morbid obesity does not cure obsessive eating disorder. Whenever surgery is undone, patients regain weight rapidly. Bariatric surgery is expensive. Bariatric surgery is reserved for morbid obesity.

A new surgical procedure - gastric electrical stimulation (GES) to treat obesity - has been investigated in 33 trials. With the endoscope an implantable gastric stimulator IGS, a muscle pacemaker (non-neural) is applied to produce anti-peristalsis of the stomach. Patients experience nausea. A meta-analysis of those 33 studies showed a low level of evidence of effectivity.[42] Weight loss in the first year after implantation was the primary outcome. Maintained significant weight loss was rarely observed. The investigators conclude that some patients may lose weight due to other variables such as postoperative effects. Surgical interventions were not attempted in early stages of overweight, when people still have intact satiety responses. Early intervention is considered unethical, because surgical intervention would bear too much risk in healthy people with overweight, who are often in the prime of their life.

Neurostimulators are widely used in medical practice for Parkinson's disease, urine incontinence, paralysis, and pain management. Their use in human immune modulation, depression, and obesity is experimental. Neither overweight nor obesity is a registered indication for neurostimulation.

We propose to treat patients with overweight,  $28 \leq BMI \leq 33$  kg/m<sup>2</sup>, who gain weight rapidly despite lifestyle advice and medicines – with a neurostimulator. The wire of that device is to be in-



- b.
- Figure 21: Anatomy of the left and right celiac plexus. The celiac plexus resides in the retroperitoneal space and is embedded in the fat anterior to the aorta, just caudad to the level of origin of the celiac artery. Its anterior relationship includes the stomach and pancreas. Posteriorly, it is separated from the vertebral column by the diaphragmatic crura, which are important anatomic barriers between the celiac plexus, situated in the antecrural space, and the splanchnic nerves, situated posterior to the crus, in the retrocrural space. The celiac plexus and its network of ganglia extend over the anterolateral aspect of the aorta for several centimeters, demonstrating considerable variability in size, number, and position.[43]



Figure 22: a. Shows the proposed technique to deliver the electrode of the neurostimulator. b. The arrow points at the left celiac plexus.[43]

troduced into the left celiac plexus by an image-guided needle technique.22 The needle technique reduces the burden and the risk of intervention, when compared to endoscopic surgery. The neurostimulator chip with its rechargeable battery needs to be brought in a pocket under the skin above the iliac crest.

People with overweight have a BMI between the 25 and the 30. People with BMI within 30-35, have low-risk obesity. Morbid obesity is defined as a BMI above the 40 or between the 35-40 with secondary disease.[44]

The current standard treatment for overweight and obese people ( $25 \leq BMI \leq 35$ ) includes weight management programs and drug therapy. Weight management programs may achieve a clinically meaningful weight reduction in a number of patients, however weight loss is maintained in the long term only in a small proportion of them. Curioni2005 At present, drug treatment of obesity is through adrenergic stimulation with glucagon-like peptides (GLPs). Targeting hormones associated with satiety. Patients lose 3 kg on average, in the short term of months. Thereafter, habituation sets in and most patients regain weight within two years of treatment. GLPs are expensive drugs, their price tag is fourteen euro per day. GLPs do not offer a solution for the obesity epidemic, due to them giving insufficient weight reduction and cost.

Despite steady research progress, mechanisms underlying the resistance to fat loss once obesity is established remain incompletely understood.[45] Functional studies suggest that overweight is caused due to a missing satiety response in the brain.[46] Our proposal focuses on patients with  $28 \leq BMI \leq 33$ . We assume, based on the literature, that people with moderate- and high-risk obesity (BMI  $\geq 35$ ) are likely to have a dysfunctional satiety response.[47] Therefore, this intervention focuses on the group of patients with overweight and low-risk obesity.

If this pilot study would prove that pacing is safe and effective in reducing weight and preventing obesity, our team will conduct further research to determine the safe and effective dose with escalating hours of stimulation.

# 8.2 MECHANISM OF ACTION OF NEUROMODULATION APPLICA-TION

The plausible mechanism of our approach is beta-adrenergic stimulation of the (sub)thalamus. The sympathetic innervation of the stomach is almost entirely supplied by the left celiac plexus, which can be identified accurately with CT.[48] The left celiac plexus is the main source of adrenergic impulses to the (hypo)thalamus. From anatomical studies it appears that – in the supply of the stomach – the sympathetic nerves dominate, including those from the vagal nerve.[49, 50] From the left celiac plexus, adrenergic nerve fibres radiate along the aorta and through the spinal cord. The adrenergic pathways of spinal cord are the ventrolateral and the dorsal celiac columns – the fasciculus cuneatus and the fasciculus gracilis. All adrenergic pathways of left celiac plexus of the stomach radiate into the medulla oblongata and connect with brain stem nuclei including the (hypo)thalamus.

In medical practice adrenergic, glucagon-like peptides are used for weight reduction. Pharmacologically, those drugs are effective in inducing satiety, however, insufficiently effective to solve the overweight epidemic. Their main problem being habituation of patients to the drug. Their mode of action is through central satiety receptors of the (hypo)thalamus.[51] Those same areas of the brain are also the target areas of the left celiac plexus.

An additional argument to support our hypothesis lies in published preclinical research. The radiation of the celiac plexus to the brain system has been researched in cats. Micro-electrodes were used to stimulate the celiac nerves of the stomach and the left celiac plexus. Evoked responses were read out in the brain stem. Researchers freed the left celiac plexus to put sensitive electrodes into it. Sagittal cuts were made of the spinal cord and the brain stem at several levels including the (hypo)thalamus. It appeared that from the left celiac plexus, nerve fibres radiate along the aorta and through the spinal cord. The pathways of spinal cord are the ventrolateral and the dorsal celiac columns – the fasciculus cuneatus and the fasciculus gracilis. All pathways radiate into the medulla oblongata and connect with brain stem nuclei including the (hypo)thalamus.[52] Recorded evoked responses established the connection between the left celiac plexus of the stomach and the hypothalamus. Those preclinical findings were corroborated in other centres.[48, 53–55]

#### 8.3 hypothesis

First hypothesis, the electronic device (also referred to as pulse generator) can be delivered to the patient as a minimal invasive technique that bears little risk.

Second hypothesis, neurostimulation of the left celiac plexus, as it concerns a beta-adrenergic stimulus, triggers a satiety response in the brain and will result in weight reduction.

# 8.4 OBJECTIVES

First objective: To prove that the neurostimulator can be delivered with minimal invasive techniques. To obtain information about the technical efficacy and safety of neurostimulation for the patients. Second objective: obtain trending evidence that neurostimulation of the left celiac plexus induces satiety, prevents weight gains and helps people lose weight.

#### 8.5 ENDPOINTS

# 8.5.1 Primary Endpoint: safety of treatment

The successful and save delivery of the pulse generator to the patient. Primary parameters concern the safety of intervention.

- 1. Infection
- 2. Skin irritation or erosion
- 3. Any other (objective) medical problem after intervention

# 8.5.2 Secondary Endpoints: tolerability of pacing

- 1. Nausea (unexpected)
- 2. Subjective feelings of agitation (unexpected)
- 3. Disturbance of sleep quality (unexpected)
- 4. Any other complaint.

#### 8.5.3 Tertiary Endpoints: efficacy of the treatment

- 1. Weight reduction in kilograms
- 2. Satiety response after standardised large meal, as determined by a subjective satiety rating. Satiety response as determined by questionnaires. Satiety response as determined by fMRI.
- 3. Need of medication;
- 4. Insulin growth factor -1, glucose, HbA1c;
- 5. Plasma lipids and cholesterol;
- 6. Blood pressure;
- 7. Cardiovascular accidents;
- 8. Marker of inflammation CRP.

#### 8.6 STUDY DESIGN

This pilot study includes minimal 3 and maximal 5 patients. The patients get a pulse generator implanted minimally invasive. The electrode of that device is to be introduced into the left celiac plexus by an image-guided needle technique. The needle technique reduces the burden and the risk of intervention, when compared to endoscopic surgery. The neurostimulator chip with its rechargeable battery needs to be brought in a pocket under the skin above the iliac crest.

Monitoring of patients at Jeroen Bosch Hospital is done in outpatient visits every three months, with blood samples taken – two tubes of 10 ml each. This pattern of care is continued into the pilot study, with the addition of questionnaires and test meals to assess the satiety response. Baseline, and from inclusion every three months for a period of 1 year.

Before insertion of the pulse generator, and immediately thereafter, and one year later, patients undergo fMRI of the brain, in order to assess whether fMRI is usable to monitor pacemaker functioning including the induction of satiety. To evaluate the efficacy of the treatment.

Monitoring of the intervention is done at the time of the intervention and three days later at the Jeroen Bosch Hospital outpatient clinic. Monitoring will be done by subjective input of the burden to the patient. In addition, the patients will be monitored for infection, and any other (S)AE the patient may have incurred. Patients will also be instructed to call the clinic if any discomfort or rise of temperature would occur.

Study timeline:

T1: patient inclusion after signed informed consent.

T2: patient get a first evaluation with :weight and blood samples measure;

standardized meal and questionnaires about eating behaviour and lifestyle; fMRI scan.

T<sub>3</sub>: patients get the pulse generator minimally invasive delivered.

T4: control of the device, implantation and whether it's effective by fMRI.

T<sub>5</sub>: every three months outpatient control of the device, weight, standardized meal and questionnaires about eating behaviour and lifestyle.

#### 8.7 TRIAL INTERVENTION

Minimally invasive implantation of a pulse generator. Follow-up and evaluation with weight and blood samples measure, standardized meal and questionnaires about eating behaviour and lifestyle. Trend of weight loss evaluation with standardized meal and questionnaires about eating behaviour and lifestyle.

Evaluation of the pulse generator and the neurological response with fMRI.

#### 8.8 STUDY POPULATION

Inclusion criteria, in order to be eligible to participate in this study, a subject must meet all of the following criteria:

- 1.  $18 \leq \text{age in years} \leq 55;$
- 2.  $28 \leq BMI \leq 33 \text{ kg/m}^2$ ;
- 3. Intact satiety response, assessed by questionnaire and by patient satiety rating of a large, standardized meal;
- 4. Weight gain of more than 2 kg in a lifestyle treatment period of at least three months. The Jeroen Bosch Hospital will hand pick patients that gain weight rapidly. Patients with insulin resistance, especially when they suffer from metabolic syndrome or diabetes, receive medicines such as metformin in a dose of at least 500 mg twice daily;

- 5. Standard treatment of co-factors of overweight and obesity such as hypertension, dyslipidemia, metabolic syndrome and diabetes;
- 6. Signed informed consent.

Exclusion criteria, a potential subject who meets any of the following criteria will be excluded from participation in this study.

- 1. Chronic nausea of any cause;
- 2. Sleep disorder;
- 3. Chronic stress disorder of any kind;
- 4. Insufficient physical activity;
- 5. Suicidal;
- 6. Prolonged PTT/aPTT or thrombocytopenia;
- 7. Heart disease of any kind;
- 8. Patient with contraindications for contrast enhanced CT or functional MRI, (renal failure).
- 9. Any severe disease except diabetes due to overweight.

# 8.9 ETHICS

Approval of the METC is necessary, the whole treatment and burden is not part of the standard care for the study population.

Clinical assessments include:

• Weight and blood sample measurements

- fMRI
- Standardized meal and questionnaires about eating behaviour and lifestyle.

# 8.10 Adverse events

The needle procedure to place the electrode of the neurostimulator that we propose has not been done before for overweight and/or with the left celiac plexus of the stomach as target. When assessing the risk of infection of the device, the procedure is comparable to a cardiac pacemaker implantation for dysrhythmia. The rate of severe adverse events of pacemaker implantation for dysrhythmia is low (0.5%). However, the burden of the expected SAE of infection is considerable, as it often requires hospitalisation, removal of the device and systemic antibiotic treatment. Other SAEs of cardiac pacemaker implantation, such as endocarditis, and thrombosis, are irrelevant to the present study. Those high burden serious adverse events are due to the vascular route. Our procedure of neurostimulation is proposed to take a subcutaneous and interstitial route through the retroperitoneum. It would not incur those SAEs of endocarditis, and thrombosis. We do not propose to take our device into the vascular space. However, (S)AE of retroperitoneal infection cannot be excluded. In conclusion, we expect a low risk of 0.5 % of infection of our neurostimulator placement, but consider the burden of that SAE considerable.

The risks of the light burden AE of skin erosion or irritation is estimated at 0.5 per cent. Easy access and effective standard medicines make those erosions and irritations easy to resolve. In addition, there are AEs specific for the activity of the neurostimulator devices. An example is a pacemaker-like device called the Maestro® Rechargeable System. About 3 per cent of patients using such unipolar systems can feel the effect of the neurostimulation at the implant site. Depending on the indication, some patients want the neurostimulator turned off. None of the patients with Parkinson's disease want that. However, a case of a patient with urine incontinence was communicated to us. That patient wanted the neurostimulator to be switched off. Our population consists of motivated patients, who want to lose weight, and we expect them to accept those AEs when occurring.

# 8.11 BIOSTATISTICS AND DATA ANALYSIS

The proposed design is a technical efficacy pilot study to prove the safety of the treatment. Our intention is to include minimal 3 and maximal 5 patients.

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