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Implications of MEDical low dose RADiation exposure  
Agreement 755523**

***Clinical study protocol:***

**EARLY-HEART  
EARLY detection of cardiovascular changes (HEART)  
after radiotherapy for breast cancer**

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**List of abbreviations and relevant definitions**

AE	Adverse Event
ASE/EAE	American Society of Echography / European Association of Echography
BC	Breast Cancer
BLOOD	Circulating biomarkers
CAC	Calcium artery calcium
3D CRT	Three Dimensional Conformal Radiation Therapy
CT	Cardiac Computed tomography
CTCA	Computed tomography coronary angiography
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical Target Volume
DCIS	Ductal Carcinoma In Situ
DICOM	Digital imaging and communications in medicine,
DVH	Dose Volume Histogram
ECHO-ST-ST	2D-speckle-tracking echocardiography
ENACT	Enabling Communication Technology
GLS/GLSR	Global and Segmental Longitudinal Strain and Strain Rate
Gy	Gray
IC	Informed Consent
IHD	ischemic heart disease
IMRT	Intensity modulated radiotherapy
MREC	Medical research ethics committee (MREC)
LVEF	Left Ventricular Ejection Fraction
MAPSE	Mitral annular plane systolic excursion
MRI	Cardiac magnetic resonance imaging
NTCP	Normal Tissue Complication Probability
OAR	Organ At Risk
PTV	Planning target volume
RT	Radiotherapy
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
Sv	Sievert
TAPSE	Tricuspid annular plane systolic excursion
VMAT	volumetric modulated arc therapy
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)

## 1. TWO-PAGE OUTLINE OF THE PROTOCOL

**1.1. Background:** Breast cancer (BC) radiotherapy (RT) leads to coincidental radiation of the heart, resulting in increased risk of a variety of heart diseases. The prevalence of BC survivors at risk of cardiac complications will gradually increase, as the incidence of BC in Europe is still rising while prognosis significantly improved over the last decades. These late cardiac complications have a major impact on quality of life and lead to subsequent morbidity and increased mortality. Therefore, identifying BC patients with the highest-risk of radiation-induced cardiac complications is crucial for developing strategies for primary and secondary prevention, which may contribute to healthy ageing. So far, little has been done on the relationship between dose distribution to different anatomical cardiac structures during RT and early cardiovascular changes that may lead to cardiac complications.

**1.2. Main study objective:** The main objective is to identify and validate the most important cardiac imaging (ECHO-ST, CTCA and MRI) and circulating biomarkers of radiation-induced cardiovascular changes arising in the first 2 years after breast cancer radiotherapy.

**1.3. Study design:** An international multicenter prospective cohort study

**1.4. Endpoints:** The primary endpoint is defined as a mean decrease in Global and Segmental Longitudinal Strain and Strain Rate (GLS/GLSR) of at least 2.5% assessed by cardiac ultrasound 6 to 24 months after RT compared to baseline.

The secondary endpoints are:

- Changes in myocardial function assessed by cardiac ultrasound 6 to 24 months after RT compared to baseline.
- Anatomical changes in coronary artery atherosclerosis (number of coronary segments containing any plaque/stenosis, and calcium score) by cardiac CT 24 months after RT compared with baseline. The endpoint is defined as 15% or greater changes.
- Myocardial changes by MRI 6 to 24 months after RT compared with baseline (morphology, function, tissue characterization by delayed enhancement and pre-/post-contrast T1 mapping). The endpoint is defined as an increase of the mean T1 mapping value of at least 7%.
- Temporal changes in circulating biomarkers at the end of RT and 6 to 24 months after RT compared with baseline. The endpoint is defined as a significant increase or decrease in each biomarker between time points.

**1.5. Selection criteria:** Female unilateral BC patients aged 40-75 years treated with primary breast conserving surgery and postoperative radiotherapy using modern planning-CT based RT technologies.

### 1.6. Interventions:

- Cardiac imaging:
  - o Electrocardiogram to detect any arrhythmia followed by Automated 2D-speckle-tracking echocardiography (ECHO-ST), the most commonly used modality to evaluate myocardial dysfunction and a new technique of assessing myocardial deformation
  - o Computed tomography (CT) to evaluate coronary artery lesions by assessing plaques (calcified and non-calcified) and stenosis of the coronary arteries, and determination of coronary artery calcium score
  - o Cardiac magnetic resonance imaging (MRI) for the evaluation of the myocardium (including tissue abnormalities, cardiac morphology and function).
- Circulating biomarkers (BLOOD) will be based on a panel of circulating classical and novel blood-based biomarkers.

Imaging and circulating biomarkers will be assessed at baseline before RT (ECHO-ST, CT, MRI, BLOOD); at the end of RT (BLOOD); 6 months after RT (ECHO-ST, MRI, BLOOD) and 24 months after RT (ECHO-ST, CT, MRI, BLOOD).

### 1.7. Statistical considerations:

With 250 women, the study will have 80% power, with an  $\alpha=0.05$  to find a mean decrease in GLS/GLSR of at least 2.5%.

The analysis plan is divided into three parts. In the first part a descriptive analysis of the data is done. Differences in biomarkers between unexposed and paired exposed groups (e.g. right vs. left-sided breast RT) at different time points are analysed to generate preliminary hypotheses on effects of RT on the heart. To investigate the time course of continuous variables extracted from ECHO-ST, CT or MRI measurements, mixed regression models are used. In the second part (anatomical) changes in cardiac biomarkers are correlated with dose distribution data. In the third part of the analysis multivariable Normal Tissue Complication Probability (NTCP) models are constructed. An integrative clinical-biological risk score is developed for individual risk prediction.

## 2. BACKGROUND AND INTRODUCTION

### 2.1. Introduction

Radiotherapy (RT) plays an important role in the treatment of breast cancer (BC), as over 60% of all BC patients are irradiated as part of their curative treatment. BC radiotherapy generally leads to coincidental irradiation of the heart, resulting in an increased risk of a variety of heart diseases, including ischemic heart disease (IHD), congestive heart failure, arrhythmias, conduction defects, valvular disease and pericarditis with relative risks within the range of 1.2 to 3.5 by comparing left-sided BC patients (with higher exposure to the heart) to right-sided BC patients<sup>1-4</sup>. Moreover, cardiac damage was shown to be correlated with the mean heart dose with 7.4% rate increase of acute coronary events per one Gray (95% confidence interval, 2.9-14.5;  $P < 0.001$ ), with no minimum threshold for risk, recently the risk of acute coronary events within the first 9 years after RT was confirmed by another publication<sup>4,5</sup>.

The incidence of BC in Europe is still rising while prognosis significantly improved over the last decades. Therefore, the prevalence of BC survivors at risk for cardiac complications will gradually increase<sup>1,6</sup>. There is a clear evidence that RT may cause, in organs and tissues close to the planning target volume (PTV), but also in organs at higher distances, an increased risk for late and very late clinically relevant side effects that have a major impact on quality of life.

Technological developments in RT, such as intensity modulated radiotherapy (IMRT)/Volumetric modulated arc therapy (VMAT) and deep inspiration breath hold, have allowed for a significant reduction of cardiac doses<sup>7</sup>. However, as there appears to be no threshold dose below which cardiac complications do not appear; radiation-induced cardiac diseases remain potential severe late complications of BC radiotherapy.

Therefore, there is an urgent need for primary and secondary preventive measures. Primary prevention includes radiation dose optimisation to the most critical structures of the heart. Secondary prevention requires identification of patients at risk as early as possible after RT treatment.

Long before the onset of clinically significant cardiac complications occurring many years after RT, subclinical cardiac changes can occur over weeks, months or first years after RT, that can be detected using anatomical and functional cardiac imaging or circulating biomarkers.

#### *Anatomical and functional cardiac imaging*

Using a recent advanced echocardiographic technique, automated 2D-speckle-tracking echocardiography / cardiac strain, for detecting and quantifying subtle disturbances in left ventricular systolic function; strain and strain rate were significantly decreased (mean 5%) during the first year following breast RT. In patients with left-sided BC global longitudinal strain and apical strain was diminished. The basal regions showed a compensatory increase in function, though not enough to compensate for the global functional loss resulting in a decrease in the global

longitudinal strain<sup>8-11</sup>. Tuohinen et al. also showed deterioration in basal anterior strain segments after right-sided radiotherapy, whereas the global function remained unaffected. They also observed with tissue Doppler imaging that RT increased ECHO-ST density in the RV free wall and in the septum at the end of RT in patients with left-sided BC, but there were no changes observed in cardiac ECHO-ST density in patients with right-sided BC<sup>8</sup>.

Cardiac computed tomography (CT) without contrast and coronary computed tomography angiography (CTCA) provides morphological information of the coronary arteries, visualization of the coronary artery anatomy, determination of plaques and stenosis of the coronary arteries, and determination of the calcium artery calcium (CAC) score. This reflects the evolution of coronary artery disease. Three studies have measured the amount of CAC in the years following RT treatment for BC. In two studies, no elevated CAC scores in BC patients were found 5 to 15.7 years after RT treatment, whereas 1 study did find an increase in CAC score depending on radiation dose to the heart<sup>12-14</sup>. Of the studies that did not find a CAC score increase, one did not include baseline CAC scores and the other only included a relatively small number of patients, which makes it difficult to draw definitive conclusions from these two studies. In young Hodgkin's lymphoma survivors (all under 55 years) elevated CAC scores have been found in the 5 to 35 years after RT<sup>15-17</sup>. Based on the analysis of 15 segments of coronary arteries per patient, an increase of calcified and non-calcified plaques of around 15% was observed during a 2-year follow-up. A study concerning the general population investigated CAC scores at baseline and after 10 years of follow-up<sup>18</sup>. The results showed that the diagnosis of cancer and its treatments were significantly associated with the development of CAC, even after accounting for cardiac risk factors. The results of these studies suggest that RT is associated with increased CAC scores in the long term and therefore supports the hypothesis that accelerated atherosclerosis is one of the mechanisms contributing to an increase of radiotherapy induced cardiac events after cardiac irradiation.

Finally, with cardiac magnetic resonance imaging (MRI), which is considered the gold standard to characterize myocardial tissue and to measure ventricular volumes and function, it has been shown that right ventricular systolic function (TAPSE) was decreased in a BC cohort at 24 months<sup>9</sup>. Furthermore, temporary ejection fraction decreases were observed on MRI (in patients treated with 3DCRT and not in patients treated with IMRT) at 6 months resolving at 24 months. Left (MAPSE) and right (TAPSE) ventricular systolic function determined by MRI were reduced at 24 months (but still within normal range) for the whole cohort. Furthermore, with T1 mapping, a promising technique to quantify morphologic tissue injuries, it was shown in cancer survivors (including BC patients) that interstitial/diffuse myocardial fibrosis was elevated 3 years after anthracycline-based chemotherapy independent of the underlying cancer or comorbidities, suggesting that imaging biomarkers of interstitial fibrosis are related to prior receipt of potentially cardiotoxic cancer treatment<sup>19</sup>.

### *Circulating biomarkers*

Many classical biomarkers (e.g., C-reactive protein, N-terminal pro-B-type natriuretic peptide (NT-proBNP) and troponin (TnI)) were shown to be potential biomarkers for cardiac damage after radiotherapy<sup>20</sup>. In addition, circulating inflammatory cytokines also signified tissue inflammation<sup>21</sup>. Furthermore, it was shown that irradiation induced acute endothelial activation or dysfunction that can be observed many weeks after irradiation and resulting in a pro-inflammatory endothelial phenotype.

Another hypothesis to explore is that the irradiation may be responsible for an increase in the circulating levels of certain miRNAs expressed by cells of the heart tissue. Currently, the potential function of extracellular miRNAs is being studied intensively, and the first studies have confirmed that miRNAs may indeed function in cell-to-cell communication<sup>22</sup>. Many studies have reported the use of miRNAs as circulating biomarkers for diagnosis or prognosis of cardiovascular diseases. Although many of those studies still require replication in multiple independent study populations, the results so far strongly suggest that some plasma miRNAs are quite specific for cardiovascular pathologies and may be useful for diagnostic and monitoring purposes.

The complex and multifactorial nature of atherogenesis and development of atherothrombotic complications involves numerous interactions between various cell types inside the vascular wall (e.g. macrophages and smooth muscle cells) and in the blood (e.g. leukocytes and platelets). One relatively recent advance in this area is the discovery of circulating microparticles. High levels of circulating microparticles found in many cardiovascular diseases demonstrate the importance of platelet, monocyte and endothelial activation and could condition remote sustainability illnesses<sup>23</sup>. The above described imaging studies have shown that early subclinical cardiac changes occur in BC patients after RT. Additionally, classical cardiac biomarkers have been shown to be potential candidates to monitor cardiac damage after radiotherapy. However, primary and secondary prevention measures require (exact) knowledge on the relationship between dose exposure to specific cardiac structures and (the timing of) early subclinical cardiac changes and their occurrence in time.

So far little has been done on elucidating the specific relationships between doses to cardiac structures and subsequent early cardiac toxicity in the published imaging or biomarker studies.

## **2.2. Summary and proposed study**

The above described imaging studies have shown that early subclinical cardiac changes occur in BC patients after RT. Additionally, classical cardiac biomarkers have been shown to be potential candidates to monitor cardiac damage after radiotherapy. However, primary and secondary prevention measures require (exact) knowledge on the relationship between dose exposure to specific cardiac structures and (the timing of) early subclinical cardiac changes and their occurrence in time. So far little has been done on elucidating the specific relationships between

doses to cardiac structures and subsequent early cardiac toxicity in the published imaging or biomarker studies.

MEDIRAD-EARLY HEART therefore aims to determine early (i.e., within 24 months) cardiovascular changes after BC radiotherapy using imaging and circulating biomarkers and to determine the relation with radiation dose to a variety cardiac structures.

### 3. OBJECTIVES OF THE TRIAL

#### 3.1. General objectives

MEDIRAD-EARLY HEART is part of the MEDIRAD project. The MEDIRAD project aims to enhance the scientific basis and clinical practice of radiation protection in the medical field and thereby addresses the need to understand and evaluate the health effects of low dose ionizing radiation exposure from diagnostic and therapeutic imaging and from off-target effects in radiotherapy.

MEDIRAD will pursue 3 major operational objectives: First, it will improve organ dose estimation and registration to inform clinical practice, optimize doses, set recommendations and provide adequate dosimetry for clinical-epidemiological studies of effects of medical radiation. Second, it aims to evaluate and understand the effects of medical exposures, focusing on the two major endpoints of public health relevance: cardiovascular effects of low to moderate doses of radiation from RT in BC treatment including understanding of mechanisms; and long-term effects on cancer risk of low doses from CT in children. Third, it will develop science-based consensus policy recommendations for the effective protection of patients, workers and the public.

The specific objective of the MEDIRAD-EARLY HEART study is to gain more insight in the relationship between radiation dose distributions to the heart, to different anatomical cardiac substructures, during RT and early cardiovascular changes (within two years).

**Primary objective:** to identify the most important cardiac imaging (ECHO-ST, CT and MRI) and circulating biomarkers of radiation-induced cardiovascular changes arising in the first 2 years after BC RT and to develop Normal Tissue Complication Probability (NTCP) models integrating these biomarkers combined with dose metrics of cardiac structures based on 3D-dosimetry.

**Secondary objectives:**

- To formulate recommendations for implementation of these multivariable NTCP models in primary and secondary prevention strategies to ultimately develop stratified therapeutic and diagnostic approaches (overarching aim of MEDIRAD):
  - Improvement of RT planning techniques to spare cardiac structures, or even selection for proton therapy;
  - First guidelines for cardiac follow up programs in high-risk BC patients;
- To implement a European repository of patient dose and imaging data (overarching aim of MEDIRAD WP2.4.1).

## 3.2. Endpoints

### 3.2.1. Primary endpoints

The primary endpoints are defined as a mean decrease in Global Longitudinal Strain or Global Longitudinal Strain Rate, determined by cardiac ECHO-ST, of at least 2.5% between baseline and 24 months after RT (*Erven et al, Int J Radiation Oncol Biol Phys, 2012; Lo et al, In J Radiation Oncol Biol Phys, 2015*).

### 3.2.2. Secondary endpoints

Secondary endpoints are other imaging and circulating biomarkers, defined as:

- Secondary echocardiographic measurements are:
  - Left ventricular ejection fraction using Simpson's biplane method
  - Left ventricular end-diastolic volume using Simpson's biplane method
  - Left ventricular end-systolic volume using Simpson's biplane method
  - Left-ventricular end-diastolic diameter using M-mode
  - Left ventricular mass measured according ASE/EAE guidelines
  - Global and segmental radial strain rate
  - E/A wave ratio
  - E/Ea wave ratio (lateral annulus)
  - TAPSE (tricuspid annular plane systolic excursion)
  - Tricuspid annular S wave
  - Pulmonary artery systolic pressure (based on the peak tricuspid regurgitation velocity estimate and by assuming a right atrial pressure of 5 mmHg)
  - Left ventricular outflow tract diameter
  - Left ventricular outflow tract velocity time integral
  - Heart rate
  - Cardiac output measured by multiplying heart rate by stroke volume
- CT: to measure anatomical changes in coronary arteries assessed by cardiac CT occurring 24 months after RT compared with baseline before RT start.
  - Individual description of stenosis or plaques of the 15 segments of the coronary arteries; left main coronary artery (LM); left anterior descending artery (LAD), left circumflex artery (LX) and right coronary artery (RCA) and evaluation of change in CAC score.
  - The progression atherosclerosis will be defined as an increase of the number of coronary segments containing any plaque and as an increase of the calcium score, of at least 15% between baseline and 24 months after RT.
- MRI: to evaluate myocardial tissue abnormalities assessed by cardiac MRI occurring 6 to 24 months after RT compared with baseline before RT start.
  - Cardiac MRI-parameters include: morphology, function, tissue characterization by delayed enhancement and pre-/post-contrast T1 mapping (at 15 minutes).
  - The corresponding main MRI-endpoint is defined by an increase of the native mean myocardial T1 mapping value of at least 7% (*Germain et al. Clin Med Insight Cardiol 2014*)
- Circulating biomarkers: to measure temporal changes in circulating biomarkers occurring at the end of RT, 6 to 24 months after RT compared with baseline before RT start.
  - The following circulating biomarkers are assessed:



- Classical markers of cardiac injury: C-reactive protein, Troponin I, Troponin T, B-type natriuretic peptide (BNP), NT-Pro BNP, beta2-Microglobulin, Galectin 3
  - Inflammatory cytokines: IL-6, IL-8, IL-18, TNF $\alpha$
  - Endothelial activation and dysfunction: sVCAM-1, s-ICAM-1, E-Selectin, P-Selectin, vWF, PAI-1, Fibrinogen, Thrombomodulin, TGF $\beta$ 1
  - Microparticles: CD14(monocytes), CD31(endothelial), CD41(platelets), CD3(lymphocyte), CD235a(erythrocyte)
  - MicroRNAs: miR-1, miR-133, miR-208, miR-499, miR-126, miR-130, miR-145, miR-181, miR-150, miR-155, miR-223, miR-17, miR-18, miR-22, miR-34, miR-92, miR-140, miR-182, miR-199, miR-423 and miR-590.
  - circulating DNA methylation
- Endpoint are defined as a significant increase or decrease in each biomarker between time points.

#### 4. PATIENT SELECTION CRITERIA

Female unilateral BC patients treated at one of the five participating centres with postoperative modern planning-CT based RT alone after breast conserving surgery, and who are aged 40-75 years at the time of RT.

##### **Inclusion criteria:**

- Female unilateral breast cancer patients
- Treated with primary breast conserving surgery for stage I-III invasive adenocarcinoma of the breast or ductal carcinoma in situ (DCIS)
- Age between 40-75 years at time of start radiotherapy
- WHO performance status 0-1
- Planned for radiotherapy alone to the breast with or without the lymph node areas
- Radiotherapy based on planning-CT scan using either 3D-CRT, IMRT, or VMAT/RapidArc
- Written Informed consent

##### **Non inclusion criteria:**

- Male breast cancer patients
- Neoadjuvant or adjuvant chemotherapy
- M1 disease (metastatic breast cancer)
- Medical history of coronary artery disease and/or myocardial infarction and/or atrial fibrillation
- Previous thoracic or mediastinal radiation
- Contraindications to injection of iodinated contrast such as allergy or renal failure
- Pregnancy or lactation

## **Exclusion criteria**

- Atrial fibrillation detected during electrocardiogram before radiotherapy
- Abnormal echocardiography before radiotherapy defined as: LVEF<50%; longitudinal strain  $\leq$  -16%; longitudinal strain rate  $<$ -1%, and/or abnormal wall motion
- Presence of myocardial infarction detected during MRI before radiotherapy
- CTCA or cardiac MRI results before radiotherapy requiring revascularisation

▶ See CRF ELIGIBILITY in appendix for further details

## **5. TRIAL DESIGN**

MEDIRAD EARLY HEART is a multicentre prospective cohort study that will include 250 female BC patients treated with post-operative RT alone after primary breast conserving surgery to assess imaging and circulating cardiac biomarkers the first 2 years following RT.

## **6. THERAPEUTIC REGIMENS, EXPECTED TOXICITY, DOSE MODIFICATION**

### **6.1. Radiotherapy**

All patients will undergo computerized tomography (CT) in treatment position to prepare the treatment plan.

### **6.2. Patient positioning**

The patient will be immobilized with an appropriate immobilization aid in supine position. Patients will be treated according to own center specificities (active breathing control for left BC, for left and right BC, ...) in order to lower the cardiac dose as much as possible.

### **6.3. Planning CT scan acquisition**

A planning CT-scan is made with the patient in treatment position with the immobilisation device in place, according to own center specificities regarding breathing control. Slice thickness of maximum 2 mm will be used

Images will be constructed with at least 512 x 512 pixel matrix. DRRs (digitally reconstructed radiographs) of all beams including the orthogonal verification beam pair will be generated from the planning CT scan for comparison with portal images.

#### **6.4. Target volumes and organs at risk**

The definition of target volumes will be in accordance with the ICRU 50 report.

##### **6.4.1. Gross tumour volume (GTV)**

Not applicable.

##### **6.4.2. Clinical target volume (CTV)**

The CTV includes the entire breast with the exclusion of the skin (5 mm).

##### **6.4.3. Planning target volume (PTV)**

To account for set up errors, a CTV-PTV margin is used according to institutional standards.

##### **6.4.4. Organs at risk (OAR)**

For all centres of investigation, the following OAR will be delineated: Contralateral breast, lung, heart.

In addition, other OAR could be delineated according to the routine of centres: heart structures, LAD coronary, oesophagus and thyroid (in case of periclavicular lymph nodes are irradiated).

#### **6.5. Treatment planning**

The total dose for the breast will be in accordance with center practices (50 Gy/25 fractions, or 40.05 Gy/15 fractions or isoeffective schemes). The possible boost can be applied with photons or electrons both sequentially or simultaneously.

##### **6.5.1. Limit of dose in organs at risk**

In all cases, dose will be prescribed according to the ICRU criteria and dose constraints are according to QUANTEC. Algorithms are used for the calculation of the dose distribution, considering lack of homogeneity in the tissue

##### **6.5.2. Irradiation techniques**

The treatment techniques based on planning-CT scan consist of 3D-CRT, IMRT, or VMAT/RapidArc.

##### **6.5.3. Patient position verification**

To ensure quality of positioning, patient positioning is verified. This can be done with MV imaging (Electronic Portal Imaging Device, EPID) or with kV imaging (cone beam CT).

## 7. CLINICAL EVALUATION, LABORATORY TESTS AND FOLLOW-UP

### 7.1. Before inclusion

In each centre, radiation oncologists will enable first contact with women diagnosed with breast cancer: during first visit with the radiation oncologist, he/she will present the study and its implications to women patients for whom radiation therapy is planned. This consultation is 1 to 4 weeks before the start of radiotherapy, depending on the center. The radiation oncologist will ensure that women meet the criteria for inclusion in the study and study information leaflet detailing the protocol will be given with a consent form (► see *INFORMATION LETTER* and *INFORMED CONSENT FORM* in Appendix).

### 7.2. Before start of treatment protocol

About 1 to 2 weeks before the start of radiotherapy, during the visit for the RT planning-CT, women agreeing to participate in the study will give their signed written informed consent form and will then be considered as included. Cardiac MRI will not be mandatory for inclusion in EARLY HEART Study (in contrast with ECHO-ST, CT and BLOOD).

► See *CRF ELIGIBILITY*, *CRF CANCER*, *CRF planned RT* and *CRF CARDIOLOGY*, in appendix for further details

From this inclusion visit on, women's follow-up protocol will be realized. Before start of RT the following interventions will have to be performed:

- Cardiac imaging:
  - An electrocardiogram to detect any arrhythmia followed by an Automated 2D-speckle-tracking echocardiography (ECHO-ST) the most commonly used modality to evaluate myocardial dysfunction and a new technique of assessing myocardial deformation;  
► See *CRF ECHO-ST* in appendix for further details
  - Computed tomography (CT) by using both low dose non enhanced and enhanced CT scans to evaluate coronary artery lesions by assessing morphological information including plaques and stenosis of the arteries, and determination of the CAC score;  
► See *CTCA PROTOCOL* and *CRF* in appendix for further details
  - Cardiac magnetic resonance imaging (MRI) for the measurement of ventricular function, size of the two heart chambers, and wall thickness; tissue characterization by delayed enhancement; and pre-/post-contrast T1 mapping mapping and pre contrast T2 mapping of the left ventricle.  
► See *MRI PROTOCOL* and *CRF* in appendix for further details
- Circulating biomarkers (BLOOD) will be based on a panel of circulating classical and novel blood-based biomarkers (see 7.5 *Blood samples for biomarkers analysis* for further details)

Furthermore, toxicity will be assessed according CTCAE 4.03 and patient rated outcome

measures. ► See *CRF TOXICITY in appendix for further details*

### **7.3. During treatment**

As planned in routine follow up of patients in each center, toxicity will be assessed according CTCAE 4.03 and patient rated outcome measures.

### **7.4. Subsequent follow-up**

During subsequent follow up imaging and circulating biomarkers will be assessed at specific time points after RT up to 24 months:

- At the end of RT: BLOOD.
- Six months after RT: ECHO-ST, MRI, BLOOD.
- Two years after RT: Electrocardiogram and ECHO-ST, MRI, CT, BLOOD.

Furthermore, in addition to routine follow-up of patients in each center, acute and late toxicity will be assessed according CTCAE 4.03 and patient rated outcome measures at the end of RT, 6 months, and 24 months after RT.

### **7.5. Blood samples for biomarkers analysis**

Each patient will have 4 blood samples. For each blood sample, 30mL of blood will be collected and divided in 6 tubes of 5 mL as follows: 2 tubes heparin; 2 tubes EDTA; 2 tubes CITRATE (2 x 5ml).

Blood samples will be collected: before RT, at the end of RT, 6 months after RT and 24 months after RT. Once blood sample is collected, a standard operation procedure will be followed ► See *BLOOD PROTOCOL in appendix for further details*.

All prepared aliquots of 500 µl (approximately 30 aliquots per patient per blood sample) will be stored and freeze at –80°C in the local investigating center for a short time period of few weeks or months (depending on the capacity of storage of the local center), and then periodically sent with a medical specialized carriers to University of Bristol which is the centre for central storage of aliquots for biomarkers analysis (Workpackage 4.2.2 Preclinical and clinical identification of standard and innovative biomarkers of radiation-induced cardiovascular toxicity).

All blood samples and aliquots will be labelled using the same anonymised code assignment for patient as the one used in CRF.

Once received at University of Bristol, for each patient at each time of blood sample, 20 aliquots will be used for biomarkers analysis, the 10 remaining aliquots will enter a long term storage collection for 15 years. After 15 years, all aliquots will be destroyed except if a patient asks for early destroy of her aliquots. Aliquots of the long term storage collection could only be used in the frame of research on cardiovascular diseases.

Responsible party for EARLY HEART aliquots collection: Pr Constanza Emanuelli, Bristol Heart

Institute, School of Clinical Sciences, University of Bristol, Bristol Royal Infirmary, Upper Maudlin Street, BS2 8HW, Bristol, United Kingdom.

## 8. FLOWCHART

The flow chart below gives an overview of the EARLY HEART study design and the main procedures that subjects will undergo during this research.

In the Standard Follow-up Program only toxicity assessment (CTCAE 4.03) is performed. ECHO-ST, CT, MRI and BLOOD are performed for the research study.

	<b>Baseline</b>	At the end of RT	6 ms	24 ms
<b>Informed Consent</b>	X			
<b>In- and exclusion criteria</b>	X			
<b>Medical history</b>	X			
<b>Electrocardiogram (ECG) followed by ECHO-ST</b>	X		X (ECHO alone, no ECG)	X
<b>CT</b>	X			X
<b>MRI</b>	X		X	X
<b>BLOOD</b>	X	X	X	X
<b>Toxicity assessment (CTCAE 4.03)</b>		X	X	X

## 9. STATISTICAL CONSIDERATIONS

### 9.1. Study Design

**MEDIRAD EARLY HEART** is a multicentre prospective cohort study that will include female BC patients treated with post-operative RT alone after primary breast conserving surgery to assess imaging and circulating cardiac biomarkers the first 2 years following RT.

### 9.2. Sample Size

The sample size was based on a statistical power of 80%, an alpha-risk of 5%, the definition of the primary endpoint (a decrease in the global and segmental longitudinal strain or strain rate of at least 2.5%) and baseline measurements hypothesis (mean global longitudinal strain before RT : -16.5%  $\pm$  2.1% from Dalen et al, European Journal of Echocardiography : the Journal of the Working Group on Echocardiography of the European Society of Cardiology. 2010) Considering paired test for comparisons, but also possible lost to follow-up due to death or other reason, the inclusion of 250 women is necessary for EARLY-HEART study.

Centre	Recruitment rate per month	Total number of patients to recruit in 1 year
IRSN	4.2	50
UMCG	5	70
TUM-MED	4.6	55
CCUL	2.1	25
ICO	4.2	50
Total		250

### 9.3. Analysis plan

IRSN and UMCG will be in charge of main statistical analysis in close collaboration with other investigating centres.

The analysis plan consists of three stages:

#### *Stage I: Descriptive analysis*

Means, standard deviations, percentages, ranges and confidence intervals of 95 % are used to summarize:

- The questionnaire medical data;
- The 2D-speckle-tracking echocardiography (ECHO-ST) measurements including strain and strain rate.
- The Coronary computed tomography angiography (CT) measurements including mean number of coronary segments with plaques and/or stenosis, and CAC score (Agatston, Volume), total and per coronary artery;
- The MRI measurements include ventricular function, size of the heart chambers and wall thickness, tissue characterization by delayed enhancement and pre-/post-contrast T1 mapping of the left ventricle;
- The measurements of all biomarkers;
- Dose distribution to the several heart substructures including ventricles and coronaries arteries.

Paired non-parametric tests (Wilcoxon signed rank test to compare medians, McNemar and Bowker to compare paired proportions). The correlation between the different covariates will be investigated using the Spearman's rank correlation coefficient.

#### *Stage II: Radiation-induced Cardiovascular Changes Models (RCCM)*

The Radiation-induced Cardiovascular Changes Models (RCCM) aim to investigate the dose-

response relationships between 3D-dimensional dose distributions in cardiac substructures and cardiovascular changes in term of imaging and circulating biomarkers time-kinetics occurring in the 2 years after radiotherapy for breast cancer (before RT, 6 and 24 months after RT).

To investigate the time course of continuous variables extracted from ECHO-ST, CT or MRI measurements, mixed regression models are used since these longitudinal data present a hierarchical structure where serial measurements are nested within individuals over time. In this framework, a variable selection is possible by an AIC or BIC model selection or by incorporating a lasso or an elastic net penalty especially for the imaging and circulating biomarkers selection. To investigate some non-linear predictor effects, a fractional polynomial approach could be considered.

The radiation exposure could be included in this model by several ways: point wise dosimetric parameters (mean dose,  $D_x$  or  $V_x$ ), DVH reduction equivalent uniform dose (EUD) or through a functional data analysis approach by estimating a functional coefficient associated to a functional predictor (here the DVHs or the probability density function).

To exploit the richness of the longitudinal global or regional strain curves, a myocardial deformation analysis will be conducted using a functional mixed effect model to deal with the infinite-dimensional functional responses measured at multiple time points.

### *Stage III: NTCP and functional NTCP models (F-NTCP).*

In presence of cardiac toxicity outcome, a multimetric NTCP modelling is constructed through time-dependent covariates and time dependent coefficients Cox model.

The individualized risk estimation is calculated from an integrative clinical-biologic risk score obtained at the end of a variable selection process (lasso or elastic-net partial likelihood penalization for example).

The radiation exposure could be included in this model by several ways: point wise dosimetric parameters (mean dose,  $D_x$  or  $V_x$ ), DVH reduction equivalent uniform dose (EUD).

Using a time-dependent Cox regression performed in a functional data analysis way, a functional NTCP model (F-NTCP) will provide a volume-effect functional parameter which allows a risk weighting across the considered dose range and especially for the lowest one.

Furthermore, as a complementary approach for cardiovascular risk modelling, the cardiac imaging and circulating biomarkers will be integrated into a mechanistic model of cardiovascular disease, including atherosclerosis (Work package 4.3 Cardiovascular risk modelling, HMGU).



## 10. REPORTING ADVERSE EVENTS

This is a prospective observational cohort study in which radiotherapy and other oncologic treatments will be performed according to current standard of the participating centres without additional risks.

Serious adverse events related to blood samples or cardiac imaging exams are not expected. The subjects with possible abnormal findings are referred for further examination in accordance with normal procedures in each country.

Minor adverse events are those related to blood samples and cardiac imaging exams.

- Blood collection (pain at veins at the elbow, allergy to products used to clean the skin, hematoma)
- Echocardiography is based on the use of ultrasound. This is a non-invasive method of investigation, non-traumatic and painless. It can be repeated and there are no contraindications. It has not known side effects. It lasts about 15 minutes.
- The CT lasts about 20-30 minutes. The CT requires the injection of iodinated contrast with contraindications (renal failure, allergy). The injection of iodinated contrast material is made in compliance with the contraindications of the latter. The place of injection is done simply at the arm vein. Potential side effects of iodine contrast include flushing, and (mild) skin rash.
- For CT, patient is subject to a scanning X-ray beam. This examination is relatively simple, painless, and safe if one respects the contra-indications. The examination can be done as an outpatient without hospitalization. In terms of radiation dose, the latest techniques in cardiac CT achieve very low levels of radiation, equivalent to one to two years of natural background radiation (average of 2.4 mSv / year), considered acceptable for exam screening for which the radiation-induced risk should be minimal or nil.
- Nitroglycerine may be administered prior to the CT angiography, which is a safe and often used medication for patients with CAD. Side effects include flushing, headache and hypotension, and will not be given to patients with a low blood pressure, left ventricular outflow obstruction or using sildenafil or related medication.
- Betablockers may be used in patients with a fast heart rate before CT. Beta-blockers are used by many patients and regarded as safe. They should not be given to patients with hypotension or conduction disorders as described in the contra-indications to the study.
- MRI is based on magnetic field and radio waves. This examination is relatively simple, painless, and safe if one respects the cons-indications. The examination can be done as an outpatient without hospitalization. MRI is the safest of the advanced imaging techniques.

However, it is known that for certain patients who undergo MRI examinations, the experience may be associated with emotional distress, anxiety and claustrophobia, which could limit the consent of patients to participate in our study. MRI lasts about 45 minutes. This point must be considered in the design of the study by proposing additional MRI examinations as an option in the protocol (in contrast with blood collection, ECHO-ST and CT that would be mandatory).

- Cardiac MR including gadolinium (Dotarem 0.2 mmol/kg) enhancement will be performed. Potential side effects of gadolinium include brief headache, nausea (feeling sick) and dizziness for a brief time following the injection. Allergic reactions are rare.

The investigator will inform the patients and the reviewing accredited Medical research ethics committee if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited Medical research ethics committee, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

## **11. ETHICAL CONSIDERATIONS**

### **11.1. Regulation statement**

This study will be conducted in accordance with the Declaration of Helsinki (amended at the 64th WMA General Assembly, Fortaleza, Brazil, October 2013) (appendix 1) and in accordance with the principles of 'Good Clinical Practice' and the Medical Research Involving Human Subjects Act (WMO).

### **11.2. Recruitment and consent**

The study aims and procedure will be explained orally and in writing in a study information leaflet to each eligible patient, by each specific participating centre. All study patients are also informed that she will be part of a larger European study.

The patients will have ample opportunity to ask questions they might have and they will have 48 hours to consider the implications of the study before deciding to participate.

Patients consent will be noted on an informed consent form compliant with the local and ethical regulations.

If during the study the patient for whatever reason no longer wishes to participate, she can withdraw her consent at any time.

All countries involved in the multicentre study will contact the local ethics committee and are familiar with the national procedures. Prior to the start of the study, the protocol has to be approved

by the medical ethics review committee of the participating institution. Approval will be indicated in writing with reference to the final protocol number and date.

### **11.3. Objection by minors or incapacitated subjects**

Not applicable.

### **11.4. Benefits and risks assessments, group relatedness**

Participation in this study does not involve any additional risk to patients, besides the risk incurred by additional MRI and CT-scans. Patients will undergo 2 extra CT-scans. For CT, patient is subject to a scanning X-ray beam. The latest techniques in CTCA achieve very low levels of radiation (below 4mSv) , equivalent to one to two years of natural background radiation (average of 2.4 mSv / year), considered acceptable for exam screening for which the radiation-induced risk should be minimal or nil. Additionally, compared to the radiation dose of the treatment the dose of the extra CT scans is very low and the risks therefore are negligible and the burden low.

Participation in this study may have benefits. When cardiac imaging reveal severe abnormal findings, such as the presence of severe coronary artery disease which may require a revascularization or specific treatment due to the presence of a myocardial infarction, patients even in absence of symptoms will be excluded of the present study and referred to the cardiologist . In absence of severe coronary artery disease, all results of cardiac imaging will be blinded to the medical staff in order to avoid changes in medical treatment likely to mask effects of XRay radiation which the main objective of the present study.

### **11.5. Compensation for injury**

The sponsor has an insurance which covers for damage to research subjects through injury or death caused by the study protocol interventions (not breast cancer treatment RT).

The insurance should cover for damage related to EARLY HEART research (ie CTCA, ECHO-ST, blood samples, MRI) but not related to RT treatment, until the end of EARLY HEART follow-up.

## **12. DATA COLLECTION, DATA MANAGEMENT, MONITORING AND PUBLICATION**

### **12.1. Data management**

The data managed during, and used by, MEDIRAD will be managed by the different partners throughout the project. A project-internal Data Management Board will ensure data is stored

securely and according to international standards, both from a technical as well as an ethical standpoint (de-identification, anonymization). The Data Management Board includes a data manager for each center, responsible for the data generated by their clinical/research work and is chaired and overseen by a Project Data Manager from ISGlobal. Information on the data generated during the project (source, volume, standards, storage, exploitation and accessibility) is shown in the data management overview below:

Data generated or stored	Source	Volume	Standards used	Storage, curation & preservation	Exploitation & accessibility
Cardiac imaging data (ECHO-ST, CT and MRI)	Adult female BC patients undergoing RT and RT treating physicians in participating centres	250; numerous scans and images for each subject	eCRF	Anonymised eCRFs on secure central server at IRSN. All questionnaires stored in locked filing cabinets with limited access	For study activities , only accessible to local investigators involved in the study
			DICOM	Anonymised dose and imaging data on centralized MEDIRAD-ENACT database at UMCG. Non-identifiable study ID to link different databases	

In all cases, relevant metadata will be stored alongside of the data, as well as software and documentation for future use. Weekly backups of data and images will be made to ensure security of collected data.

## **12.2. eCRF**

Wherever possible, all non-imaging/dose (non-DICOM) data will be entered directly into an anonymised eCRF on a secure central database at IRSN. The Source Identification List will identify any data to be recorded directly in the eCRF (i.e., no prior written or electronic record of data), and which data should be considered source data.

Where needed, paper source documents can be used. An audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of person authorizing entry or change. For each subject enrolled, an eCRF must be completed and electronically signed by the principal investigator or authorized delegate from the study staff. If a subject withdraws from the study, the reason must be noted on the end of study form of the eCRF. If a subject is withdrawn from the study because of a treatment limiting adverse event, thorough efforts should be made to clearly document the outcome.

The investigator should ensure the accuracy, completeness and timeliness of the data recorded in the eCRF and in all required reports.

## **12.3. Dose data repository; storage of DICOM data**

The MEDIRAD-ENACT database of partner UMCG will be used for MEDIRAD EARLY-HEART to enable integrated data-collection, quality control and management for the clinical study on low-dose radiation-induced early cardiovascular changes after BC therapy.

A centralised integrated imaging and dose repository will be set up to serve the needs of the research and studies carried out in MEDIRAD based on anonymised data (Work Package 2.4.1 ).

All participating centres will transfer relevant DICOM-data (i.e. imaging, planning-CT scans, RT-STRUCT, RT-DOSE, CTCA and MRI (all native images from all series with and without additional image (including additional image (T1 and T2 mapping, aortic 3D images... ))) to the ENACT data bank managed by UMCG. The ENACT environment provides easy and secure upload of (image/DICOM) data to a central archive located at the UMCG. De-identification of the (image) data will be performed at the site of origin before sending according to a de-identification strategy. After upload, researchers involved in the reading of the imaging data will be provided access to the ENACT environment using a virtual workspace with two-way authentication (login + SMS-token). The virtual workspace can be accessed from any location and from different platforms (Windows/Apple/Linux) allowing selection of expert readers to perform the reading regardless of their location. Each reader will be provided with an identical workspace with the same software tools and imaging data, no subsequent transfer of (imaging) data is needed except a secured transfer of all anonymized Cardiac CT and Cardiac MR from the ENACT database to Université Paris Descartes which is Core center for reading all CTCA and Cardiac MRI of patients included in

EARLY HEART Study (Responsible party: Professor Elie Mousseaux, Univ Paris Descartes). Indeed for analysis of cardiac imaging, ENACT transfer of DICOM anonymized images will be required by the core lab in order to use research softwares dedicated to specific tasks and softwares routinely used by expert readers. Electronic CRF will be filled by the core lab during such analysis.

Within the ENACT environment automated segmentation of all cardiac structures (including coronary arteries) is performed to ensure uniformity of the segmentation procedure between centres. In addition, storage of all DICOM-data in ENACT will enable co-registration of the different imaging data.

#### **12.4. Monitoring and quality assurance**

IRSN is designated as the leading organism of the multicentre EARLY-HEART study.

We call the sponsors of the study the organisms that coordinate the study at the scale of centre: IRSN for France, UMCG for Netherlands, TUM-MED for Germany and CCUL for Portugal, ICO for Spain. Each sponsor will have a representing person.

Each medical centre (IRSN, UMCG, TUM-MED, CCUL, ICO, UPDescartes) will have a Local Management team including a representing person of sponsor, a Principal Investigator, a Local clinical research associate (Monitor).

To ensure the EARLY-HEART study management, a Clinical Operations Management and Support group will be composed including the study leader (IRSN Researcher) in collaboration with French, Dutch, German, Portuguese and Spanish Local Managing teams. The Clinical Operations Management and Support group will decide on the type of monitoring undertaken, either onsite, remote or central, and the frequency and focus of monitoring visits will be determined by the risk rating allocated. The intervals for monitoring visits may be revised dependent on subject enrolment rate, quality issues, site compliance or other trial issues. This group will meet regularly for global Management of the study.

At the scale of each centre, the Local Clinical Research Associate (Monitor) will perform monitoring tasks in accordance with the protocol specific requirements.

#### **Study monitoring plan (monitoring visits etc.)**

These monitoring visits will be supervised by the leader of the EARLY-HEART study, in collaboration with Monitors of each centre. To limit costs travels at this stage, these visits will be “virtual”, the leader and Monitors having teleconference meetings.

Monitoring visits:

*1.1 Initiation visit (M4)*

The Initiation Visit will be conducted prior to site activation to confirm preparedness for protocol execution, satisfactory site facilities, clarify the applicable regulations and requirements of the protocol, carefully review the process of implementing the protocol at the site and conduct any necessary training prior to activating the site for enrolment.

*1.2 First monitoring visit (M4)*

The First Monitoring Visit will be conducted at the beginning of inclusion to confirm subjects' rights are being protected; the study is being conducted according to the protocol and applicable regulations; confirm accurate reporting of subject safety data and study endpoints.

*1.3 Interim monitoring visits*

The Interim monitoring visits will be conducted regularly to confirm subjects' rights are being protected; the study is being conducted according to the protocol and applicable regulations; confirm accurate reporting of subject safety data and study endpoints.

*1.4 Close out visit (M39)*

A Close-Out Visit will be conducted to ensure that all study data and other study documentation is complete and accurate and that all study records have been reconciled.

The Local monitors will meet the Local Principal Investigators at each of the above-mentioned visits to discuss study progress and issues.

Any significant deviation from the planned monitoring timelines will be explained and documented in the monitoring visit report and the plan amended if appropriate. If the site does not enrol any patients or enrolment is stopped, regular monitoring visits will not be scheduled. If there is an extended gap in trial activities the monitor will ensure that site staffs are appropriately trained when trial activities recommence.

The monitor should complete and sign a Trial Monitoring Visit Document at each visit, including:

*2.1 Recruitment*

The study specific recruitment plan and recruitment timeframe as per specific protocol.

*2.2 Eligibility*

The following inclusion and exclusion criteria should be checked in full as per Protocol

*2.2.1 Inclusion and exclusion criteria*

All subjects participating in the study should meet ALL the inclusion criteria and NONE of the exclusion criteria. Any deviations from the inclusion/exclusion criteria should be documented as a protocol breach/deviation.

*2.3. Primary/Secondary endpoints: As per Protocol*

## **12.5. Quality assurance**

### *Imaging*

At the start of the project, criteria will be determined for imaging protocols and image quality. Example CT and MR scans will be collected from all participating scan sites with the protocol as defined by the MEDIRAD proposal. All collected scans will be provided through the ENACT workspace and the selected image reading experts will assess the quality of the scans and the correct setting and performance of the scan protocols.

When additional scanning is required using phantoms, these phantoms should be made available or bought to assure scan quality. All data acquired can, again, be made available in the workspaces of the experts.

### *Sample Management*

Each centre is initially responsible for its sample management and the IRSN (researcher of the Epidemiology laboratory) will be in charge of the whole cohort data management (including data of the 5 centres).

At a local scale, data (from questionnaires, medical examinations, biomarker measurements) will be put in local database. For control of data, data consistency checks to detect inconsistencies and outliers present in the questionnaires will be programmed (about 5 case reports selected at random and checked to ensure consistency and quality of data collected in medical questionnaires and report forms, and verifying the accuracy of a limited number of major information gathered).

Then the 5 local databases will be centralized in one big EARLY-HEART database at IRSN and a final quality control will be carried out on a sample of  $\sqrt{n} + 1$  subjects drawn randomly. The final database will be fixed once all control data and coding will have been finished.

## **12.6. Anonymization of data**

All files used for analysis will be anonymized to ensure patient privacy.

Anonymization will be performed as follows: Central data management (IRSN) will give out a study number for each participating patient based on a randomised code assignment list. Only the Principal investigator and the data management will have access to the source data.

## **12.7. Retention of records**

In each center, only the principal investigators and the data management will have access to the source data. All data will be stored during a period of twenty years.



## **12.8. Amendments**

A 'substantial amendment' is defined as an amendment to the terms of the MERC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the MREC.

Non-substantial amendments will not be notified to the accredited MREC, but will be recorded and filed by the sponsor.

< Examples of non-substantial amendments are typing errors and administrative changes like changes in names, telephone numbers and other contact details of involved persons mentioned in the submitted study documentation.>

## **12.9. Annual progress report**

The sponsor/investigator will submit a summary of the progress of the trial to the accredited MREC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/serious adverse reactions, other problems, and amendments.

## **12.10. Temporary halt and (prematurely) end of study report**

The investigator will notify the accredited MREC of the end of the study within a period of eight weeks. The end of the study is defined as the last patient's last visit.

The investigator will notify the MREC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the investigator will notify the accredited MREC within fifteen days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited MREC.

## **13. TRIAL INSURANCE**

An insurance against the legal liability resulting from medical procedures will be present.

## 14. PUBLICATION POLICY

The trial will be registered at [clinicaltrials.gov](http://clinicaltrials.gov) and published in a major scientific journal regardless of its results. MEDIRAD will follow an open access approach to its peer-reviewed scientific publications. All publications will be under the name of the consortium, and all authors involved will be listed either in the by-line or in an appendix in such a way that all authors will be found on literature searches. All scientific publications will be available through open access repositories such as

OpenAIRE ([www.openaire.eu](http://www.openaire.eu)) and/or the project website; the scientific and clinical communities will clearly benefit from the freely accessible publications of the MEDIRAD methodology and results in high impact journals.

The results of the project will be disseminated by publishing in international, peer-reviewed journals and proceedings of scientific conferences, after any intellectual property has been secured. Authors will endeavour to target journals with the widest audiences and highest impact in the clinical, public health, biology and radiation protection fields. Wherever possible gold open access options will be chosen.

The scientific coordinator of the MEDIRAD project, Prof. Elisabeth Cardis (ISGlobal), in consultation with the clinical coordinator, Prof. Guy Frija (UPDescartes), are responsible for the review and final approval of all publications.

## 15. REFERENCES

1. Clarke, M. *et al.* Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet (London, England)* **366**, 2087–106 (2005).
2. Darby, S. C., McGale, P., Taylor, C. W. & Peto, R. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. *Lancet. Oncol.* **6**, 557–65 (2005).
3. Giordano, S. H. *et al.* Risk of cardiac death after adjuvant radiotherapy for breast cancer. *J. Natl. Cancer Inst.* **97**, 419–24 (2005).
4. Darby, S. C. *et al.* Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N. Engl. J. Med.* **368**, 987–98 (2013).
5. van den Bogaard, V. A. B. *et al.* Validation and Optimization of a Cardiac NTCP Model for Breast Cancer Patients Based on Cardiac Substructures and 3-dimensional Dose Distributions. *Int. J. Radiat. Oncol. Biol. Phys.* **96**, S4–S5 (2016).

6. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), E. B. C. T. C. G. *et al.* Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet (London, England)* **378**, 1707–16 (2011).
7. Taylor, C. W. *et al.* Exposure of the Heart in Breast Cancer Radiation Therapy: A Systematic Review of Heart Doses Published During 2003 to 2013. *Int. J. Radiat. Oncol.* **93**, 845–853 (2015).
8. Tuohinen, S. S. *et al.* Early effects of adjuvant breast cancer radiotherapy on right ventricular systolic and diastolic function. *Anticancer Res.* **35**, 2141–7 (2015).
9. Heggemann, F. *et al.* Cardiac Function After Multimodal Breast Cancer Therapy Assessed With Functional Magnetic Resonance Imaging and Echocardiography Imaging. *Int. J. Radiat. Oncol. Biol. Phys.* **93**, 836–44 (2015).
10. Erven, K. *et al.* Subclinical cardiotoxicity detected by strain rate imaging up to 14 months after breast radiation therapy. *Int. J. Radiat. Oncol. Biol. Phys.* **85**, 1172–8 (2013).
11. Erven, K. *et al.* Acute Radiation Effects on Cardiac Function Detected by Strain Rate Imaging in Breast Cancer Patients. *Int. J. Radiat. Oncol.* **79**, 1444–1451 (2011).
12. Tjessem, K. H. *et al.* Long-term Cardiac Mortality After Hypofractionated Radiation Therapy in Breast Cancer. *Int. J. Radiat. Oncol.* **87**, 337–343 (2013).
13. Chang, M. *et al.* Coronary Calcium Scanning in Patients after Adjuvant Radiation for Early Breast Cancer and Ductal Carcinoma In situ. *Front. Oncol.* **3**, 253 (2013).
14. Mast, M. E. *et al.* Less increase of CT-based calcium scores of the coronary arteries. *Strahlentherapie und Onkol.* **192**, 696–704 (2016).
15. Andersen, R. *et al.* Relation of Coronary Artery Calcium Score to Premature Coronary Artery Disease in Survivors >15 Years of Hodgkin's Lymphoma. *Am. J. Cardiol.* **105**, 149–152 (2010).
16. Apter, S. *et al.* Cardiovascular calcifications after radiation therapy for Hodgkin lymphoma: computed tomography detection and clinical correlation. *Coron. Artery Dis.* **17**, 145–51 (2006).
17. Rademaker, J. *et al.* Coronary artery disease after radiation therapy for Hodgkin's lymphoma: coronary CT angiography findings and calcium scores in nine asymptomatic patients. *AJR. Am. J. Roentgenol.* **191**, 32–7 (2008).
18. Whitlock, M. C. *et al.* Cancer and Its Association With the Development of Coronary Artery Calcification: An Assessment From the Multi-Ethnic Study of Atherosclerosis. *J. Am. Heart Assoc.* **4**, e002533–e002533 (2015).
19. Jordan, J. H. *et al.* Anthracycline-Associated T1 Mapping Characteristics Are Elevated Independent of the Presence of Cardiovascular Comorbidities in Cancer Survivors. *Circ. Cardiovasc. Imaging* **9**, e004325- (2016).
20. D'Errico, M. P. *et al.* N-terminal pro-B-type natriuretic peptide plasma levels as a potential

- biomarker for cardiac damage after radiotherapy in patients with left-sided breast cancer. *Int. J. Radiat. Oncol. Biol. Phys.* **82**, e239-46 (2012).
21. Ito, T. & Ikeda, U. Inflammatory cytokines and cardiovascular disease. *Curr. Drug Targets. Inflamm. Allergy* **2**, 257–65 (2003).
  22. Creemers, E. E., Tijssen, A. J. & Pinto, Y. M. Circulating MicroRNAs: Novel Biomarkers and Extracellular Communicators in Cardiovascular Disease? *Circ. Res.* **110**, 483–495 (2012).
  23. Boulanger, C. M. *et al.* Circulating microparticles from patients with myocardial infarction cause endothelial dysfunction. *Circulation* **104**, 2649–52 (2001).

## 16. APPENDICES

### Declaration of Helsinki

#### INTRODUCTION

The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.

In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The needs of the economically and medically disadvantaged must be recognised. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

#### BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of

information, and on adequate laboratory and, where appropriate, animal experimentation.

Appropriate caution must be exercised in the conduct of research, which may affect the environment, and the welfare of animals used for research must be respected.

The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

The subjects must be volunteers and informed participants in the research project.

The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorised representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorised representative.

Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorised surrogate.

Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

#### ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. See footnote

At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

## Appendix

### INFORMED CONSENT FORM

#### MEDIRAD EARLY-HEART

**Study on early detection of cardiovascular changes after radiotherapy for breast cancer**

**Name of Principal Investigator:** *To complete for local investigating center*

**Name of Organization:** *To complete for local investigating center*

**Name of Sponsor:**

- European Commission Horizon 2020 - MEDIRAD project Implications of MEDical low dose RADiation exposure - Agreement 755523
- *Local investigating center to complete*

**Name of Proposal and version:** **EARLY HEART Study, version 1.2 July 5<sup>th</sup> 2017**

Madam,

This information letter is for women who attend *hospital X*, and who we are inviting to participate in research EARLY-HEART Study on early detection of cardiovascular changes after radiotherapy for breast cancer.

This Informed Consent Form has two parts:

- Information Sheet (to share information about the research with you)
- Certificate of Consent (for signatures if you agree to take part)

You will be given a copy of the full Informed Consent Form.

#### **PART I: INFORMATION SHEET**

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##### **Introduction**

I am Dr/Pr X, working for the Hospital X. We are doing research on cardiovascular changes that may arise after radiotherapy for breast cancer. I am going to give you information and invite you to be part of this research. You do not have to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research.

##### **Context and Purpose of the study**

For the treatment of your breast cancer, you will receive radiotherapy treatment in our hospital. The efficacy of radiotherapy in the treatment of breast cancer has been validated by several researches and is now a standard. During radiotherapy, in addition to the breast, some organs close to the chest wall receive an irradiation part, in particular the heart. During your treatment with radiotherapy, an optimal balance is going to be sought allowing irradiating your breast as well as possible while minimizing as much as possible irradiation of your heart. However, heart irradiation may sometimes induce long-term cardiac complications in some infrequent cases. As life expectancy in general and after treatment of breast cancer is increasingly favorable, research on possible cardiac consequences for patients who have been treated for breast cancer is important.



The purpose of our study is to enhance knowledge on the possible cardiovascular changes that may arise in the first 2 years after radiotherapy, taking into account your individual risks factor as well as the dose of irradiation that your heart will have received.

Our study should allow us formulating possibly necessary recommendations for future prevention strategies and for future improvement of radiotherapy technique to spare cardiac structures.

### **Participant selection**

We are inviting all patients with breast cancer aged between 40 and 75 years old who are going to be treated with radiotherapy without chemotherapy to participate in the research. Patients who would have already been treated with radiotherapy for breast cancer or thoracic irradiation, or patients who already present cardiovascular diseases can't be included. Moreover, if we discover during cardiac examination at the beginning of the study that you would need a specific cardiac medical care, you should be excluded from our study in order to benefit for your situation the most adapted cardiac follow up.

### **Voluntary Participation**

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at this hospital will continue and nothing will change. If you choose not to participate in this research project, you will be offered the follow up that is routinely offered in this hospital for breast cancer. You may change your mind later and stop participating even if you agreed earlier.

### **Procedures and Protocol**

During and after your radiotherapy for breast cancer, you will have regular visits with the radiation oncologist. If you participate in our study, you will have additional visits and cardiac imaging examinations as well as regular blood samples. We give you the details below:

#### ***A. Unfamiliar Procedures***

For this study, we ask you before the start of radiotherapy and at regular intervals up to 2 years after radiotherapy to submit you to 3 cardiac imaging and blood tests to determine the markers of heart damage.

Cardiac echography:

To study the functioning of your heart, a cardiac echography with ultrasound will be performed. An cardiac echography works with sound waves and is a secure and non-harmful method of getting a picture of your heart. With an ultrasound study, the shape, construction, function of pump and function of heart valves and blood circulation can be visualized.

Computed tomography coronary angiography:

To determine the calcium and limestone content of your coronary arteries, a CT scan will be performed before treatment begins and 6 and 24 months after treatment. Calcium in the coronary arteries indicates arteriosclerosis which is the most important cause of cardiovascular disease. The calcium score is based on the principle that calcium does not pass X-rays. When the calcium score is too high, then we can only say that the risk of heart disease is greater.

Cardiac Magnetic Resonance Imaging:

With MRI, or magnetic resonance imaging, the heart and blood vessels are replicated before treatment and 6 and 24 months after treatment. With an MRI, the shape, construction, narrowing of the coronary arteries and function of the pump and the operation of heart valves and blood circulation can be visualized. It can then be determined if the heart tissue is damaged and has a lack of oxygen or if the heart tissue is healthy.

Blood samples:

Cardiac biomarkers will be quantified and identified in your blood to determine the damage of the heart. If the heart and coronary arteries are damaged, these substances end up in the blood. The amount of cardiac markers in the blood gives an idea of the extent of damage to the heart. Blood tests are used to determine the concentrations of cardiac markers.

Using a part of your blood samples, we will analysis a list of biomarkers that is based on current

knowledge. This part of blood samples obtained during this research procedure will be used only for this research, and will be destroyed after 2 years, when the research is completed.

However, as research is advancing, the list of biomarkers to study the cardiotoxicity of radiotherapy could be enlarged in the future, including any new circulating biomarkers that would be discovered in the coming years. So, if you agree, the other part of your blood samples may be stored for duration longer than the research purpose, 15 years, this biological collection being justified to analyze possible new biomarkers and improve knowledge. The Responsible party for this biological collection is Professor Constanza Emanuelli from the Bristol Heart Institute, School of Clinical Sciences, University of Bristol, Bristol Royal Infirmary, Upper Maudlin Street, BS2 8HW, Bristol, United Kingdom.

### **B. Description of the Process**

By being included in the EARLY HEART study, your participation in this research will require the following steps:

At inclusion, before radiotherapy, you will have:

- a participation questionnaire, completed by your radiation oncologist, to check that you are eligible for the study. Medical information will also be recorded in an observation book.
- a consultation with a cardiologist, during which a medical questionnaire will be completed and an electrocardiogram performed
- a blood sample, for the measurement of biomarkers of cardiovascular disease (6 tubes of blood)
- a cardiac echography (non-invasive and painless technique) will be performed
- a computed tomography coronary angiography
- a cardiac magnetic resonance imaging

Just at the end of the radiation therapy, you will have:

- a consultation of end of radiotherapy with your radiation oncologist
- a blood sample (6 tubes of blood)

Six months after radiotherapy:

- a follow-up consultation with your radiation oncologist
- a blood sample (6 tubes of blood)
- a cardiac echography
- a cardiac magnetic resonance imaging

Two years after radiotherapy:

- a follow-up consultation with your radiation oncologist
- a blood sample (6 tubes of blood)
- a cardiac echography
- a computed tomography coronary angiography
- a cardiac magnetic resonance imaging

The total duration of your participation is therefore 2 years. All information collected will be coded to preserve your anonymity.

### **Risks and Benefits:**

#### **Risks:**

You will be subjected to a total of maximum 8 cardiac imaging tests and 4 blood tests to determine cardiac markers. To determine the calcium score, two additional CT scans should be performed for irradiation in addition to the scheduled CT Scan for radiotherapy. Compared to the radiation dose you receive for breast cancer radiotherapy, the additional dose for this scientific study is limited. We therefore assume that these scans will have no effect on your health.

The additional exams will be combined as much as possible with the appointments you have for your treatment. However, for logistical reasons, this will not always be possible and you will be asked to come to the hospital.

**Benefits:**

When a cardiac damage appears that requires a visit from a cardiologist, you will benefit early medical care.

More generally, the results of this study may lead in the future to improvements in current irradiation techniques, as well as better prevention strategies for cardiac follow up in patients treated with breast radiotherapy.

You will be irradiated according to the current standard and therefore you will not benefit from any direct benefit from your participation in this study.

**Reimbursements**

As a result of your participation, we may reimburse travels costs for your additional travels to the hospital for the study.

**Confidentiality**

The information that we collect from this research project will be kept confidential. Information about you that will be collected during the research will be put away and no-one but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up with a lock and key. It will not be shared with or given to anyone except the five other European Research centers that are involved in the study.

**Right to Refuse or Withdraw**

You do not have to take part in this research if you do not wish to do so. You may also stop participating in the research at any time you choose. It is your choice and all of your rights will still be respected.

**Insurance**

For possible negligent or non-negligent harms during your participation in our study, it is XXX insurance policies which applies to this study. Please contact the Principal Investigator (Dr XX) if you would like further information about the insurance arrangements which apply to the study.

**Who to Contact**

If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact:

*Dr/Pr XX name of the local Principal investigator*

*Dr / Pr XX name of the referent local cardiologist*

*Dr / Pr XX name of the local referent radiologist*

**This proposal has been reviewed and approved by the Medical Research Ethical Committee of XX, which is a committee whose task it is to make sure that research participants are protected from harm.**

You can ask me any more questions about any part of the research study, if you wish to. Do you have any questions?

**The next part of the Informed Consent Form (Part II: Certificate of consent for MEDIRAD EARLY HEART Study ) for signatures is on the next page**

## **PART II: CERTIFICATE OF CONSENT MEDIRAD EARLY HEART STUDY**

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### **Certificate of consent to participate to the clinical study EARLY HEART for the study on early detection of cardiovascular changes after radiotherapy for breast cancer**

#### **Statement by the patient**

I have read the information letter for EARLY HEART Study, or it has been read to me.

I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction.

I have understood that I do not have to take part in this research if I do not wish to do so and refusing to participate will not affect my treatment in any way. I will still have all the benefits that I would otherwise have at this hospital. I may stop participating in the research at any time that I wish without losing any of my rights as a patient here. My treatment at this hospital will not be affected in any way

I consent voluntarily to participate as a participant in this research

I also consent specifically for long term blood sample storage and use  Yes  No

Print Name of Participant \_\_\_\_\_

Signature of Participant \_\_\_\_\_

Date \_\_\_\_\_  
Day/month/year

#### **Statement by the radiation oncologist taking consent**

I have accurately read out the information letter to the potential participant, and to the best of my ability made sure that the participant understands that the following interventions will be done:

1. Cardiac echography before radiotherapy, 6 months and 24 months after radiotherapy
2. Electrocardiogram before radiotherapy and 24 months after radiotherapy
3. Cardiac CT before radiotherapy and 24 months after radiotherapy
4. Cardiac MRI before radiotherapy, 6 months and 24 months after radiotherapy
5. Blood samples before radiotherapy, at the end of radiotherapy, 6 months and 24 months after radiotherapy

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this Informed Consent Form has been provided to the participant.

Print Name of Researcher/person taking the consent \_\_\_\_\_

Signature of radiation oncologis taking the consent \_\_\_\_\_

Date \_\_\_\_\_  
Day/month/year

## Appendix

### CRF ELIGIBILITY

**Inclusion Number:** .....

**Date of the visit :** .....

**Date of Birth:** .....

➤ **Inclusion Criteria (check each point)**

- Female breast cancer patients
- Treated with primary breast conserving surgery for stage I-III invasive adenocarcinoma of the breast or ductal carcinoma in situ (DCIS)
- Age between 40-75 years at time of start radiotherapy
- WHO performance status 0-1
- Planned for radiotherapy alone to the breast with or without the lymph node areas
- Radiotherapy based on planning-CT scan using either 3D-CRT, IMRT, or VMAT/RapidArc
- Written Informed consent

➤ **Non Inclusion Criteria (check each point)**

- Male breast cancer patients
- Neoadjuvant or adjuvant chemotherapy
- M1 disease (metastatic breast cancer)
- Medical history of coronary artery disease and/or myocardial infarction and/or atrial fibrillation
- Previous thoracic or mediastinal radiation
- Contraindications to injection of iodinated contrast such as allergy or renal failure
- Pregnancy or lactation

## Appendix

### CRF CANCER

**Inclusion Number:** .....

**Date of the visit :** .....

**Date of Birth:** .....

• **Left breast**       **Right breast**

• **Date of the surgery :** .....

• **Type of surgery :** breast conserving surgery       mastectomy

• **Axillary lymph node exploration :**

axillary sentinel lymph node biopsy       axillary lymph node dissection

• **Histology :** In situ       invasive

• **Size (mm) :** .....

• **Regional lymph nodes (N)**

**NX** (Regional lymph nodes cannot be assessed (eg, previously removed))

**N0** (No regional lymph node metastasis)

**N1** (Metastasis to movable ipsilateral level I, II axillary lymph node(s))

**N2** (Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted or in clinically detected\* ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastasis)

**N2a** (Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures)

**N2b** (Metastases only in clinically detected\* ipsilateral internal mammary nodes and in the *absence* of clinically evident level I, II axillary lymph node metastases)

**N3** (Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s), with or without level I, II axillary node involvement, or in clinically detected \* ipsilateral internal mammary lymph node(s) and in the *presence* of clinically evident level I, II axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s), with or without axillary or internal mammary lymph node involvement)

**N3a** (Metastasis in ipsilateral infraclavicular lymph node(s))

**N3b** (Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s))

**N3c** (Metastasis in ipsilateral supraclavicular lymph node(s))

• **Grade :** Grade 1       Grade 2       Grade 3

• **Vascular invasion :** yes       no

• **Presence of a component in situ :** yes       no

• **Multifocality :** yes       no

• **Her-2** : negative  positive (amplification or overexpression)

• **Oestrogen Receptor**: negative  positive

• **progesterone receptor**: negative  positive

• **Menopause** : No  Yes  Since : .....

• **Hormone therapy** Yes  No

If yes, which one : Tamoxifene  Aromatase inhibitors  Others

Date of the beginning of hormone therapy : .....

• **Date of the beginning of radiotherapy** : .....

• **Irradiation volumes** :

Breast  Chest wall

Nodes : Yes  No

If yes,

Supraclavicular node : Yes  No

Infraclavicular (subclavicular) node : Yes  No

Internal Mammary node : Yes  No

Axillary node: Yes  No

• **Boost** : Yes  No

**Appendix**

**CRF PLANNED RT**

**Inclusion Number:** .....

**Date of the visit :** .....

**Date of Birth:** .....

• **Type of radiotherapy :**

3D-CRT       IMRT       VMAT/RapidArc

• **Breath hold :**

yes       no

• **Boost electrons/photons:**

photons       electrons

<i>Complete :</i>	Dose/fraction	Number of fractions	Total Dose	Comments, if any :
Breast or Chest wall				
Boost				



## Appendix

### CRF RT TOXICITY

**Inclusion Number:** .....

**Date of the visit :**.....

**Date of Birth:** .....

**Precise if it is : during radiotherapy**

**at the end of radiotherapy**

**6 months after the end radiotherapy**

**2 years after the end of radiotherapy**

**Acute toxicity of grade >2 :**

Dermatitis Yes  No

Chest wall/breast pain Yes  No ,

Edema Yes  No ,

Breast and arm Yes  No

Esophagitis Yes  No

**Late toxicity of grade >2 :**

Telangiectasia Yes  No

Fibrosis in boost and out boost area Yes  No

Global cosmetic result Yes  No

Edema breast, edema arm Yes  No

Function of the shoulder Yes  No

Chest wall/breast pain Yes  No

Rib fracture Yes  No

Brachial plexopathy Yes  No

Pneumonitis Yes  No

**Appendix**

**CRF CARDIOLOGY**

**Inclusion Number:** .....

**Date of the visit :** .....

**Visit 1 at baseline**

**Visit at 2 years**

**Date of Birth:** .....

Weight : .....kg

Size : .....m.....

• **Blood Pressure - Hypertension**

Systolic Blood Pressure : .....mmHg

Diastolic blood Pressure : .....mmHg

Treatment  Yes  No

Hypertension:  Yes  No Defined as having Systolic BP > 140 or Diastolic BP > 90 mmHg, or treatment for hypertension

• **Tobacco :**

Non smoker

Former smoker

- Year of beginning: ..... Year of stop : .....

Mean Number of cigarettes/day during the smoking period: .....

Active Smoker

- Age or year of beginning .....

Mean Number of cigarettes/day : .....

• **Diabetes :**

No

Yes  type 1  type2

- Beginning of the diabetes (year) : .....

Actual treatment : .....

• **Cholesterol:**

LDL Cholesterol mg/dL:.....

HDL Cholesterol mg/dL.....

Total Cholesterol mg/dL: .....

Triglycerides : .....

Treatment for hypercholesterolemia (statin) :  Yes  No

SI conversion factors: To convert total, HDL, and LDL cholesterol from mmol/L to mg/dL , divide by 0.0259; triglyceride to from mmol/L to mg/dL , divide by .0113.

• **Fasting glucose** :..... mmol /L

• **Urea**:..... mmol /L

• **Creatinine** : .....  $\mu$ mol/L

• **eGFR (MDRD formula)** : ..... mL/min per 1.73 m<sup>2</sup>

-> < 50 ml/min/1.73 m<sup>2</sup>  Yes  No (if yes, the patient should be excluded of the study (exclusion criteria) )

•  $\beta$  HCG ..... mmol /L

• **Electrocardiogram (ECG)**

Atrial fibrillation detected  Yes  No (if yes, the patient should be excluded of the study (exclusion criteria) )

ECG sign of myocardial Infarction  Yes  No if yes, the patient should be excluded of the study (exclusion criteria) )

**Other medical cardiology treatment**  Yes  No  
If yes, precise in clear: .....

**Specific part of CRF at Visit 2 at 2 years follow up:**

The medical cardiology treatment has been introduced or changed since V1 at inclusion  
 Yes  No

If yes precise the date : .....

Modification of the ECG compared to the ECG at inclusion  Yes  No

Occurrence of Cardiovascular Event since inclusion  Yes  No

Occurrence of cardiac symptoms,  Yes  No

▶ If Yes to event or symptoms,  
please specify the date and type of event or symptoms (dyspnea, palpitation, chest pain...), death, myocardial infarct, heart failure, hospitalization for cardiac diseases, atrial fibrillation or other significant arrhythmia, stroke etc...

.....  
.....

## Appendix

### LOCAL CRF ECHO-ST

**Inclusion Number:** .....

**Date of the visit** : .....

**Date of Birth:** .....

Name and version of the of the ultrasound system:

- General Electric Health Care , version:
- Philips, version:
- Siemens, version:
- Toshiba, veesion
- Other to precise:

Precise if it is : before radiotherapy

6 months after the end radiotherapy

2 years after the end of radiotherapy

- Global longitudinal strain: .....
- Segmental longitudinal strain (Segment 1 to 16) : .....
- Global longitudinal strain rate: .....
- Segmental longitudinal strain rate (Segment 1 to 16) : .....
- Global radial strain : .....
- Segmental radial strain (Segment 1 to 16) : .....
- Global radial strain rate: .....
- Segmental radial strain rate (Segment 1 to 16) : .....
- Left ventricular ejection fraction using Simpson's biplane method: .....
- Left ventricular end-diastolic volume using Simpson's biplane method: .....
- Left ventricular end-systolic volume using Simpson's biplane method: .....
- Left-ventricular end-diastolic diameter using M-mode: .....
- Left ventricular mass measured according ASE/EAE guidelines: .....
- E/A wave ratio : .....
- E/Ea wave ratio (lateral annulus) : .....
- TAPSE (tricuspid annular plane systolic excursion) : .....
- Tricuspid annular S wave : .....
- Pulmonary artery systolic pressure (based on the peak tricuspid regurgitation velocity estimate and by assuming a right atrial pressure of 5 mmHg) : .....
- Left ventricular outflow tract diameter: .....
- Left ventricular outflow tract velocity time integral: .....
- Heart rate: .....
- Cardiac output measured by multiplying heart rate by stroke volume: .....

**In case of abnormal echocardiography before radiotherapy defined as: LVEF<50%; longitudinal strain  $\leq$  -16%; longitudinal strain rate <-1%, and/or abnormal wall motion, the patient should be excluded of the study (exclusion criteria )**

## Appendix

### CTCA PROTOCOL AND LOCAL CRF AT TIME OF ACQUISITION

#### ➤ Objectives of Cardiac and aortic CT

- To estimate scores of calcification in each main coronary arteries (LM, LAD, Cx, RC), in aortic valve and in each segment of the thoracic aorta (ascending, arch and descending aorta) by using non enhanced CT.
- To estimate plaque and stenosis in all the 16 coronary artery segments by using CT angiography.
- To estimate global score per artery and per patient of calcification and plaque along coronary arteries and thoracic aorta.
- To estimate evolution of such scores between basal CT and CT at 2 years after XRay radiation.

#### ➤ Protocol

##### 1. Non enhanced CT

- **Data acquisition parameters:**
  - Slice collimation 0.5 - 0,6 mm (the smallest one)
  - Tube voltage 120 kV.
  - Tube current dependent on local expertise, typically 50-100 mAs
  - Diastolic imaging
  - Please note heart rate during scan acquisition, or save ECG's during acquisition in the patient folder.
- **Acquisition range:**
  - Include the entire heart and thoracic aorta within the field of view
  - Cranial demarcation: origin of supra aortic branches
  - Caudal demarcation: at least until RV/LV apex, including all pericardial adipose tissue (or more caudal).
- **Reconstruction process**
  - One series with the conventional local calcium score method including 2.4 to 3- mm slice thickness, associated with 1.2-1.5 increment (half the slice thickness) and 220 mm FOV; conventional reconstruction without iterative reconstruction.
  - Second series with 1 mm thick slices with 0.5 mm increment and 220 mm FOV and some iterative reconstruction, leading to close signal to noise ratio regarding the first 2.4-3 mm slice thickness series (the iterative reconstruction will be fixed in each center at the beginning of the study in relation with the corelab).

➤ **Enhanced CT**

- **Data acquisition parameters:**
  - Slice collimation 0.5 - 0,6 mm (the smallest one)
  - Tube voltage 80 - 120 kV
  - Tube current dependent on local expertise and tube modulation
  - Diastolic imaging, including RR interval coverage from to 30 to 80%
  - Please note heart rate during scan acquisition, or save ECG's during acquisition in the patient folder.
  - Injection: quantity, rate depending on patient size and circulation; 100 ml of maximal volume of a solution with  $\geq 350$  ml/l of a iodinated contrast medium.
  - Betablockers if Heart rate  $> 60$  /min
  - Sublingual Nitrate always
  
- **Acquisition range:**
  - Include entire heart with all coronaries within the field of view (the aorta is not required here)
  - Caudal demarcation: at least until RV/LV apex
  
- **Reconstruction process**
  - One series with 0.5 - 0.625 mm and half slice thickness increment with 220 mm FOV and some iterative reconstruction and optimal filter based on the local expertise and CT system. The series will included different ECG timing between 30 to 80% of the RR interval

➤ **Local CRF at time of CT Acquisition**

Inclusion Number: .....

Study Date:.....

Date of Birth: .....

Weight :.....

Height : .....

Name and version of the of the CT system:

- Siemens version: .....
- General Electric Health Care , version:.....
- Toshiba, version:.....
- Philips, version :.....
- Other to precise: .....

**Non enhanced series:**

Heart rate in bpm:.....

Reconstruction 1 without iteration:

Slice thickness (mm): .....

Reconstruction 2 with 1 mm thick and iteration:  
Iteration mode: expressed as the vendor name with the associated strength:

Enhanced series:

Contrast medium:

Name of the CM:.....

Iodinated Concentration of the CM in g/l : .....

Slice thickness in mm:.....

Heart rate in bpm:.....

Betablockers given at time of CT:      yes      no

Nitrate during CTA:                      yes      no

Reconstruction:

Slice thickness (in mm): .....

Increment (in mm):.....

Iteration mode: expressed as the vendor name with the associated strength: .....

Local Analysis given to the Patients and to the medical staff in charge of the patient:

Is there a  $\geq 50\%$  stenosis of the left main coronary artery: Yes      No

Is there  $\geq 70\%$  stenosis of the proximal Left Anterior Descending artery (LAD1):

Yes      No

If yes : an ischemic test have been done :                      Yes      No

A coronary revascularization has been done:                      Yes      No

**A revascularization means that the patient will be excluded of the study and follow up.**

Other information (calcium score, other CTA results) will be blinded to the clinician team

.....

## Appendix

### CARDIAC MRI PROTOCOL AND LOCAL CRF AT TIME OF ACQUISITION

#### ➤ Objectives of Cardiac Magnetic Resonance

- To estimate systolic and diastolic pressure during acquisition
- To estimate aortic strain at 2 levels (ascending aorta and descending aorta) at the level of pulmonary bifurcation leading to distensibility, local pulse wave velocity estimates.
- To estimate regional pulse wave velocity of the aortic arch (Phase contrast)
- To estimate global function of the left and right ventricle: End diastolic volume, end-systolic volume, and mass and derived estimates with stroke volume, ejection fraction, wall stress and remodeling indices.
- To estimate systolic left and right atrial areas.
- To estimate native myocardial T1 of the left ventricular wall by using 2 small axis levels (base and mid left ventricle).
- To estimate myocardial T2 (oedema) of the left ventricular wall by using the same 2 small axis levels (base and mid left ventricle).
- To detect and quantitate late gadolinium enhancement between 10 and 14 min after Gadolinium injection
- To estimate the myocardial post gadolinium T1 and extra cellular volume at 15 minute at the same 2 small axis levels as native myocardial T1

Most variables will be estimated by the core lab only, by using the same software for included patients.

#### ➤ Protocol

1- Blood sample at the time of CMR to estimate the hematocrit if no other blood sample has been done the same day.

2- Scout

3- Calibration before parallel imaging.

4- Axial SSFP cine series with 8-12 levels to widely cover right and left atrium. 2 to 3 levels per breath hold using 12-16 ; at least 40 cardiac phases / level

5-Small axis SSFP cine series from apex to base with 2 to 3 levels per breath hold.

- i. shim well center on the left ventricle
- ii. FOV < 360 mm,
- iii. At least 50 phases / level
- iv. With high image quality without aliasing or parallel imaging artefact on ventricles



Blood pressure 1 Systolic BP :..... Diastolic BP : .....

6- T1 MAP (MOLLI) before Gadolinium : 2 small axis views (basal/median) 1 level per breath hold : scheme 5(3)3(3)3 with immediate control to obtain high image quality.

7- T2 MAP (3 to 5 echo) before Gadolinium in the same 2 small axis views (basal/median). 1 level per breath hold: with immediate control to obtain high image quality.

8- Aortic SSFP or SPGR 3D series in sagittal and oblique direction to cover the all thoracic aorta (to estimate the length between ascending and descending aorta) in free breathing

9- Contrast enhanced angiography of the thoracic aorta acquired by using sagittal oblique direction during injection of 0.2 mmol/kg gadoterate meglumine (Dotarem, Guerbet, Villepinte, France) and breath hold.

Blood pressure 2 Systolic BP :..... Diastolic BP : .....

10- Aortic SSFP or SPGR 2D I breath hold 1 minute after injection: perpendicular to both the ascending and descending aorta at the level of the pulmonary artery bifurcation, as detected in series 8. Control for the optimal image (shim +++) to obtain high image quality to have an automated detection of aortic borders. Do not hesitate to rescan after gadolinium injection at the end of examination.

Blood pressure 3 Systolic BP :..... Diastolic BP : .....

11- Aortic Phase contrast in free breathing perpendicular to both the ascending and descending aorta at the level of the pulmonary artery bifurcation, as detected in series 7. Only one VPS, VENC = 160 cm/sec, at least 50 cardiac phases, optimal spatial resolution and FOV in less than 2 minutes. Please verify the absence of aliasing (spatial and velocity aliasing). Do not hesitate to rescan at the end of examinationr.

12-Radial SSFP cine series with 2,3- and 4 chamber views of the left ventricle ; at least 40 cardiac phase, optimal FOV.

13- Scout cine IR to detect optimal TI of the inversion recovery sequence

14- Optimal inversion recovery sequence to detect Late Gadolinium enhancement in one or

several breath hold between 10 and 14 minutes post gadolinium injection.

15- T1 MAP post Gado 15-16 minutes : at the two same pre-gadodilium levels.

➤ **Local CRF at time of CMR Acquisition**

Inclusion Number: .....

Study Date:.....

Date of Birth: .....

Weight :..... Height : .....

Name and version of the of the CMR system:

- Siemens version:
- General Electric Health Care , version:
- Philips, version :
- Other to precise:

Intensity of the Magnet

- 3T
- 1.5 T
- other

Hematocrit the day of CMR:..... %

Blood pressures 1 Systolic BP in mmHg :..... Diastolic BP : .....

Blood pressures 2 Systolic BP in mmHg :..... Diastolic BP : .....

Blood pressures 3 Systolic BP in mmHg :..... Diastolic BP : .....

Does the patient present signs of myocardial infarction:

- No
- Yes

If yes, this information should be given to the medical staff in charge of the patient.

Please note that, **when the patient required a vascularization or when a myocardial infarction is detected, the patient should be excluded from the study.**

Open question concerning the transfer of images:.....

**Appendix**  
**BLOOD SAMPLE PROTOCOL**



Blood collection  
≈ 30 ml

