Implication of MEDIcal low dose RADiation exposure _ EARLY detection of cardiovascular (HEART) changes after radiotherapy for breast cancer (MEDIRAD-EARLY HEART)

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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...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac disorders, signs and symptoms NEC
Study type	Observational invasive

Summary

ID

NL-OMON44264

Source
ToetsingOnline

Brief title
MEDIRAD-EARLY HEART

Condition

- Cardiac disorders, signs and symptoms NEC

Synonym
early heartdamage, Subclinical cardiovascular changes

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Europese Commissie Horizon 2020

Intervention

Keyword: Breast cancer, Cardiac events, NTCP models, Radiotherapy

Outcome measures

Primary outcome

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).

Secondary outcome

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

* Secondary echocardiographic measurements are:

o Left ventricular ejection fraction using Simpson*s biplane method

o Left ventricular end-diastolic volume using Simpson*s biplane method

o Left ventricular end-systolic volume using Simpson*s biplane method

o Left-ventricular end-diastolic diameter using M-mode

o Left ventricular mass measured according ASE/EAE guidelines

o Global and segmental radial strain rate

o E/A wave ratio

o E/Ea wave ratio (lateral annulus)

o TAPSE (triscuspid annular plane systolic excursion)

o Tricuspid annular S wave

o Pulmonary artery systolic pressure (based on the peak tricuspid regurgitation velocity estimate and by assuming a right atrial pressure of 5 mmHg)

o Left ventricular outflow tract diameter

o Left ventricular outflow tract velocity time integral

o Heart rate

o 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.

o 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.

o 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.

o Cardiac MRI-parameters include: morphology, function, tissue characterization by delayed enhancement and pre-/post-contrast T1 mapping (at 15 minutes).

o 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.

o 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*

* Endothelial activation and dysfunction: sVCAM-1, s-ICAM-1, E-Selectin,

P-Selectin, vWF, PAI-1, Fibrinogen, Thrombomodulin, TGF*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

o Endpoint are defined as a significant increase or decrease in each biomarker

between time points.

Study description

Background summary

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. 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. 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. 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.

Study objective

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):
o Improvement of RT planning techniques to spare cardiac structures, or even selection for proton therapy;
o 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).

Study 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.

Study burden and risks

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).

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.

Patients will not benefit from participation with the study. However, hhen 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

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

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

Exclusion criteria

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 < -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

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-12-2017
Enrollment:	70
Type:	Actual

Ethics review

Approved WMO Date:	25-09-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL62360.042.17
Other	Submitted, identificationnumber to be received by IRSN