Early detection of imaging-derived subclinical cardiac injuries after radiotherapy and chemotherapy for breast cancer

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

Summary

ID

NL-OMON48680

Source
ToetsingOnline

Brief title
EMIRA

Condition

- Cardiac disorders, signs and symptoms NEC

Synonym
early heart damage, Early subclinical cardiac injuries

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Breast cancer, Early cardiac injuries, Prediction models, Radiotherapy

Outcome measures

Primary outcome

There are 3 primary endpoints, 2 for functional ESCIs and 1 for morphological ESCIs:

• The change in left ventricle systolic (dys)function is determined by cECHO using left ventricle global longitudinal strain (LV-GLS) at 6 and 24 months after radiotherapy with reference to baseline.

• The change in LV diastolic function (LV-DF) is determined by cECHO, defined as a decrease of the average of e* septal and e* lateral together at 6 and 24 months after completion of radiotherapy with reference to baseline.

• The increase of diffuse myocardial fibrosis determined by cMRI morphology, using LV T1 mapping, defined by an increase of the native mean LV myocardial T1 mapping value of the entire population at 6 and 24 after completion of radiotherapy.

Secondary outcome

The secondary endpoints are measured with cECHO, cMRI and cCT on an exploratory basis. They can be used to obtain more insight in the different underlying biological mechanisms of treatment-related cardiac toxicity.

Secondary endpoints measured with echocardiographic parameters - most of which are considered standard measurements in evaluating cardiac function with cECHO, except for the strain measurements:

• global longitudinal strain rate;

• global and segmental radial strain rate;

• 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.

Secondary endpoints measured with cMRI parameters are:

• myocardial edema based on T2 mapping;

• perfusion in rest and stress using adenosine;

• presence and extent of focal infarction/fibrosis by late gadolinium enhancement (LGE) imaging;

• myocardial function based on cine imaging of the left and right ventricle.

Secondary endpoints measured with cCT are:

• Anatomical changes in coronary arteries assessed by cCT occurring 24 months after radiotherapy, compared to baseline before radiotherapy start;

• Individual description of stenosis or plaques of the 15 segments of the coronary arteries; left main coronary artery; left anterior descending artery (LAD); left circumflex artery and right coronary artery and evaluation of change in the CAC score (Agatston-score). The progression of atherosclerosis will be defined as an increase in the number of coronary segments containing any plaque and as an increase in the CAC score of at least 15% before the start of radiotherapy and 24 months after radiotherapy.

Study description

Background summary

Breast cancer (BC) radiotherapy with X-rays (photons = XRT) leads to incidental cardiac irradiation, resulting in an increased risk of various MAjor Cardiac Events (MACE). Due to an increased incidence of BC and improved survival, the prevalence of BC survivors at risk of MACE increases every year. In addition, recent studies indicate that for the treatment of BC, the addition of chemotherapy further enhances the risk of MACE, thus affecting quality of life and increasing morbidity and mortality.
With proton therapy (PT), incidental cardiac dose can be markedly reduced. However, as this radiation technique is more expensive and limited available, BC patients are only eligible for PT when they are at high risk of MACE based on the model-based approach and national selection criteria. Although the cardiac dose can be markedly reduced with protons, parts of the heart will still be exposed to a low dose radiation.
Information regarding morphological and functional early subclinical cardiac injuries (ESCI) induced by XRT that develop into MACE is largely lacking in scientific literature. Limited data exists on the relationship between radiation dose to cardiac substructures and ESCI (dose-effect relationship), or the effect of chemotherapy on this dose-effect relationship. Finally, no data exist on the effect of proton therapy on the development of ESCI. Information on ESCI is essential for the development of optimised radiation dose distributions aiming at reduction of ESCI and subsequent MACE. In addition, tools are needed to identify BC patients treated with radiotherapy combined

with chemotherapy who are at high risk of future MACE, and who may benefit from secondary preventive strategies. Potential targets for developing these strategies will help to avoid or delay progression into clinically apparent MACE (secondary prevention).

Study objective

The first primary aim of this project is to detect ESCI, that are considered risk factors for clinically apparent MACE in BC patients treated with photon radiotherapy and chemotherapy. The second is to investigate whether proton therapy results in less or different ESCI. Finally, this information is used to develop prediction models describing the relationship between the radiation dose to cardiac substructures and ESCI.
In details, we aim to:
1. identify longitudinal morphological and functional ESCI using echocardiography (cECHO), cardiac magnetic resonance imaging (cMRI) and cardiac computed tomography (cCT) before and after BC treatment, [prospective observational cohort study in BC patients treated with photon radiotherapy and chemotherapy];
2. determine the relationship between 3D-dose distributions to cardiac substructures and ESCI [WP2] for BC patients treated with XRT and chemotherapy;
3. establish the effect of chemotherapy on the dose-effect relationship between radiation dose and ESCI by comparing results to those obtained in the MEDIRAD-EARLY HEART study (XRT alone);
4. explore the effect of proton therapy on the development of longitudinal morphological and functional ESCI in BC patients treated with PT and chemotherapy.

Study design

A single centre prospective observational cohort study [n=148] combined with a prospective explorative cohort study [n=50].

Study burden and risks

Participation in this study does not involve any additional risk to subjects, besides the risk incurred by additional MRI and CT-scans. Subjects will undergo 2 extra CT-scans. For CT, subjects are subjected to a scanning X-ray beam. The latest techniques in cCT 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 cCT- scans is very low and the risks therefore are negligible and the burden low.

Participation in this study may have benefits. When cardiac imaging reveals

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, subjects 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 BC patients
Primary breast conserving surgery or mastectomy for stage I-III invasive adenocarcinoma of the breast or ductal carcinoma in situ (DCIS)
Age >=18 years at time of adjuvant radiotherapy/(neo)adjuvant chemotherapy
WHO performance status 0-1
Planned radiotherapy to the breast/chest wall with or without the lymph node

areas
Photon radiotherapy based on planning CT-scan, using either 3D CRT, (partial) IMRT, or (partial) VMAT/RapidArc with or without deep inspiration breath-hold, or proton therapy in free breathing (1 of more beams technique)
(Neo)Adjuvant chemotherapy (before or after radiotherapy)
Written informed consent

Exclusion criteria

Male breast cancer patients
M1 disease (metastatic Breast cancer)
Previous thoracic of mediastinal radiation
Targeted HER2 therapy not allowed
Medical history of coronary artery disease and/or myocardial infarction and/or atrial fibrillation
Contraindications to injection of iodinated contrast such as allergy or renal failure
Pregnancy or lactation
Atrial fibrillation detected during electrocardiogram before radiotherapy
Abnormal echocardiography before radiotherapy defined as: LVEF <50%, and/or abnormal wall motion
Presence of myocardial infarction detected during cMRI before radiotherapy
cMRI or cCT 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:	Recruiting
Start date (anticipated):	15-01-2019
Enrollment:	198
Type:	Actual

Ethics review

Approved WMO Date:	09-11-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Not approved Date:	25-09-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-01-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-06-2023
Application type:	Amendment
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
Other	ClinicalTrials.gov, NCT03575650
CCMO	NL66438.042.18