

## EARLY SUBCLINICAL CARDIOVASCULAR CHANGES AFTER RADIOTHERAPY FOR BREAST CANCER DETECTED BY ECHOCARDIOGRAPHY: *CONTRIBUTION OF THE MEDIRAD EARLY-HEART COHORT*

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# Introduction

## Background

Breast cancer (BC): a major public health burden

A large amount of BC treated by radiation therapy (RT)

Unfortunately, BC RT can lead to long-term CV diseases



To detect early subclinical cardiac dysfunction in BC patients is important.

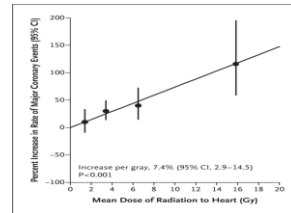
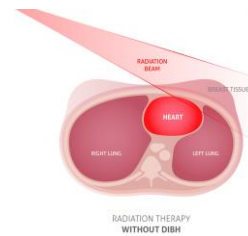


## Cardiotoxicity of radiotherapy (breast cancer)

A wide spectrum of cardiac pathologies, such as coronary artery disease, myocardial dysfunction, valvular disorders, pericardial disease, conduction abnormalities

Dose-response relationship for coronary events:  
+7.4%/Gy (Darby et al. NEJM 2013)

Radiation-related heart diseases, usually present 10–15 years after exposure, *although non-symptomatic abnormalities may develop much earlier*



## Objectives

To early determine the impact of RT on cardiac function by means of echocardiography

To explore dose-response relationship with early subclinical left ventricular dysfunction

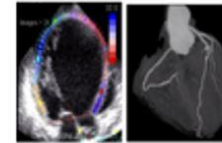
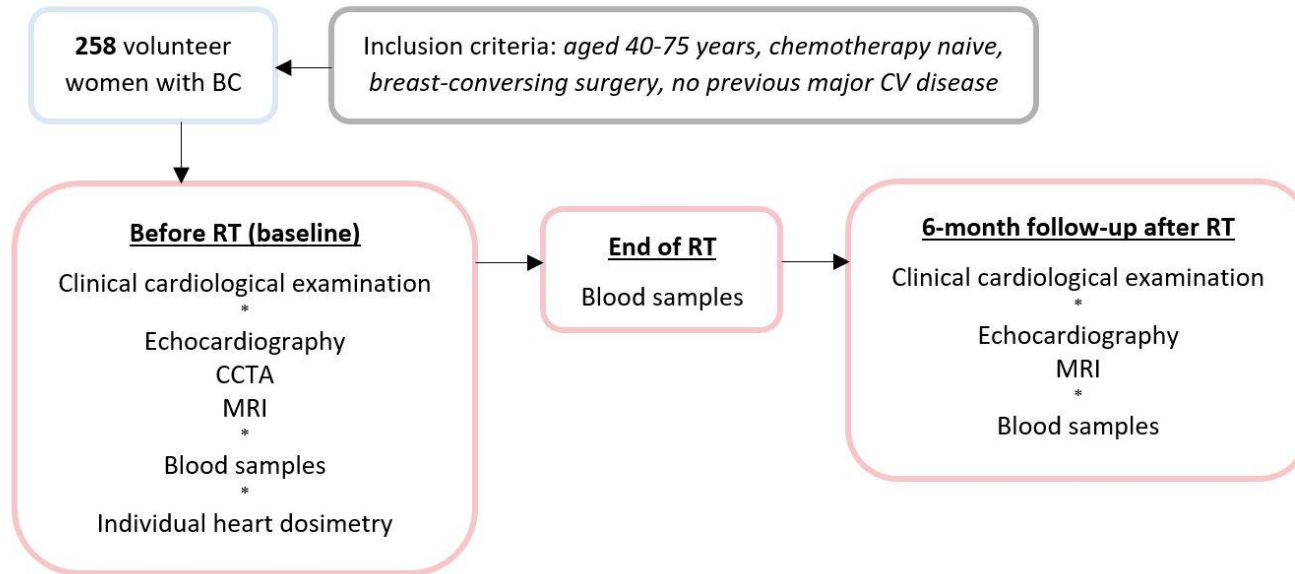


**MEDIRAD EARLY-HEART study**

# Methods - The MEDIRAD EARLY-HEART COHORT - General

**ClinicalTrials registration:** ClinicalTrials.gov Identifier: NCT03297346 , Sept 2017

Walker et al. *Early Detection of Cardiovascular Changes After Radiotherapy for Breast Cancer: Protocol for a European Multicenter Prospective Cohort Study (MEDIRAD EARLY HEART Study) JMIR Res Protoc 2018 | vol. 7 | iss. 10 | e178*

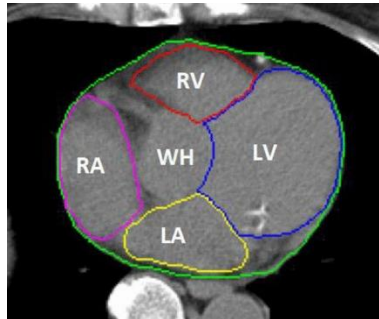


## Methods - The MEDIRAD EARLY-HEART COHORT – Echocardiography data

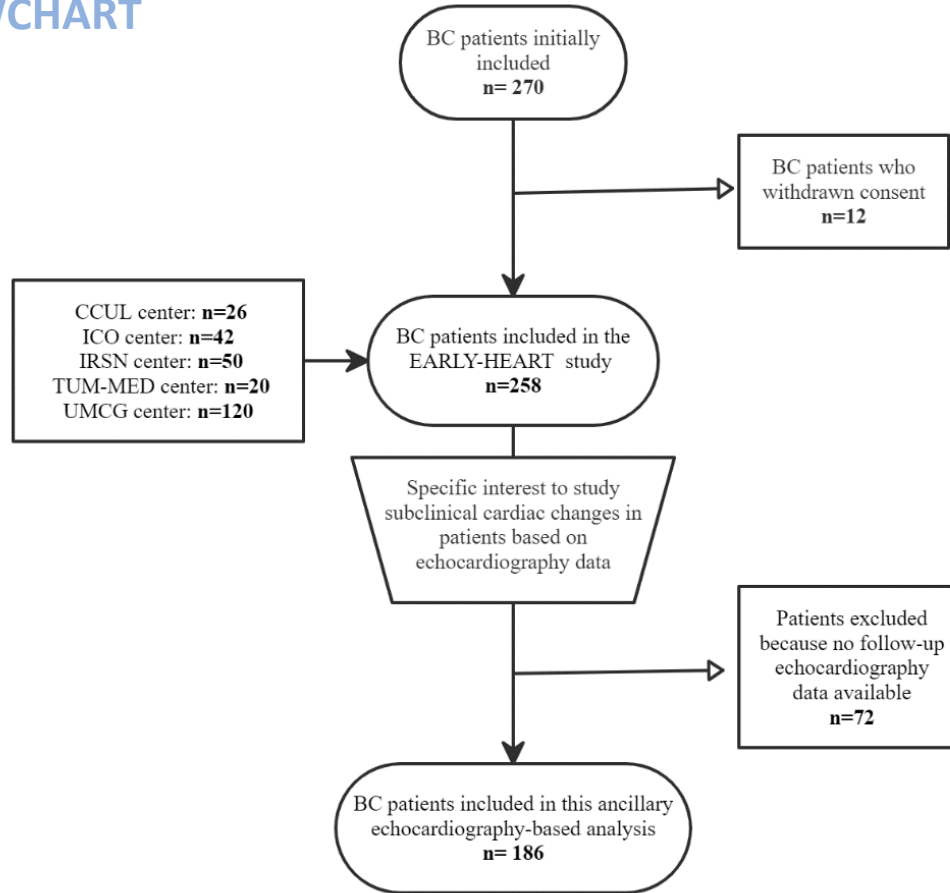
- **LVEF** not sensitive enough parameter in order to detect early cardiac dysfunction after RT
- Global Longitudinal Strain measurement (**GLS**): appears more sensitive than LVEF
- Previous studies:
  - a decrease in GLS from few weeks to many months after RT (mainly based on 3D-CRT, sometimes combined with chemotherapy)
  - Impact of laterality of breast cancer/possibly cardiac dose
- In the field *chemotherapy* :
  - Cancer Treatment Related Cardiac Dysfunction (**CTRCD**):  
a decrease of 10% in LVEF to a level < 53%
- **GLS relative decrease > 15% can predict CTRCD – Is it the case in radiation therapy?**

## Methods - The MEDIRAD EARLY-HEART COHORT – Dosimetry data

- **Individual heart dosimetry for each BC women (centralized in one center).**
- Cardiac structure delineation was performed centrally by the UMCG using multi-atlas based automatic segmentation of the heart and its substructures.
- Two contoured cardiac structures were considered in our analysis: the whole heart (WH) and the left ventricle (LV), their relevance being highlighted in previous researches.
- The mean dose (**D<sub>mean</sub>**, in Gy), minimum dose (**D<sub>min</sub>**, in Gy), and maximum dose (D<sub>max</sub>, in Gy) were studied as well as relative volumes of the WH and LV receiving at least 5 Gy (**V<sub>5</sub>**, in %) and 20 Gy (**V<sub>20</sub>**, in %), both suggested as good prognostic parameters of cardiac complications.



# Results - FLOWCHART



## Results - DESCRIPTION

### BASELINE CHARACTERISTICS

- 186 BC patients
- 14.5% obese
- 52.7% non-smokers
  
- 78.0% invasive cancer
- 51.9% grade 2
  
- 60.2% treated by 3D-CRT
- 33.9% 15frac/40.05Gy

### CARDIAC RADIATION DOSIMETRY

- Mean whole heart dose:  $1.76 \pm 1.16$  Gray
  
- Mean left ventricle dose:  $2.09 \pm 1.91$  Gray

### ECHOCARDIOGRAPHY PARAMETERS

- No significant change of GLS/GLS rate/LVEF between baseline and the 6-month follow-up after RT
- Trend forwards a decrease after RT
- **Subclinical left ventricle dysfunction, defined by a relative decrease of GLS >15%, was observed in 22 patients (14.5% of the sample).**

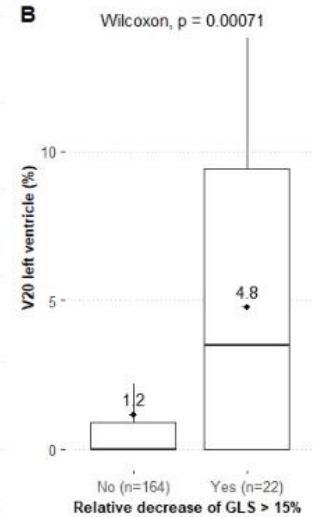
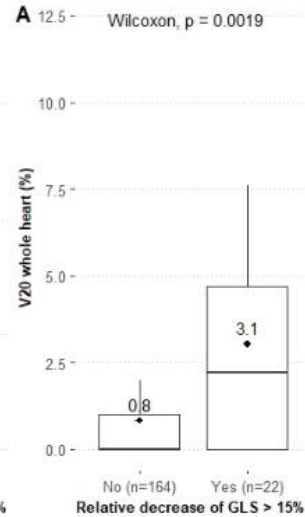
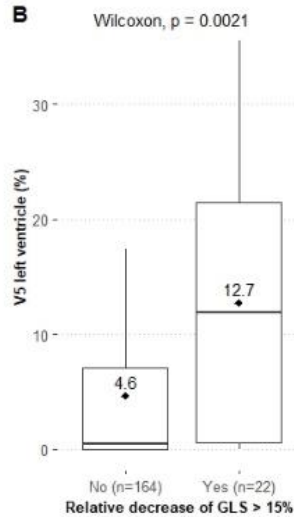
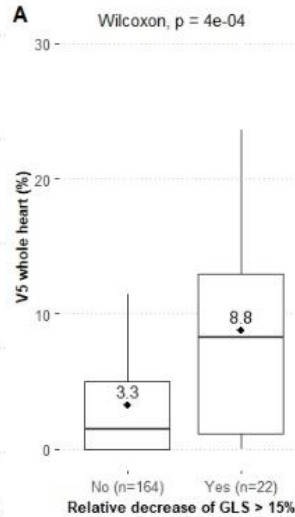
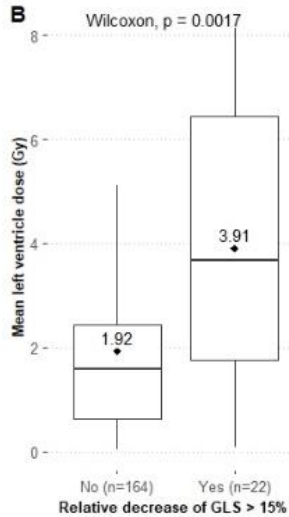
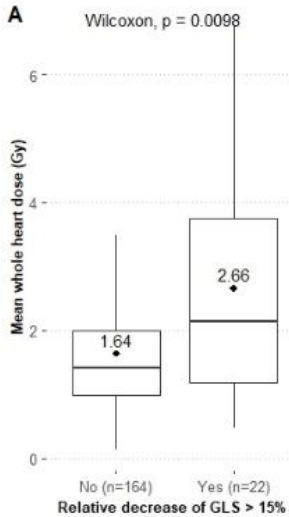


# Results - DIFFERENCE DOSIMETRY/DECREASE OF GLS

COMPARISONS OF MEAN DOSE BETWEEN PATIENTS WITH OR WITHOUT A DECREASE OF GLS >15%

COMPARISONS OF V5 BETWEEN PATIENTS WITH OR WITHOUT A DECREASE OF GLS >15%

COMPARISONS OF V20 BETWEEN PATIENTS WITH OR WITHOUT A DECREASE OF GLS >15%



## Results - DOSE RESPONSE RELATIONSHIP

Relationships between dose-volume parameters and a decrease of GLS > 15 % occurring after the 6-month follow-up after radiotherapy using binary logistic regression (n=186 BC patients).

Dosimetry	Crude OR (95%CI)	Unadjusted <i>p</i> -value	Adjusted <sup>a</sup> OR (95%CI)	Adjusted <sup>a</sup> <i>p</i> -value
<b>Whole heart</b>				
Dmean (Gy)	1.85 (1.31-2.68)	0.0005	1.74 (1.20-2.61)	0.005
Dmin (Gy)	0.24 (0.02-1.86)	0.20	0.36 (0.02-3.49)	0.40
Dmax (Gy)	1.04 (1.01-1.07)	0.0009	1.03 (0.99-1.06)	0.02 <sup>b</sup>
V5 (%)	1.14 (1.06-1.23)	0.0004	1.13 (1.05-1.23)	0.002
V20 (%)	1.47 (1.21-1.81)	0.0001	1.39 (1.13-1.75)	0.003
<b>Left ventricle</b>				
Dmean (Gy)	1.51 (1.23-1.88)	0.00008	1.46 (1.17-1.87)	0.003
Dmin (Gy)	3.59 (0.80-16.33)	0.09	5.11 (0.91-3.30)	0.07
Dmax (Gy)	1.04 (1.01-1.06)	0.005	1.03 (1.01-1.06)	0.02 <sup>b</sup>
V5 (%)	1.10 (1.05-1.16)	0.0001	1.10 (1.05-1.17)	0.001
V20 (%)	1.26 (1.12-1.42)	0.00009	1.20 (1.07-1.37)	0.003

<sup>a</sup> Model adjusted for age, smoking status, hypertension, cholesterol and hormonotherapy

<sup>b</sup> Not significant after Bonferroni correction for multiple tests (significant threshold:  $\alpha/k$ )

## Results – Predictors of GLS-based subclinical LV dysfunction

**TABLE** Relationship between dose-volume parameters and a relative reduction of GLS >15% occurring 6 months after BC RT highlighted by binary logistic regressions and ROC analyses ( $n = 186$  patients from the EARLY-HEART cohort).

Dosimetry	Crude OR (95% CI)	p-value	Adjusted <sup>a</sup> OR (95% CI)	p-value	Adjusted <sup>a</sup> AUROC (95% CI)	p-value
<b>Whole heart</b>						
D <sub>mean</sub> (Gy)	1.85 (1.31–2.68)	0.0005	1.74 (1.20–2.61)	0.005	0.794 (0.688–0.902)	0.02
D <sub>min</sub> (Gy)	0.24 (0.02–1.86)	0.20	0.36 (0.02–3.49)	0.40	0.575 (0.492–0.655)	0.28
D <sub>max</sub> (Gy)	1.04 (1.01–1.07)	0.0009	1.03 (0.99–1.06)	0.02 <sup>b</sup>	0.765 (0.651–0.878)	0.004
V <sub>5</sub> (%)	1.14 (1.06–1.23)	0.0004	1.13 (1.05–1.23)	0.002	<u>0.813 (0.712–0.914)</u>	<u>0.001</u>
V <sub>20</sub> (%)	1.47 (1.21–1.81)	0.0001	1.39 (1.13–1.75)	0.003	<u>0.804 (0.703–0.906)</u>	<u>0.001</u>
<b>Left ventricle</b>						
D <sub>mean</sub> (Gy)	1.51 (1.23–1.88)	0.00008	1.46 (1.17–1.87)	0.003	0.807 (0.704–0.909)	0.004
D <sub>min</sub> (Gy)	3.59 (0.80–16.33)	0.09	5.11 (0.91–3.30)	0.07	0.629 (0.457–0.706)	0.06
D <sub>max</sub> (Gy)	1.04 (1.01–1.06)	0.005	1.03 (1.01–1.06)	0.02 <sup>b</sup>	0.770 (0.660–0.878)	0.003
V <sub>5</sub> (%)	1.10 (1.05–1.16)	0.0001	1.10 (1.05–1.17)	0.001	<u>0.815 (0.717–0.914)</u>	<u>0.005</u>
V <sub>20</sub> (%)	1.26 (1.12–1.42)	0.00009	1.20 (1.07–1.37)	0.003	<u>0.808 (0.701–0.909)</u>	<u>0.004</u>

<sup>a</sup>Model adjusted for age, smoking status, hypertension, total cholesterol level, and hormonotherapy.

<sup>b</sup>No longer after Bonferroni correction for multiple tests (significant threshold:  $\alpha/k$ ).

Sensitivity analyzes by deleting one center at a time confirmed the robustness of our results.

## Discussion & Conclusion

### KEY MESSAGE

**Our European study suggested an increased risk of subclinical left ventricle cardiac dysfunction occurring 6 months after RT among BC patients**



**However :**

- **Some other potential confounding factors (lifestyle factors)**
- **Further follow-up is needed to determine if this dose-response relationship will persist at longer term (i.e., the 24-month follow-up).**



# Subclinical Left Ventricular Dysfunction Detected by Speckle-Tracking Echocardiography in Breast Cancer Patients Treated With Radiation Therapy: A Six-Month Follow-Up Analysis (MEDIRAD EARLY-HEART study)

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## Discussion & Conclusion

**THANK YOU FOR YOUR ATTENTION**

**Questions ?**

