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# **Routine first-line detection of breast cancer therapy-related cardiotoxicity by serial, fast and ultra-low-dose equilibrium radionuclide angiography**

Charles-Edouard Decorads, MD;<sup>1</sup> Aurélien Lambert, MD;<sup>2</sup> Véronique Roch, MSc;<sup>1</sup> Laetitia Imbert, PhD;<sup>1,3</sup> Mathieu Perrin, MD;<sup>1</sup> Marine Claudin, MD;<sup>1</sup> Julia Salleron, MSc<sup>4</sup>; Nicolas Veran, PharmD;<sup>1</sup> Zohra Lamiral, MSc;<sup>5</sup> Catherine Henneon, MD;<sup>2</sup> and Pierre-Yves Marie, MD, PhD.<sup>1,6</sup>

<sup>1</sup> Université de Lorraine, Department of Nuclear Medicine and Nancyclotep Imaging Platform, CHRU Nancy, F-54000, Nancy, France.

<sup>2</sup> Institut de cancérologie de Lorraine, Department of Medical Oncology, F-54500, Vandœuvre-lès-Nancy, France.

<sup>3</sup> Université de Lorraine, INSERM, UMR1254, 54000, Nancy, France.

<sup>4</sup> Institut de cancérologie de Lorraine, Biostatistics Unit, F-54500, Vandœuvre-lès-Nancy, France.

<sup>5</sup> Université de Lorraine, CHRU-Nancy, INSERM, CIC 1433, Nancy, France.

<sup>6</sup> Université de Lorraine, INSERM, UMR 1116, 54000, Nancy, France.

**Address for correspondence:** Pierre-Yves Marie, Médecine Nucléaire, Hôpital de Brabois, CHRU-Nancy, Allée du Morvan, 54500 Vandoeuvre-lès-Nancy, France.

Tel: (+33) 3 83 15 39 09; Fax: (+33) 3 83 15 44 78; E-mail: py.marie@chru-nancy.fr

**Running head:** Ultra low-dose ERNA for cardiotoxicity detection

## Abstract

**Background.** This study assesses a first-line left ventricular ejection fraction (LVEF) monitoring provided by an ultra-low-dose equilibrium radionuclide angiography (ERNA) in breast cancer women treated with potentially cardiotoxic drugs and analyzes patient outcome based on the ERNA results.

**Methods.** Breast cancer women treated with anthracyclines, followed or not by trastuzumab, were monitored using ERNA with a high-sensitivity CZT-camera. Calibrated LVEF measurements were obtained with an almost 3-fold reduction of radiation doses and 10-min recording times.

**Results.** During a mean  $24\pm 6$  months follow-up, 552 ERNAs with a mean effective dose of  $2.3\pm 0.6$  mSv were performed in 195 women, among whom 22 (11%) presented both ERNA criteria of cardiotoxicity (LVEF  $< 50\%$  and  $> 10\%$  drop from baseline; Tox+ group), 35 (18%) only one criterion (Tox± group), and 138 (71%) neither (Tox- group). This ERNA-based classification correlated with trastuzumab-anthracycline treatment ( $p=0.001$ ), prior cardiovascular disease ( $p=0.018$ ), and cardiac outcome, with a 30-month survival with no cardiotoxicity-driven drug regimen changes of  $97\pm 2\%$  in Tox-,  $60\pm 13\%$  in Tox± and  $36\pm 13\%$  in Tox+ ( $p<0.001$ ) groups.

**Conclusion.** First-line detection of breast cancer therapy-related cardiotoxicity by ultra-low-dose ERNA provides consistent results, confirming the excellent cardiac outcome for the greatest majority of women with no ERNA cardiotoxicity criteria.

**Keywords:** equilibrium radionuclide angiography, breast cancer, cardiotoxicity, ionizing radiations, chemotherapy.

## Abbreviation list

ACEI: angiotensin-converting enzyme inhibitors

ARA-II: angiotensin-II receptor antagonists

CZT: Cadmium Zinc Telluride

ERNA: equilibrium radionuclide angiographies

HER2: epidermal growth factor receptor 2

HR: hormone receptor

ICL: Institut de Cancérologie de Lorraine

LVEF: left ventricular ejection fraction

SPECT: single-photon computed tomography

TNBC: triple-negative breast cancer

## Introduction

Equilibrium radionuclide angiography (ERNA) provides a robust, reliable, and cost-effective count-based method for determining the left ventricular ejection fraction (LVEF) [1–3]. The main indication for ERNA is serial monitoring of the LVEF in patients receiving potentially cardiotoxic chemotherapies, even though echocardiography is now a more widely accepted imaging method [4,5]. The main rationale for this preference is to avoid exposures to ionizing radiation, despite the lower reproducibility of LVEF measurements achieved with echocardiography compared to ERNA [6] and the highly time-consuming nature of serial echocardiography evaluation for onco-cardiologists.

Each conventional ERNA investigation is associated with a patient effective dose ranging from 6 to 10 mSv [7], a level increasingly considered excessive for the serial monitoring of patients undergoing multiple ionizing examinations or treatments throughout their lives [2,4]. However, this issue can now be overcome by high-sensitivity gamma-cameras equipped with semiconductor Cadmium Zinc Telluride (CZT) detectors as well as new collimation and image reconstruction systems. With a greater than sevenfold increase in tomographic-count sensitivity [8], these CZT cameras are capable of handling an almost threefold reduction in injected doses whilst keeping the recording time to no more than 10 min [9–11]. However, it should be noted that the enhancement is primarily due to the heart-centric positioning of the detectors. This enhancement is lost when detectors are oriented in the parallel direction which is required for planar recording. Ultra-low-dose procedures have nevertheless already been validated in routine stress myocardial SPECT studies with CZT cameras [9,10]. Although the methodology has been adapted to ERNA [11–14], it remains to be assessed under the real-life conditions of the routine monitoring of oncology patients. There is a specific need to ensure that patient outcomes are

genuinely free of any cardiac complications when none of the ERNA cardiotoxicity criteria are detected using this ultra-low-dose protocol.

This study assesses an original protocol of a first-line detection of breast cancer therapy-related cardiotoxicity by serial, fast and ultra-low-dose ERNA and analyzes patient outcome based on the ERNA results.

## **Materials and Methods**

### **Study population, treatment, and follow-up**

We retrospectively included consecutive breast cancer women referred to investigate potentially cardiotoxic drug effects (i.e., anthracyclines followed or not by trastuzumab) on the premise that they had undergone: 1) ERNA-based monitoring with a reference pre-therapeutic ERNA recorded post-January 2019 (the date that our nuclear medicine department replaced its conventional ERNA protocol with the low-dose protocol) and 2) at least one follow-up ERNA examination prior to December 2020.

Cancer treatments were administered in a single cancer center (Institut de Cancérologie de Lorraine (ICL), France) and generally included anthracycline followed by a subsequent one year of trastuzumab treatment for breast cancers overexpressing the human epidermal growth factor receptor 2 (HER2+). The prescribed time interval between serial ERNA measurements of the LVEF was based on the estimated risk [4] and was usually three months.

Second-line management, which included a specialist onco-cardiology consultation and echocardiography, was additionally scheduled when a  $> 10\%$  LVEF drop from baseline

was associated with an LVEF below or approaching the 50% level during follow-up [15], as well as for any other signs or symptoms arising from suspected cardiac origins.

Cancer treatment was always suspended until the onco-cardiology consultation. Thereafter, cardiotoxicity-driven changes in cancer treatment and/or the introduction or increased doses of cardioprotective drugs were ordered or not, depending on whether evidence of left ventricular dysfunction persisted on echography and other medical data. Cardioprotective drugs consisted of beta-blockers, angiotensin-converting enzyme inhibitors (ACEI), and angiotensin-II receptor antagonists (ARA-II) [15–17].

In the five years following the oncology treatments, the breast cancer women had regular oncology consultations at the ICL which included a physical examination, the search for any signs or symptoms of possible cardiac origins, and the reporting of any changes in medical therapy. The follow-up data were extracted from these consultation reports.

All patients investigated in our nuclear medicine department and all those undergoing cancer treatments at the ICL were informed that their medical data might be used for research purposes, and the study was approved by the local Ethics Committee.

### **ERNA recording and analysis**

The ERNA methodology has been described elsewhere [11]. Briefly, red blood cells were labeled in vivo by the intravenous injection of 250 to 650 MBq (7 to 18 mCi) of  $^{99m}\text{TcO}_4^-$  as a proportion of body weight (Table 1), 20-30 minutes after injecting approximately 6 mg of stannous pyrophosphate. Five to 15 minutes later, patients were set in a semi-reclining prone position with ECG leads placed on their backs. Projections were recorded during a 10-min period with a 'region-centric' acquisition maximizing the counts arising from a heart area previously defined on a short pre-scan [9–11].

Tomographic images were reconstructed using the following parameters: 16-interval frames, 4 iterations, 32 subsets, Kernel and Gaussian filters of respectively 0.125 and 5 mm, and a 128 x 128 matrix, resulting in a voxel size of 4.92 x 4.92 x 4.92 mm<sup>3</sup> [11].

The LVEF was computed using the count-based method of the Quantitative Blood Pool software (Cedars-Sinai Medical Center) and with manual displacements of LV limits if obvious errors in the automatic contouring process were apparent [11,12]. The final LVEF values were obtained after correcting for the relative underestimation of end-systolic volume, according to a calibration procedure based on count/volume correlations [11,12].

Effective doses were calculated by applying a ratio of  $7.09 \cdot 10^{-3}$  mSv/MBq of injected Tc-99m [18] according to the activity measured in the syringe, before injection, with a dedicated dose calibrator (CRC®-15R, Capintec, Inc., Ramsey, NJ, USA).

### **Statistical analyses**

Quantitative parameters were described by mean  $\pm$  SD and qualitative parameters by frequency and percentage. Three-group comparisons of quantitative parameters were performed using ANOVA or the Kruskal-Wallis test, depending on whether the data were distributed normally or not, and the Chi-square test or Fisher Exact test for qualitative parameters. Probabilities of survival and survival with no cardiotoxicity-driven drug regimen changes were estimated and plotted for all three Tox-, Tox+, and Tox $\pm$  groups. Survival curves span the entire follow-up period, starting from the day of the pre-therapeutic ERNA to the last reported medical consultation. Cox proportional hazards models were used to obtain unadjusted hazard ratios. Cox regression proportionality assumptions were verified. Statistical analyses were performed using the SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA). The significance threshold was set at a p-value of 0.05.



## Results

Among the 197 consecutive women treated for breast cancer that underwent ERNA-based monitoring during the two-year time frame from January 2019 to December 2020, 2 were excluded because of an LVEF of  $< 50\%$  on the baseline pre-therapeutic ERNA, leaving 195 women in the current analysis. A total of 552 ERNAs were recorded in these 195 women: 122 women had 2 ERNAs, 29 women had 3, and 44 women had 4 or more ERNAs. Mean injected activity and effective dose per ERNA investigation were only  $325 \pm 82$  MBq ( $8.8 \pm 2.2$  mCi) and  $2.3 \pm 0.6$  mSv, respectively, and the mean cumulative effective dose per patient was  $6.2 \pm 2.3$  mSv.

### Baseline data

The key data collected on the day of the baseline pre-therapeutic ERNA are summarized in Table 2. The mean age was  $54 \pm 13$  years (ranging from 25 to 81 years). Only 15 out of the 195 women (8%) had a previously diagnosed metastasis, and 44 (23%) women had undergone prior oncology treatment; 2 (1%) had surgery, and 42 (22%) had radiotherapy. In addition, only 5 (3%) women had a prior cardiovascular disease diagnosis (4 hypertension and 1 cardiac arrhythmia), and 6 (3 %) women took medication with a potentially cardioprotective effect (beta-blockers in all cases).

### Follow-up data

During a mean  $24 \pm 6$ -month follow-up, 22 (11%) women exhibited conventional ERNA criteria of cardiotoxicity (a  $> 10\%$  LVEF drop from baseline and an LVEF of  $< 50\%$ ) and were included in the Tox+ group. Thirty-five (18%) women were included in the Tox± group because of dissociated signs, with 27 exhibiting only a  $> 10\%$  drop in the LVEF (baseline LVEF:  $71 \pm 5\%$  and follow-up LVEF:  $59 \pm 5\%$ ), and the remaining 8 women, only a follow-up

LVEF < 50% (baseline LVEF:  $55\pm 2$  % and follow-up LVEF:  $47\pm 1$  %). The remaining 138 patients (71%) with neither a > 10% drop in the LVEF nor an LVEF of < 50% during follow-up constituted the Tox- group.

As illustrated in Figure 1, in Tox- patients, the final follow-up LVEF was  $66\pm 7\%$ , and the difference between final and initial LVEF was  $1\pm 6\%$ . The corresponding values were significantly lower in Tox $\pm$  patients ( $56\pm 7$  % and  $-12\pm 3$  %, respectively, both  $p<0.001$  vs. Tox+) and even lower in Tox+ patients ( $43\pm 8$  % and  $-21\pm 7$  %, respectively, both  $p<0.001$  vs. Tox $\pm$ ). Only 5 patients had an LVEF < 40% during follow-up (all being in Tox+ group).

During follow-up, 10 (5%) women died (death of a non-cardiac cause in all cases), and 16 (9%) had cardiotoxicity-driven changes to their drug regimen (all received additional prescriptions for cardioprotective drugs, and one discontinued all cardiotoxic drugs).

As detailed in Table 2, the ERNA-based classification correlated with (i) established cardiotoxicity risk factors -i.e., association of trastuzumab to the anthracycline treatments (Tox+: 55%, Tox $\pm$ : 60%, and Tox-: 30%,  $p=0.001$ ), and prior cardiovascular disease (i.e., cardiac arrhythmia or hypertension; Tox+: 18%, Tox $\pm$ : 3% and Tox-: 1%,  $p=0.018$ ), and (ii) rate of cardiotoxicity-driven drug regimen changes during follow-up (Tox+: 63%, Tox $\pm$ : 38% and Tox-: 0%,  $p=0.001$ ), but not mortality (Tox+: 14%, Tox $\pm$ : 6% and Tox-: 4%,  $p=0.219$ ).

As illustrated in Figure 1, the 30-month survival with no cardiotoxicity-driven changes in drug regimen was as high as  $97\pm 2\%$  in Tox-, but only  $60\pm 13\%$  in Tox $\pm$  ( $p=0.020$  vs. Tox-) and  $36\pm 13\%$  in Tox+ ( $p=0.026$  vs. Tox $\pm$ ). Hazard ratios for death or cardiotoxicity-driven drug changes were 5.14 (95% confidence interval: 1.63 - 16.22,  $p=0.005$ ) in the Tox $\pm$  and 14.63 (5.14 - 41.64,  $p<0.001$ ) in the Tox+ group.

## Discussion

The high tomographic count sensitivity of the cardiac CZT-camera and the calibrated method of count-based LVEF determination allowed to implement a fast and ultra-low-dose ERNA protocol which provides highly consistent results in terms of routine first-line assessment of breast cancer therapy-related cardiotoxicity during cancer treatment follow-up. Our results (i) confirm an association with well-established risk factors for cardiotoxicity (the association of trastuzumab to an anthracycline treatment, a previous history of significant cardiac arrhythmia or hypertension [19]) and (ii), demonstrate an excellent cardiac outcome in the greater majority of women that did not exhibit any of the ERNA cardiotoxicity criteria. Indeed, these Tox- women represented as many as 71% of the overall cohort, and  $97\pm 2\%$  had a 30-month survival period with no cardiotoxicity-driven drug changes. In addition, none of these Tox- women reported any signs or symptoms evocative of cardiotoxicity, which would have required any therapeutic changes during follow-up.

The mean injected activity was only 325 MBq (8.8 mCi) and thus, 62% lower than that previously prescribed for planar ERNA with a standard gamma-camera in our department ( $\approx 850$  MBq (23 mCi)). Therefore, the mean effective dose per ERNA investigation was only 2.3 mSv and, thus, almost three times lower than doses reported for standard ERNA protocols (6 to 10 mSv) [7]. The cumulative radiation dose was therefore dramatically lower (6.2 mSv per patient, on average), making this technique much more acceptable for women who are likely to undergo multiple irradiating diagnostics or therapeutic procedures throughout their lives.

Contrary to echocardiography, ERNA provides count-based measurements of the LVEF, which are automated and independent of LV shape and patient echogenicity [2]. The high

reproducibility of the automated LVEF measurements has been previously established for conventional planar ERNA protocols [13], as well as for the current ultra-low-dose protocol for which the 95% confidence interval ranged from -7.6% to 6.9% [11]. The LVEFs in our present study were also computed with a further count/volume calibration, which ensures that these LVEF measurements are concordant with those obtained by conventional planar ERNA [12,19]. This allowed us to apply the same cardiotoxicity diagnostic criteria as those extensively used and validated for planar ERNA (an LVEF of < 50% associated with a > 10% drop in LVEF from baseline) [1,15].

The number of cases with ERNA-criteria of cardiotoxicity doubled when anthracycline was followed by a trastuzumab treatment and also increased when there was a previous history of significant cardiac arrhythmia or hypertension, which is consistent with results from previously published studies [15,20,21].

The risk of death or cardiotoxicity-driven drug regimen changes was 14.6 higher in the presence of both ERNA criteria of cardiotoxicity (Tox+ group) than in the absence of any of these criteria (Tox- group). However, this risk was still 5.4 higher in women with dissociated ERNA criterion (i.e., the Tox± women showing either a > 10% LVEF drop from baseline or an LVEF of < 50%, but not both) and for whom the follow-up LV dysfunction was less severe than for Tox+ patients (see Figure 1). This provides supportive evidence that dissociated signs should not be ignored but should lead to monitoring at closer follow-up intervals to preclude the worsening of any signs of cardiotoxicity [15].

Our study has the limitation of a mean 24-month follow-up from the pre-therapeutic ERNA to the last follow-up (last consultation in the current study period), and a mean 20-month follow-up from the last ERNA to the last follow-up. As signs and symptoms may develop over a more extended follow-up period in certain breast cancer patients [22], our data would require a longer follow-up to provide a more precise evaluation.

Another limitation is that we used an *in vivo* red blood cell labeling method with a potentially higher background noise level than *in vitro* labelling approaches. Although we note that we now use  $^{99m}\text{Tc}$  *in vitro* labelled albumin which did not require changing injected activities. The increased blood signal and signal/noise ratio obtained with  $^{99m}\text{Tc}$ -labelled albumin has allowed to reduce the recording time from 10 to 8 minutes.

An additional limitation is that the evolution of an LV dysfunction, detected or suspected from the ERNA, was subsequently monitored by onco-cardiologists with only echography. ERNA was only used as a first-line detection of LV dysfunction. Objective comparisons with the simultaneous LVEF determination provided by other reference techniques (echography, MRI) are still required.

Our data also showed that cardiotoxicity-driven medical drug changes were not ordered in almost one-third of women exhibiting both of the two ERNA criteria of cardiotoxicity (the Tox+ group). This observation was predominantly due to the lack of any apparent left ventricular dysfunction and with a  $\geq 50\%$  LVEF on echography, which was systematically scheduled between 2 to 4 weeks after any ERNA yielding abnormal results. Any potentially cardiotoxic drugs were systematically suspended during this 2 to 4-week period, potentially resulting in the spontaneous recovery of left ventricular dysfunction in some cases, as has previously been reported for trastuzumab therapy [15,23–27]. However, the actual rates of cardiotoxicity may equally be overestimated by ERNA, underestimated by echography, or both, a point that needs to be more specifically addressed in studies with longer follow-up periods and larger patient populations. A larger study cohort with a longer follow-up would also allow to analyze the impact of cardiotoxicity-driven medical adjustments.

Nevertheless, the main findings of the present study are the excellent overall and especially the cardiac prognosis for the great majority of women who have no criteria of cardiotoxicity using this ultra-low-dose ERNA protocol (see Figure 2). These women more

specifically did not exhibit any signs or symptoms of possible cardiac origins and did not require a medical adjustment up to the date of the last oncology consultation (i.e., during a mean 20-month follow-up from the last ERNA). This information is crucial for these women who will not have a dedicated consultation with a cardiologist.

Our current study assessed as many as 552 fast and ultra-low-dose ERNAs over a two-year time frame. This first-line ERNA-based cardiotoxicity detection allowed to ease the monitoring burden placed on onco-cardiologists by providing them with a more focused cardiac follow-up program.

## **Conclusion**

The present routine protocol of first-line detection of breast cancer therapy-related cardiotoxicity by fast and ultra-low-dose ERNA provides very consistent results. It also reinforces the evidence of an excellent cardiac outcome for the largest group of women with no ERNA cardiotoxicity criteria.

**New Knowledge Gained:** The present retrospective clinical study shows that fast and ultra-low-dose radionuclide angiographies obtained on a high sensitivity CZT camera may be very efficient for the routine first-line detection of breast cancer therapy-related cardiotoxicity and with as much as 70% reduction of injected doses.

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## Legends

**Figure 1:** Mean  $\pm$  SD for the baseline reference LVEF (white columns), the final follow-up LVEF (grey columns), and the difference between final and baseline LVEF in each of the three groups - i.e., the Tox+ group of women presenting a  $> 10\%$  LVEF drop from baseline and an LVEF of  $< 50\%$  LVEF during follow-up, Tox $\pm$  group with either a  $> 10\%$  drop or a  $< 50\%$  LVEF, and the Tox- group with neither a  $> 10\%$  drop in the LVEF nor an LVEF of  $< 50\%$ .

**Figure 2.** Kaplan-Meier curves for survival with no cardiotoxicity-driven changes in drug regimen in the three categories of women exhibiting: (i) both of the ERNA criteria of cardiotoxicity during follow-up (a  $> 10\%$  LVEF drop from baseline and an LVEF of  $< 50\%$ , Tox+ group), (ii) either a  $> 10\%$  drop in the LVEF or an LVEF of  $< 50\%$  LVEF (Tox $\pm$  group), and (iii) neither a  $> 10\%$  drop in the LVEF nor an LVEF of  $< 50\%$  (Tox- group). The number of event-free patients at each of the 5-month follow-up intervals is given below the x-axis.

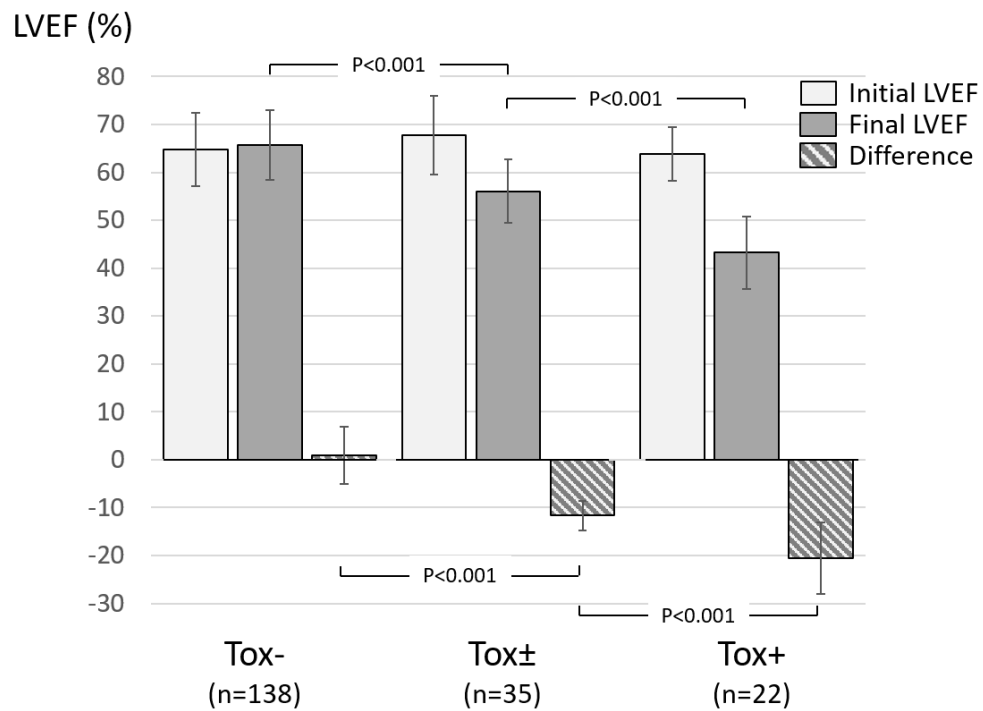
**Table 1:** Prescribed  $^{99m}\text{TcO}_4^-$  doses as a proportion of body weight, with the number of patients included in each weight category.

<b>Bod weight</b>	<b>Number of patients</b>	<b>Prescribed doses</b>
≤ 60kg	58	250 MBq
61 to 70 kg	57	300 MBq
71 to 80 kg	38	350 MBq
81 to 90 kg	21	400 MBq
91 to 100 kg	13	460 MBq
101 to 110 kg	6	520 MBq
111 to 120 kg	2	590 MBq
121 to 250 kg	0	650 MBq

**Table 2:** Main data collected at baseline (i.e., before chemotherapy) and during follow-up in the overall population and comparatively in women exhibiting conventional ERNA criteria of cardiotoxicity during follow-up (a > 10% LVEF drop from baseline and an LVEF of < 50%, Tox+ group), either a > 10% drop in the LVEF or an LVEF of < 50% (Tox± group), and neither a > 10% drop in the LVEF nor an LVEF of < 50% (Tox- group). The p-value refers to the 3-group comparison for each individual characteristic.

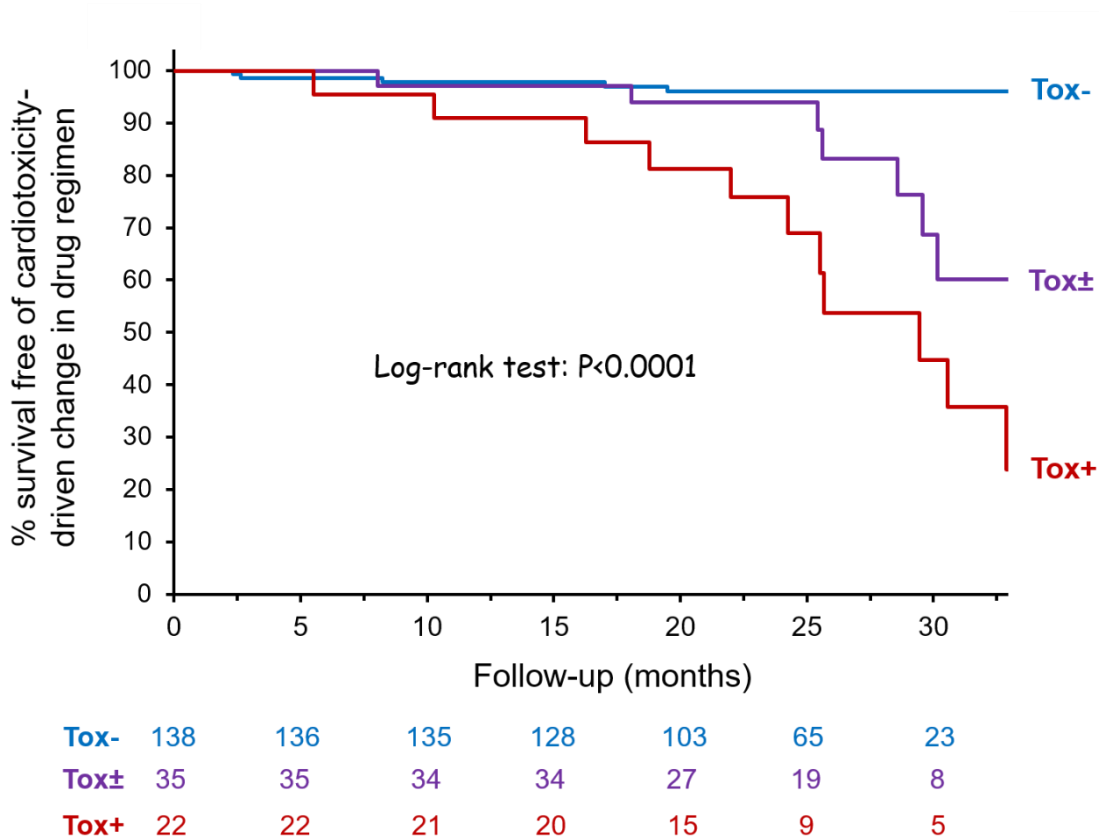
	Overall population (n=195)	Patient groups			P value
		Tox- (n=138)	Tox± (n=35)	Tox+ (n=22)	
<b>Baseline</b>					
Age (years)	54±13	53±14	55±14	57±12	0.440
Bodyweight (kg)	70±15	71±15	71±15	66±14	0.331
HER2 positive	75 (39%)	41 (30%)	21 (60%)	13 (59%)	<0.001
HR positive	114(59%)	84 (61%)	18 (51%)	12 (55%)	0.556
TNBC	43 (22%)	33 (24%)	5 (14%)	5 (23%)	0.470
Prior metastasis	15 (8%)	9 (7%)	5 (14%)	1 (5%)	0.250
Prior cardiovascular disease	5 (3%)	1 (1%)	1 (3%)	3 (14%)	0.018
Beta-blockers	6 (3%)	1 (1%)	1 (3%)	4 (18%)	0.001
Heart rate (bpm)	84±13	84±13	85±13	83±17	0.778
Systolic BP (mmHg)	137±21	137±22	131±19	139±19	0.290
Diastolic BP (mmHg)	75±12	75±12	73±11	73±12	0.520
Prior thorax surgery	2 (1%)	0 (0%)	1 (3%)	1 (5%)	0.079
Prior mediastinal radiotherapy	42 (22%)	26 (19%)	10 (29%)	6 (27%)	0.373
ERNA LVEF (%)	65±8	66±8	64±7	63±6	0.103
<b>Follow-up</b>					
Duration (months)	24±6	24±7	25±6	24±7	0.911
Anthracycline and trastuzumab	74 (38%)	41 (30%)	21 (60%)	12 (55%)	0.001
Only anthracycline	121 (62%)	97 (70%)	14 (40%)	10 (45%)	0.001
Death	10 (5%)	5 (4%)	2 (6%)	3 (14%)	0.219
Cardiotoxicity-driven drug changes	16 (8%)	0 (0%)	6 (38%)	10 (63%)	<0.001

BP = brachial blood pressure, ERNA = equilibrium radionuclide angiography, HER2 = human epidermal growth factor receptor 2, HR = hormone receptor, LVEF = left ventricular ejection fraction, TNBC = triple-negative breast cancer.



**Figure 1:** Mean  $\pm$  SD for the baseline reference LVEF (white columns), the final follow-up LVEF (grey columns), and the difference between final and baseline LVEF in each of the 3 groups - i.e., the Tox+ group of women presenting a  $> 10\%$  LVEF drop from baseline and an LVEF of  $< 50\%$  LVEF during follow-up, Tox± group with either a  $> 10\%$  drop or a  $< 50\%$  LVEF, and the Tox- group with neither a  $> 10\%$  drop in the LVEF nor an LVEF of  $< 50\%$ .





**Figure 2.** Kaplan-Meier curves for survival with no cardiotoxicity-driven drug regimen changes in the three categories of women exhibiting: (i) conventional ERNA criteria of cardiotoxicity during follow-up (a > 10% LVEF drop from baseline and an LVEF of < 50% LVEF, Tox+ group), (ii) either a > 10% drop or a < 50% LVEF (Tox± group), and (iii) neither a > 10% drop in the LVEF nor an LVEF of < 50% (Tox- group). The numbers of event-free patients at 5-month follow-up intervals are below the x-axis.