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Original Article

Density and volume of cardiac calcifications detected on planning CT predicts cardiotoxicity after hypo-fractionated whole breast Radiotherapy

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ABSTRACT

Background and Purpose: Cardiac calcifications (CAC) are emerging as predictors of cardiac toxicity after breast cancer Radiotherapy. Main purposes of this study were:1) to test the association between CAC scores and cardiac events in a cohort treated with moderate hypo-fractionation; b) to assess interaction between CAC and dosimetry/clinical predictors.

Materials and methods: Data of 1172 consecutive patients treated at our hospital with 3DCRT whole breast irradiation (40 Gy/15fr) were available. Heart was automatically segmented and the mean heart dose (MHD) was assessed. The Agatson score (AS), the CAC_volume and the max HU value in the heart (Max_HU) were assessed using an in-house script. Their association with cardiac events was tested by logistic regression, including the combined impact of MHD and relevant clinical parameters (including chemotherapy, age and smoking). CAC_volumes/Max_HU values were compared against the values obtained from our clinical planning system for 75 patients with calcifications.

Results: Twenty-nine patients experienced cardiac events (median follow-up:6.5y). AS/CAC_volume/Max_HU were highly significant predictors ($p < 0.005$). MHD (mean ± SD: 0.8 ± 0.1/2.4 ± 0.7 Gy for right/left) was predictive only if encoded according to the optimal cut-off based on Youden index (MHD > 1 Gy). The resulting multivariate model combined MHD > 1 Gy, age and CAC scores, with similar performances for the three different scores (AUC = 0.77/0.755, $p < 0.0001$, $R^2 = 0.99$), with the three different scores always being the major predictor. TPS gave consistent values for Max_HU while CAC_volume showed larger differences, although highly correlated.

Conclusion: CAC are the most important predictors of cardiotoxicity. Max_HU is promising for fast assessment of patients at risk. The greatest clinical benefit of further heart sparing is expected in left breast cancer patients with moderate-severe CAC scores (Max_HU > 250).

Introduction

Breast tumors are still the leading cause of female cancer death in Europe [1]. Mortality rates are continuously decreasing due to earlier detection and therapeutic improvements [2], and this translates into an increasing number of long-term survivors for whom quality of life (QoL) is a growing oncological issue. The role of Radiotherapy (RT) following breast conservative surgery is largely well-established and most patients receive RT [3]. More precise planning and delivery have allowed a reduction of the dose received by surrounding organs at risk (OARs) such as lungs and heart. Despite these continuous advancements, the dose received by OARs and the breast parenchyma may still cause radiation-induced toxicities that may affect QoL [4]. Skin/breast irradiation can lead to transient or permanent morbidities [5–8], including skin erythema, edema, liponecrosis, fibrosis, breast atrophy, pain, breast induration. Other significant long-term complications receiving

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attention in recent years concern cardio-vascular diseases (CVD [9,10]) and cardiac mortality is higher in breast cancer survivors than in women without breast cancer [11]. A linear relationship between the mean heart dose (MHD) and CVD has been suggested [9], contributing to increase attention to heart sparing over the last 10 years. This increased attention translated in significantly lower MHD [12] in recent series and, consequently, into a more blurred association between MHD (or other cardiac dosimetry predictors) [13–15] and the risk of CVD. On the other hand, other significant non-dosimetry predictors (such as anthracyclines, chronic kidney disease and smoking) are known to modulate the risk, [16–18]. In addition, pre-RT cardiac and vascular symptoms are, as expected, associated with an increased CVD risk [18] and recent investigations have shown cardiac calcifications (CAC) to be predictive of CVD and to worse survival, even for asymptomatic patients [19–23]. The most widely used index for the assessment of risk classes according to CAC severity is the Agatson Score (AS, [24,25]), which combines CAC density and extension. Interest in CAC is increasing as they could in principle identify asymptomatic patients at risk, potentially orienting plan optimization and delivery as well as selecting patients to be included in monitoring programs for the prevention, identification and early treatment of CVD symptoms [26,27].

The possible interaction between cardiac dose and CAC presence/severity in identifying patients at risk is largely unexplored; van der Bogaard et al [28] first reported more pronounced association between cardiac dosimetry metrics and acute coronary events in patients without CAC in the left anterior descending artery (LAD). A more recent study suggested AS to be a much more relevant risk factor than MHD in a large series of node-positive patients treated to the whole breast and to supraclavicular nodes, axilla and with/without internal mammary nodes irradiation [23]. The same study reported evidence of a stronger association with dosimetry factors for patients with low AS.

Thanks to a large institutional database of patients treated at our Institute, mostly with hypofractionated RT, several studies have been conducted on both outcomes and toxicity [28–32]. Within the context of cardiac toxicity, given the availability of full planning data and sufficiently long follow-up, we aimed to explore the impact of CAC on the occurrence of cardiac events in patients treated with moderate hypofractionation (40 Gy/15 fr) to the whole breast only. The aims of the current investigation were:

a) To test the impact of CAC; as AS is not currently suitable for the clinical setting, we also focused on alternative and more easily quantified scores, such as maximum CAC density (HU score) and CAC volume.
b) To investigate the role of MHD and the possible interaction with CAC scores; to develop a multi-variable model incorporating CAC scores and dosimetry/clinical predictors

Materials and methods

Patient cohort: clinical and dosimetry characteristics

Data were extracted from a prospectively filled Institutional database pertaining to all breast cancer patients having undergone postoperative Radiotherapy since 2009. For the current study, the patients treated with the hypofractionated schedule (40 Gy in 15 fractions) to the whole breast (i.e.: no nodal involvement), were considered; patients receiving a boost to the surgical bed were excluded. In addition, only patients treated before 2018 were included, allowing for recovery of follow-up data at least 5 years post-RT. The most recent follow-up was updated to December 2023. A total of 1200 patients were selected; 28 were excluded due to bilateral RT (simultaneous or delayed), leaving 1172 patients for analysis (right: 569, left: 603). Details of contouring, planning and delivery are reported elsewhere [29,31]. In short, all patients were submitted to planning CT on the same scanner (Light Speed GE MDCT) and treated with manually optimized 3D-CRT using tangential fields. CTV included the whole breast, following national guidelines [33]: Planning target volume (PTV) was generated by the expansion of CTV with 5–10 mm margins in all directions except for lung (5 mm); PTV was cropped to avoid the first 5 mm of skin. A median number of 4 segments was used to obtain homogeneous dose distribution within PTV, with hot spots < 108 % and V95%>95 %. Regarding target delineation and RT technique, clinical practice has remained stable over the years. Treatments were delivered using a Varian Linac DHX 6 MV; patients were submitted to daily image guidance through CBCT.

The main characteristics of the patients are summarized in Table 1. In particular, a patient was defined as a smoker if she was an active smoker at the date of the anamnesis, regardless of the number of smoked cigarettes. She was defined as a former smoker if she was an active smoker for a period and then quit, regardless of the period of cessation at the date of the anamnesis. For this analysis, active smokers and former smokers were considered together.

During the anamnesis, comorbidities were asked: previous medical diagnosis of obesity, diabetes and hypertension were reported by the patients and considered for the analysis. Planning data (Eclipse Varian TPS v13.7) were retrieved, including 3D dose distributions, and exported into the MIM system (MIM Inc, v7.2.8). Selected clinical information was available and is reported in the same Table 1. The only continuous variables were the three CAC scores, age and MHD; in addition, the impact of MHD was also tested as dichotomic, taking the optimal cut-off value (based on the Youden index).

Recovery of cardiac toxicity information and heart dosimetry

All cardiovascular events recorded during the follow-up, including decline in left ventricular function, arrhythmia, vascular toxic effects, conduction abnormalities, valvular heart disease, heart failure, ischemic heart disease, and cardiac deaths, were documented by the treating radiation oncologist. The events were reported during follow-up at 6, 18, 30, 42, 54 and 66 months [29]. Patients continued their follow-up up to 10 years, and data were updated for all patients in 2019 and again in 2023. The institutional ethics committee approved the study, registered to ClinicalTrials.gov (NCT03077191 and next amendments).

The heart was automatically segmented using a commercial AI-based tool (MIM_Protégé), due to the non-negligible number of right-breast cases without heart contours in the clinical plan and to eliminate

Table 1
Summary of the major clinical characteristics of the patients.

Total number of patients	1091
Age Groups (years)	
Mean	60
Median [IQR]	62[50;70]
< 45	114 (10.4 %)
45—55	278 (25.5 %)
55—65	268 (24.6 %)
> 65	431 (39.5 %)
Position of tumour	
Left	561 (51.4 %)
Right	530 (48.6 %)
Chemotherapy	
Anthracycline based	180 (16.5 %)
Other	96 (8.8 %)
Concurrent Chemo/RT	27 (2.5 %)
Other therapies	
Trastuzumab	77 (7.1 %)
Hormonal	879 (80.6 %)
Health conditions	
Obesity	251 (23.0 %)
Diabetes	150 (13.7 %)
Hypertension	376 (34.5 %)
Smoking	221 (20.3 %)
Mean Heart Dose (MHD)	
Average (SD) [Gy]	1.72 (1.23)
Patients with MHD > 1 Gy	595 (54.5 %)

inter-observer variability. The mean heart dose (MHD) was considered as the major potential predictor of cardiotoxicity and was then extracted. The dose to other cardiac sub-structures was not considered at this stage, primarily due to the significant contouring uncertainty, which makes their usability less robust than that of MHD [15]. In addition, the consistency between the MHD values obtained from clinical (manual) and automatic heart contours was assessed by comparing them in the subgroup of patients (n = 1024/1172) with the manual contour of the heart. The results, presented in the Supplementary material, showed high consistency between the two contouring methods (slope: 1.03, R2: 0.97).

Extraction of quantitative CAC information

First, patients with pacemaker/electrodes/stents were identified based on heart density histograms and automatic high-density material detection in the superior vena cava, using TotalSegmentator [34]; these patients (n = 81) were excluded due to their potentially altered baseline cardiac functionality, which could complicate the interpretation of the meaning of any reported event after RT. CAC were identified by an in-house Python script (available at https://github.com/pymaitre/cluster_score.git) that classified 'calcified lesion' as > 130 HU pixels and area ≥ 1 mm^2 or ≥ 4 adjacent pixels, according to Neves et al. [25]: the script searched all calcium deposits within the segmented heart, then included CAC in the coronary arteries, valves and myocardium. The Agatson score (AS) [24], CAC_volume and HU score (Max_HU) were assessed. Further details are reported in the Supplementary material. In addition, aiming to explore the usability of a commercial treatment planning system (TPS) in assessing CAC volume and Max_HU, CAC were segmented using the thresholding tool (HU > 130) of our clinical Eclipse TPS (v.13) on a sample of 75 patients whose CAC volume had previously been assessed as > 0.1 cc. The values of CAC volumes and Max_HU quantified by the two methods were compared.

Statistical analyses and modelling

For model training, 1091 patients were available, after the exclusion of those with pacemakers/electrodes/stents. The association between cardiac events and the available clinical/dosimetry variables was tested through logistic regression. Univariate logistic regression was first performed for each variable. The Spearman correlation matrix was used to examine inter-variable relationships in order to limit redundancy and minimize the risk of multicollinearity: apart from the CAC scores, in case of significant association between variables, only the one with the lowest p-value was further considered. Then, the resulting, independent variables with p-value < 0.20 in univariate analysis were considered for multivariate logistic regression (MLR); the three calcification scores were considered one at a time, being highly associated one each other, with the aim to generate models including only one CAC score. Analyses were performed with MedCalc software (v22), following the method of maximum likelihood estimation to compute coefficients through a backward stepwise approach. Statistical significance was tested at the conventional p-value cut-off of 0.05. The Mann-Whitney test and ROC-AUC analyses were also performed. Sensitivity, accuracy, and specificity metrics were computed; the predicted and observed probabilities were compared through calibration plot. The resulting multivariable models underwent internal validation by bootstrapping (according to TRIPOD I validation [35]): AUC corrected for optimism were obtained from 1000 bootstrap iterations.

Results

Median follow-up was 6.5 years with IQR of 5.9–8.8 years, showing that a limited, but non-negligible, fraction of patients missed long-term follow-up updates. Twenty-nine patients experienced cardiac events: 3 patients reported ischemic heart disease with one acute myocardial infarction. Heart failure were frequent, often associated with atrial fibrillation or paroxysmal atrial flutter, and requiring pacemakers or defibrillator implantation (n = 14). Several stent angioplasties were performed for critical coronary stenosis (n = 1). One patient underwent valve surgeries (aortic and mitral bioprosthesis, tricuspid plastic) for severe insufficiency. Episodes of pericarditis (n = 2), atrial extrasystole (n = 2) and advanced atrioventricular block (n = 1) were also observed.

MHD mean ± SD were 0.8 ± 0.1 and 2.4 ± 0.7 Gy for right and left respectively. Table 2 summarizes the results of univariate analysis. All three CAC scores were strongly significant predictors (p < 0.0001). Of note they still resulted significant predictors even if restricting the analysis to those events (n = 18) that may be considered more likely to be directly associated with CAC, namely coronary artery disease, acute myocardial infarction, congestive heart failure and heart valve disease: the results of this univariate sub-analysis are shown in the Supplementary material. Age was also significant while obesity and hypertension were of borderline significance. MHD was not associated with cardiac events in either overall/left cohorts: however, once encoded using the best cut-off (1 Gy, mostly representing laterality) it became predictive. Of note, 31 left patients showed MHD < 1 Gy while 61 right patients showed MHD > 1 Gy, suggesting why laterality was not significant. The best multivariate model combined MHD > 1 Gy, age and CAC scores with similar performances across the three scores, as shown in Table 3. The model using Max_HU, promising for its potential ease of clinical use, showed AUC = 0.753, p < 0.0001 and almost perfect calibration (R2 = 0.99), with Max_HU the strongest predictor (p < 0.0001). Fig. 1 shows the predicted risk as a function of Max_HU, stratified by MHD above/below 1 Gy (once fixed the age at the population median value, 62 years); Fig. 2 shows the calibration plot. Equivalent Figures, using CAC_Volume, are shown in the Supplementary material. As an example, Fig. 3 illustrates four patients (with the same age, equal to the median value) having different risks of cardiac toxicity according to their Max_HU and MHD. Considering a tentative threshold of 250 HU, the incidences of cardiac events were respectively of 5.2 % (15/288) and 1.7 % (14/802) for the subgroup pf patients with Max_HU > or < 250 respectively (p = 0.002). As detailed in the Supplementary material, the corresponding incidences were 3.1 % vs 0.8 % (p = 0.05) in the subgroup of patients with MHD < 1 Gy and 6.8 % vs 2.5 % (p = 0.013) in the subgroup of patients with MHD > 1 Gy. This suggests that the largest gain in reducing MHD < 1 Gy is expected in the patients with severe CAC (i.e.: Max_HU > 250).

Internal validation confirmed the robustness of the models, with AUC correction for the optimism within 0.015. For example, the model using Max_HU showed AUC = 0.739 compared to the original value of 0.753.

The results of the comparison of CAC_Volume and Max_HU scores

Table 2
Summary of univariate analysis (* indicates variables with p-value < 0.05). Odds ratio (OR) is per mm^3 and 1 HU for CAC "Volume score" and "Max_HU score" respectively; regarding the "Agatson score" OR referred to the score calculated taking the CAC area as measured in mm^2. OR is per year for "Age".

Variable	p-value	Odds ratio	CI at 95%
Laterality	0.1556	1.6748	[0.8163; 3.4364]
Age	0.0001*	1.0682	[1.0325; 1.1050]
Chemotherapy	0.9899	0.9639	[0.4432; 2.0964]
Anthracyclines	0.3593	0.5894	[0.2051; 1.6942]
Concomitant CT/RT	0.1627	2.6571	[0.6048; 11.6728]
Monoclonal therapy	0.6414	0.6853	[0.1616; 2.9066]
Hormonal therapy	0.7706	0.9194	[0.3941; 2.1451]
Smoking	0.8095	1.0640	[0.4561; 2.4821]
Obesity	0.0515	1.9319	[0.9379; 3.9794]
Diabetes	0.4481	1.3597	[0.5527; 3.3453]
Hypertension	0.0615	1.8217	[0.9104; 3.6451]
MHD	0.4955	0.9735	[0.7274; 1.3031]
1 Gy cutoff MHD	0.0468*	2.1662	[0.9936. 4.7226]
Agatson score	0.0046*	1.0015	[1.0010; 1.0020]
Volume score	0.0036*	1.0009	[1.0006; 1.0013]
MAX HU score	0.0001*	1.0034	[1.0019; 1.0048]

Table 3
Summary of the best logistic models resulting when considering the three considered CAC scores one at time (from top to bottom: CAC volume, Agatson score (AS) and Max_HU).

ROC-AUC [CI]	Variables	Coefficient	p-value	OR	C.I. OR
0.770 [0.744, 0.795]	**Patient Age**	0.038704	0.0343	1.0406	[1.0030, 1.0797]
	MHD > 1 Gy	1.153960	0.0093	3.3086	[1.3430, 8.1493]
	CAC Volume	0.000869	<0.0001	1.0005	[1.0010, 1.0020]
	Constant	−7.195250	/	/	/
0.771 [0.745, 0.796]	**Patient Age**	0.03897	0.0337	1.0408	[1.0031, 1.0800]
	MHD > 1 Gy	1.09609	0.0123	3.1338	[1.2811, 7.6660]
	AS	0.00135	<0.0001	1.0013	[1.0008, 1.0019]
	Constant	−7.12851	/	/	/
0.753 [0.726, 0.778]	**Patient Age**	0.04454	0.0158	1.0455	[1.0084, 1.0839]
	MHD > 1 Gy	1.03600	0.0202	2.8082	[1.1747, 6.7132]
	Max_HU	0.00274	0.0004	1.0029	[1.0013, 1.0045]
	Constant	−7.8794	/	/	/

assessed by the in-house software and those derived from the TPS are summarized in the Supplementary material. Importantly, CAC_Volume showed significant differences, being underestimated when using the TPS; much better agreement was found for Max_HU. However, when considering the patients at higher risk based on CAC_Volume (V > 0.5 cc), a threshold of > 0cc for the volume assessed via the TPS correctly classified the patients at risk with an accuracy of 94.4 %.

Discussion

Evidence that CAC are major predictors of cardiac toxicity after breast cancer RT (and are associated with reduced survival) has emerged from several investigations on modern cohorts with sufficiently long follow-up [19–23,26]. Roos et al [19] first reported results concerning acute coronary events (ACA) in a cohort of 939 patients with median follow-up of 7.5 years and a cumulative incidence of 3.2 %; risk of ACA was significantly higher in patients with intermediate-high AS compared to those with zero-low AS, with a reported Hazard Ratio (HR) of 5, after adjusting for other clinical predictors. More recently, van Velzen et al [22] analyzed the impact of coronary artery calcifications on heart disease (HD), defined as patient hospitalization due to cardiac problems (based on national registry data). They reported a cumulative incidence of 7.2 % in a population of 1871 patients with a median follow-up of 8 years. The authors retrieved cardiac dosimetry metrics including MHD and other parameters for the whole heart and various substructures, such as the left ventricle (LV) and the left anterior descending coronary artery (LAD), recently suggested as potential predictors of cardiac toxicity [26,28,36,37]. They found that the presence of CAC detected by a previously validated AI-based tool [38] was the strongest predictor of HD. They also found no interaction between CAC and cardiac dosimetry parameters, with an association between MHD and HD observed only in patients without CAC, with HR = 1.11. Similar findings were found when replacing MHD with the mean dose of few substructures, including LAD. CAC severity, however, was not considered in that work. More recently, Refsgaard et al [23] investigated the potential interplay

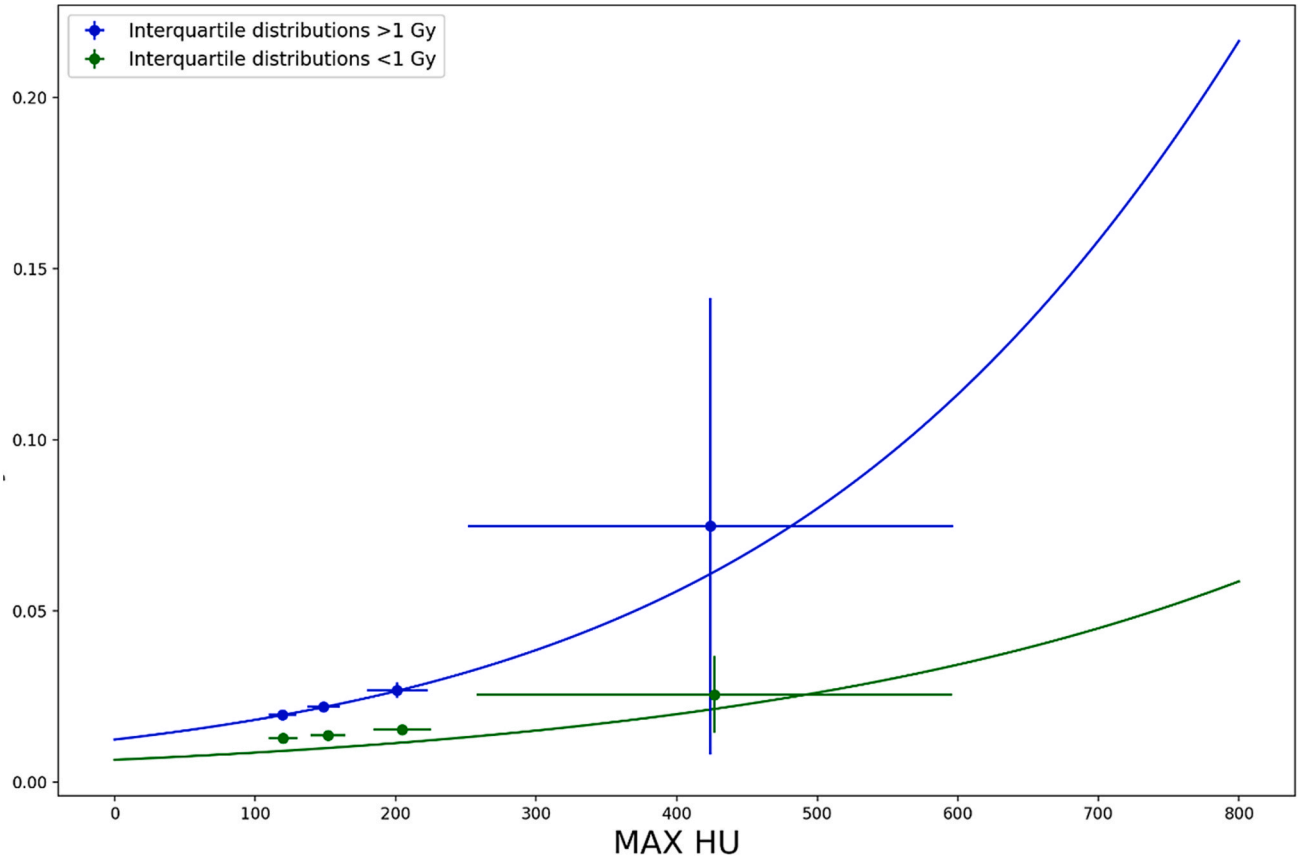

Fig. 1. Risk of late cardiac events against Max_HU in the heart for patients with mean heart dose (MHD) above or below 1 Gy (fixing the Age to the median value of the population: 62 years). Curves refer to the model's prediction while the points refer to the true incidence according to the quartiles of the cohort.

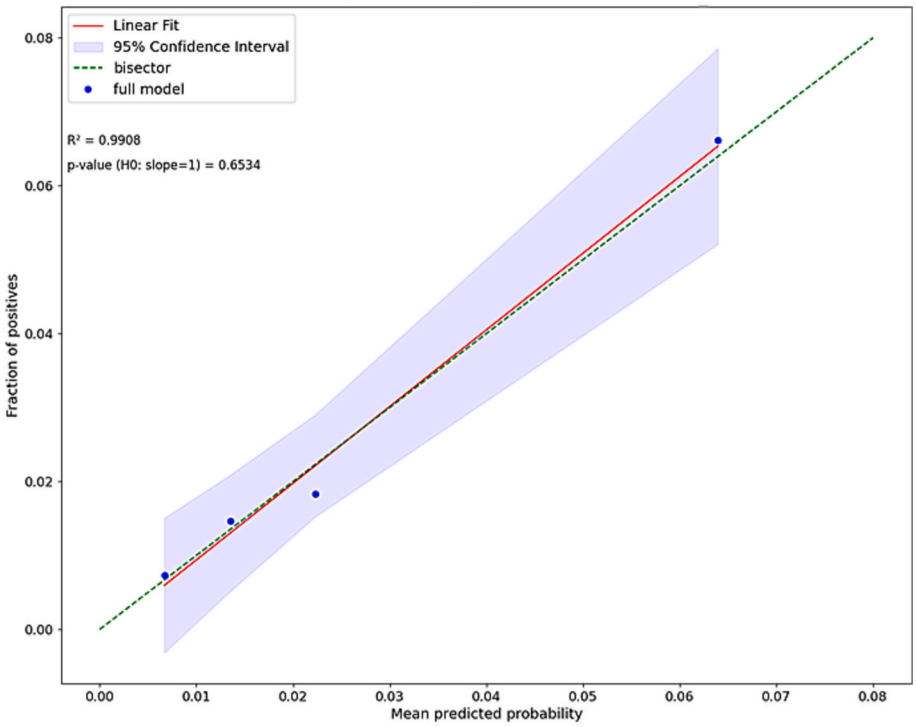

Fig. 2. Calibration plot of the model reported in Table 3, including Max_HU, MHD > 1 Gy and age.

between AS and MHD and other cardiac dosimetry predictors and the risk of CAD in 3315 node-positive patients treated to the whole breast and to supraclavicular nodes, axilla, and with/without internal mammary nodes irradiation. With a median follow-up of 8.4 years, the rate of CAD —defined as death from CAD or CAD requiring surgical intervention, based on a national registry—was 1.2 %. Severe AS (≥100) emerged as the strongest predictor, with HRs ranging between 12 and 24 ($p < 0.01$), depending on the covariates included in the Cox model. MHD was also significant, with a relatively high HR (1.25, $p = 0.04$), although with a large confidence interval. When the impact of AS was not considered, the HR for MHD was 1.12, more in line with previous findings. Interestingly, MHD proved to be the best predictor for patients with low/zero AS, outperforming substructure-specific dosimetry predictors. These results were consistent with the reduced predictive value of MHD for cardiac risk in modern cohorts [15], and with the high segmentation uncertainty for LAD [39], which undermines the robustness of its dosimetry metrics.

Our investigation continues on the path toward a more complete understanding of the interplay between CAC and cardiac dosimetry, aiming to assess practical methodologies to improve the prediction of cardiac toxicity. Our choice to focus on a cohort of patients treated with 40 Gy/15fr to the whole breast responded to the need to extend current knowledge into the setting of moderate hypofractionation, specifically 40 Gy in 15 fractions. At the same time, we also addressed the most common clinical situation of whole breast only irradiation.

In addition, we explored surrogates of CAC severity that could readily be implemented in daily clinical practice. First, we considered only CAC within the heart, as delineated by an AI-based commercial tool (showing high agreement with manual contours). Second, alongside the AS, we tested more easily accessible CAC metrics: Max_HU and CAC volume. Results showed that both of these "easy" scores could serve as effective alternatives to AS.

Likely due to its limited range of variability, the impact of MHD could not be confirmed when considered as a continuous variable, neither in the whole and in the left breast cohorts. Consequently, the previously discussed results by Refsgaard et al [23] could not be fully replicated, also likely due to our smaller cohort. However, MHD > 1 Gy was found (together with age) to be independently associated with the risk of cardiac events with a relatively high odds ratio (OR), of approximately 3, representing in large part the impact of laterality. This result confirms that, despite the drastic reduction of heart dose in the last 10–15 years [12], its impact remains not negligible. On the other hand, the relatively small number of events translated into quite large CIs in the estimate of the OR. Then, our results regarding the impact of MHD > 1 would benefit from other confirmations. Very importantly, our results suggest that left breast patients with severe CAC score (i.e: volume > 0.5–1.0 cc or Max_HU > 250) may derive the largest benefit from further MHD reduction. Achieving reduced MHD values comparable to those typically observed for right-sided case could be considered a major goal for these high-risk patients. This finding could support prioritizing DIBH approaches for such patients, with strong cost-benefit advantages.

The systematic difference observed in CAC volume quantification between the dedicated in-house script and our clinical TPS highlights a critical limitation regarding the reliability of assessing small calcification volumes. However, the results also show that for higher risk patients —those with CAC volumes > 0.5 cc—the > 0cc threshold seems to be effective when using the TPS.

Uncertainty in calculating AS (and CAC volumes) is well documented [25,40,41], as well as the variability of the methods implemented in the TPS to calculate volumes, leading to not negligible differences in case of small volumes mostly depending on how TPSs manage the end slices [42]. Nevertheless, our findings suggest that, despite this uncertainty, the clinical impact in identifying patients at risk should be minimal as the high-risk patients present with "massive", highly visible, CAC. Max_HU seems to be a more reproducible and practical metric, which could immediately be implemented in clinical practice, based on values extracted directly from the TPS.

More in general, comparison between the few studies dealing with the topic (i.e., CAC and heart dose) is challenging, partly due to differences in end-point definitions and methods of event collection. A limitation of our study in this context is the mixed prospective/retrospective retrieval of information, which may have missed several events. As is known, the collection of cardiac events is difficult, due to the long

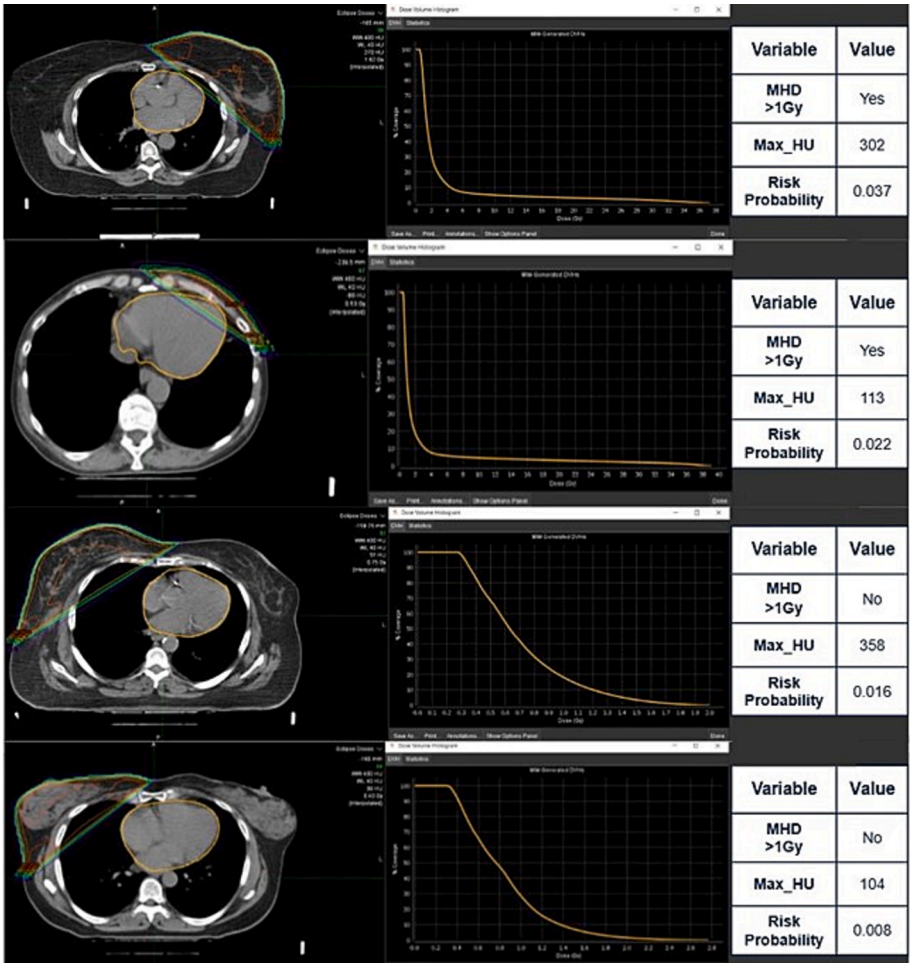

Fig. 3. As an example, four patients with different cardiac risk and the same age (median value for the population, 62 years) are shown including the dose distribution on planning CT, heart DVH and the Max_HU value.

follow-up: notably, even the use of registries is not free from the risk of under-reporting [22]. However, it is important to underline that, despite these differences and uncertainties, results from different groups have been largely consistent. A multi-centric prospective trial currently in progress [43] is expected to confirm this evidence, making the assessment of CAC scores as a routine practice using the planning CT scan. Another limitation of the study dealt with the exploration of the dose received by cardiac sub-structures as well as the lack of information concerning the spatial location of CAC. Current study is part of the EU-funded project TETRIS [44]: within this project, we planned to perform these analyses merging our data with three other large cohorts, for a total of > 4000 patients. This future work promises to better enlighten the possible interplay between CAC and spatial patterns of dose. On the other hand, as previously said, the uncertainty in segmenting cardiac sub-structures (especially the LAD) is still an issue and is likely a major cause of the controversial results reported in the literature.

The importance of assessing patients' cardiac risk class is well recognized, as recently highlighted in the ESC cardio-oncology guidelines [19]: specifically, improved understanding of dose-volume effects and the development of toxicity risk prediction tools—combining treatment- and patient-related factors—are recognized as major research priorities in the field of cardio-oncology. Although most patients today fall within a relatively low-risk category due to limited heart irradiation, the absolute number of breast cancer patients treated with RT worldwide makes the issue highly significant. Importantly, beyond enabling refinement of planning and delivery approaches, the *a priori* assessment of patients at risk is essential for personalizing follow-up programs—ideally through close collaboration between radiation oncologists and cardiologists—to help prevent and identify early signs of cardiac diseases.

Conclusions

CAC scores extracted from planning CT were the strongest predictors of cardiotoxicity after breast RT in a large, modern, cohort of patients treated to the whole breast with 40 Gy/15fr. Despite the relatively low MHDs, a residual interaction between CAC scores and MHD was found. These findings suggest that left-sided breast patients with Max_HU > 200–250 and/or CAC_volume > 0.5–1.0 cc may benefit more from further heart dose reduction, likely through the use of DIBH. Care should be regarded in assessing CAC volumes using TPS, due to their small values. On the other hand, Max_HU should be considered a robust parameter even when assessed by the TPS.

CRediT authorship contribution statement

Alfonso Belardo: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Kerby Bjorn Dimayuga:** Writing – original draft, Software, Methodology, Investigation, Formal analysis, Data curation. **Lucia Perna:** Writing – review & editing, Supervision, Methodology, Data curation, Conceptualization. **Andrei Fodor:** Writing – review & editing, Validation, Supervision, Investigation, Data curation. **Laura Giannini:** Writing – review & editing, Data curation. **Paola Mangili:** Writing – review & editing, Validation, Supervision, Data

curation. **Gabriele Palazzo:** Software, Methodology, Formal analysis, Data curation. **Marcella Pasetti:** Writing – review & editing, Supervision, Data curation. **Miriam Torrisi:** Writing – review & editing, Data curation. **Roberta Tummineri:** Writing – review & editing, Data curation. **Antonella Del Vecchio:** Writing – review & editing, Validation, Supervision. **Nadia Gisella Di Muzio:** Writing – original draft. **Claudio Fiorino:** Writing – original draft, Supervision, Resources, Methodology, Investigation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2025.111098.

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