Heart sparing radiotherapy in breast cancer: the importance of baseline cardiac risks

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Abstract

Background

Patients with left-sided breast cancer have an increased risk of developing cardiovascular disease (CVD) after radiotherapy (RT). While the awareness of cardiac toxicity through irradiation has increased enormously over the last decade, the role of individual baseline cardiac risks has not been systematically investigated. Aim of the present study was to evaluate the impact of baseline CVD risks on radiation-induced cardiac toxicity.

Methods

210 patients with left-sided breast cancer treated in the prospective Save-Heart Study using a modern heart sparing technique (deep inspiration breath-hold, DIBH), were analysed regarding baseline risk factors for CVD. Three frequently used prediction tools (Procam, Framingham and Reynolds score) were applied to evaluate the individual CVD risk profiles. Moreover, 10-year CVD excess absolute risks (EAR) were estimated using the individual mean heart dose (MHD) of treatment plans in free breathing and DIBH.

Results

Overall, a large number of the 200 non-diabetic patients had a very low 10-year CVD baseline risk of ≤1% according to all three prediction tools. However, 8-9% of patients reached higher risk scores of ≥10% baseline 10-year CVD risk. The mean baseline risks for the non-diabetic cohort ranged from 3.11% (±5.14%, Procam score), 3.39% (±3.67%, Framingham score) to 3.58% (±4.70%, Reynolds score). The mean 10-year cumulative risk following RT was 3.41% (± 5.66%) using the heart sparing DIBH technique (mean heart dose 1.42 Gy ±0.60 and 3.61% (± 6.06%) in free breathing (mean heart dose 2.33Gy ± 1.17, Procam score). This corresponds to a mean radiation-induced EAR of +0.30% (±0.55%) in DIBH and +0.50% (±1.02%) in free breathing (Procam score). The 10 diabetic patients had higher baseline CVD risks (11.76% ±12.43% Procam score, 24.23% ±14.59% Framingham score, 10.66% ±9.46% Reynolds score). After taking into account DIBH irradiation, the mean 10-year cumulative risk scores rose to 13.28% ±13.84%, 27.60% ±16.93% and 12.13% ±10.70%, respectively. However, smoking status was one of the most important and modifiable baseline risk factors for CVD in the present study. After DIBH-RT, 182 non-smoking patients had a mean 10-year cumulative risk of 3.55% ±5.87% (3.20% ±5.23% baseline risk, 0.35% ±0.67% risk excess through RT) and 28 smokers a mean risk of 6.07% ±9.91% (5.60% ±9.17% baseline risk, 0.47% ±0.74 risk excess through RT, Procam score).

Conclusion

In the present study, three different clinically applicable CVD prediction tools were used, which all showed comparable results and can be easily integrated into daily clinical routine in radiation oncology. A systematic evaluation and screening could identify patients with high baseline CVD risk factors who may benefit from primary prevention through counselling or pharmacotherapy interventions. As shown in the present study, this could result in a much higher benefit as from heart-sparing irradiation techniques alone.

Background

Multimodal breast cancer therapies have evolved rapidly over the last decades and nowadays breast cancer patients represent one of the largest survivorship groups[2]. Minimizing therapeutic morbidity has therefore become a major topic of concern.

It is well known, that the risk of developing cardiovascular disease (CVD) is significantly higher in breast cancer patients treated with radiotherapy [1]. Especially in left-sided breast cancer, the dose to the heart is approximately two or three times higher than in right-sided breast cancer.[3] Frequently, the apex of the heart is close, or even within the radiation field, resulting in a maximum dose exposure of the heart of up to >20Gy.[4] Recently, the awareness of heart toxicity has increased enormously and new heart sparing irradiation techniques as (deep inspiration breath-hold (DIBH), prone position or intensity modulated radiotherapy (IMRT)) have been applied, to significantly reduce the heart dose and the risk of future cardiac events.[5]

Nevertheless, the role of individual baseline cardiac risks within this setting has not yet been systematically investigated in real-world cohorts. Pre-existing cardiac risk factors can further increase the risk of heart disease following radiotherapy.[6] These factors include age, history of hypertension or diabetes mellitus, elevated cholesterol levels, positive family history (myocardial infarction <60 years), smoking habits or individual sensitivity to late heart disease.[7,8] However, to date, very few studies have addressed the significance and influence of baseline cardiac risk factors prior to radiotherapy in breast cancer.[9–12] The ground-breaking case-control study of Darby et al.[1] analysed the incidence of major coronary events (myocardial infarction, coronary revascularization, or death from ischemic heart disease) in 2168 women who underwent radiotherapy for breast cancer between 1958 and 2001. The MHD using elderly techniques was 6.6 Gy in left-sided BC, which was significantly higher than using modern DIBH techniques. Darby calculated a linear increase of the relative cardiovascular risk (excess relative risk, ERR) of 7.4% per Gray mean heart dose (95% confidence interval, 2.9 to 14.5; P<0.001) for the entire cohort. This fact gained wide public attention and was the beginning of the heart sparing area in modern breast radiotherapy. While the most radiation oncologists are aware of the rule of thumb of 7.4% per Gray ERR, there were further interesting details regarding cardiac risk factors in the study, which have not received comparable attention. Women without a history of ischemic heart disease and the presence of one or more cardiac risk factors at the time of BC diagnosis (e.g. current smoker, high body-mass index, diabetes, chronic obstructive pulmonary disease) had a significantly elevated rate ratio for major coronary events of 2.60 (95% CI, 1.89 to 3.57 during the first 10 years). After taking into account dose exposure to the heart, the relative percentage increase in the rate of major coronary events per Gray was similar for women with and those without cardiac risk factors, leaving the baseline cardiac risks as the most important predictor for absolute 10-year CVD risks.

Aim of the present study was to systematically evaluate cardiovascular risk factors and their influence on cardiovascular risk estimates in a cohort of left-sided breast cancer treated with modern radiotherapy techniques using a DIBH technique in clinical practice.

Methods

All patients were enrolled in the prospective Save-Heart study for deep-inspiration breath hold (DIBH) in patients with left-sided breast cancer. The study was approved by the ethical committee of the LMU

medical faculty (13.09.2016, No. 355-16) and registered in the German Clinical Trials Register (DRKS-ID: DRKS00011213). Inclusion criteria were informed consent, left-sided breast cancer or carcinoma in-situ and patient compliance for DIBH (ability of breath-hold for 20 seconds).[14]

From October 2016 to January 2019, a total of 352 patients were enrolled in the present study and gave informed consent. An individual cardiovascular risk profile assessment was performed for all eligible patients. For this purpose, a specific questionnaire was elaborated to record all baseline cardiovascular risk factors. The evaluated parameters included smoking behaviour, history of diabetes mellitus, antihypertensive therapy and family history of cardiovascular disease. If available, CRP and cholesterol levels (LDL, HDL, triglycerides) were reported. Patients with prior cardiac events were excluded from this analysis. All patients were treated using surface-guided DIBH as described elsewhere.[15]

Patients with diabetes mellitus were analysed separately, as cardiovascular risk prediction is more challenging in patients with diabetes. Most CVD risk prediction tools were developed in the general population and are likely to underestimate the cardiovascular risk in patients with diabetes.[16] Nevertheless, diabetes-specific risk scores were used to estimate cardiovascular risks in individuals with diabetes.

For the analysis of the baseline cardiac risk scores, three different clinically used risk scores were applied: the Procam Score, the Framingham Score and the Reynolds Score. Various risk scores for the assessment of cardiovascular risks were used, to compare the results and evaluate their complementary or additive value in risk estimation in clinical practice.

The Procam score calculates the risk of major coronary events (sudden cardiac death or myocardial infarction) over the next 10 years, based on cholesterol levels (HDL, LDL and Triglycerides), gender, age, systolic blood pressure, smoking habits, family history and diabetes.[17] The Procam coronary risk score was derived from data of the Prospective Cardiovascular Münster (PROCAM) study in Germany, using data from 18460 men and 8515 women who were recruited from 1978 to 1995 and had a mean follow-up period of 12 ±6 years. In the Save-Heart study, the Procam score was routinely applied to assess cardiovascular risks. Each patient with an estimated risk of >10% was informed and counselled regarding primary prevention.

The Framingham score estimates the 10-year risk of any cardiovascular event (coronary heart disease, cardiovascular disease, cerebrovascular events, peripheral artery disease and heart failure). The score was developed based on findings from the longitudinal Framingham Heart Study on residents of the city of Framingham, Massachusetts USA since 1948. It takes into account the following parameters: gender, age, smoking habit, diabetes, total cholesterol, HDL cholesterol, systolic blood pressure and antihypertensive medication. [18]

Similarly, the Reynolds score predicts the 10-year risk of cardiovascular events (myocardial infarction, ischemic stroke, coronary revascularization, and cardiovascular death). The Reynolds Risk Score for women was developed and validated using data from 24558 initially healthy American women who were followed over a 10-year period. The score uses the variables: gender, age, smoking habit, diabetes, systolic blood pressure, total cholesterol, HDL cholesterol, (hs)CRP and family. [19]

For each patient, all three risk scores were used to estimate the individual baseline cardiovascular risk before radiotherapy. Univariate ANOVA with repeated measures was used for differences between

the three risk scores. Correction of Holms-Bonferroni regarding multiple testing was applied. For continuous data the Wilcoxon Signed-Rank test was used for paired samples and the Mann-Whitney U-test for independent samples. Significance level of p = 0.05 was applied for all statistical analyses. For calculation of the 10-year CVD excess absolute risk (EAR), the relative increase of baseline risks after radiotherapy was calculated using the mean heart dose (MHD) according to Darby et al.[1] This calculation assumes a linear increase of the relative cardiovascular risk (excess relative risk, ERR) of 7.4% per Gray mean heart dose. The MHD was derived from DVHs of treatment plans in free breathing and DIBH. Thereafter, the impact of radiotherapy was analysed using the baseline risk of all scores to define the absolute 10-year risk for cardiovascular events after radiotherapy as follows:

$$Cumulative\ risk = baseline\ risk + EAR$$

$$EAR = ERR * baseline risk = MCD * \delta_{Darby} * baseline risk;\ (\delta_{Darby} = 0.074 Gy^{-1})$$

Results

After exclusion of patients with a history of CVD events, the individual cardiovascular baseline risk scores of 200 non-diabetic and 10 diabetic breast cancer patients were calculated based on individual cardiovascular risk factors. An overview of the evaluated cardiovascular risk factors is given in Table 1. Overall, a large number of patients was estimated to have a very low 10-year CVD baseline risk of ≤1% according to all three prediction tools: 45% using the Procam score (90/200 patients), 46% using the Framingham score (92/200 patients) and 48% as predicted by the Reynolds score (96/200 patients) (Table 2). In contrast, only 8-9% of the non-diabetic patients reached high risk scores of ≥10% baseline 10-year CVD risk. The mean risks of the non-diabetic cohort ranged from 3.11% (±5.14%, Procam score), 3.39% (±3.67%, Framingham score) to 3.58% (±4.70%, Reynolds score).

The same analysis was performed for the 10 diabetic patients included in the present analysis (Table 2). These patients had significantly higher baseline CVD risks (11.76% ±12.43% Procam score, 24.23% ±14.59% Framingham score, 10.66% ±9.46% Reynolds score) as compared to non-diabetic patients (for each pair p<0.01). Only one diabetic patient had a calculated risk of ≤1% using the Procam and Reynolds CVD prediction, in contrast to the Framingham estimate (0 patients) (Table 2).

To estimate the impact of baseline CVD risk estimates on the absolute 10-year risk of cardiovascular events after heart-sparing DIBH-radiotherapy, the individual mean heart doses were taken into account. The mean absolute 10-year risk increase (EAR) following DIBH-RT in non-diabetic patients was +0.30% (±0.55; with a maximum increase of +5.33%; Procam score), +0.34% (±0.42; with a maximum increase of +3.14%, Framingham score) and +0.37% (±0.56; with a maximum increase of +6.00%, Reynolds score) (Figure 1, Table 3). In other words, the absolute cumulative 10-year CVD risk rose to 3.41% (±5.66, Procam score), 3.73% (±4.04, Framingham score) and 3.95% (±5.22, Reynolds score). To give an order of magnitude, 18 of 200 patients evaluated with the Procam score had an absolute baseline risk of ≥10%, including 3 patients with a risk of ≥20% to encounter a sudden cardiac death or myocardial infarction in the 10 years following radiotherapy. After taking into account the radiation-induced risk increase through adjuvant DIBH-RT, two low-risk patients moved to this high risk group.

In the Save-Heart Study, all patients were irradiated using a heart-sparing DIBH technique. Nevertheless, for every study patient, an additional RT plan in free-breathing (FB) was calculated to analyse the dosimetric benefits of the DIBH-technique. This dual treatment planning allowed to

compare the cardiovascular risks of DIBH and FB (Figure 2). The ERR was 11% (±5) following DIBH-RT and 17% (±9) following FB-RT, corresponding to a relative cardiac risk increase of +64.7% for FB as compared to DIBH. The cumulative absolute 10-year CVD risks after left-sided breast irradiation are listed in Table 3.

Furthermore, the patient cohort was analysed with regard to their smoking habits and baseline risks using the Procam score (Figure 3). A total of 28 active smokers were identified in the entire cohort of 210 left-sided breast cancer patients. Regarding 10-year cumulative risk following DIBH-RT, smokers had a risk of 6.07% (5.60% baseline risk, +0.47% EAR), in contrast to 3.55% (3.20% baseline risk, +0.35% EAR) in non-smoking patients. If patients had been treated with a FB technique, smokers would have an estimated 10-year cumulative risk of 6.35% (5.60% baseline risk, +0.75% EAR), while non-smokers have a lower CVD risk of 3.75% (3.20% baseline risk, +0.55% EAR).

Discussion

In the last decade, the awareness of heart toxicity through irradiation of left-sided breast cancer has increased enormously. As a result, new heart sparing RT techniques have been introduced into clinical practice that can significantly reduce dose exposure of the heart in order to prevent cardiac morbidity. Nevertheless, the role of individual baseline cardiac risk factors has never been evaluated systematically within this context. There is only some evidence for single CVD risk factors, like smoking or hypertension. The retrospective study of Hooning et al.[11] found that a more than additive effect of smoking and cardiac radiation exposure leads to significantly increased rates of fatal myocardial infarction (HR= 3.04, 95%CI: 2.03-4.55 vs non-smokers without radiation) in patients treated with breast irradiation. Similarly, Harris et al.[12] found increased rates of coronary artery disease in patients receiving left-sided radiation that had a history of hypertension (HR=11.4, 95%CI: 5.0-26.2 vs no high blood pressure with right-sided radiation).

As reported in the present study, the main factors influencing 10-year CVD excess absolute risk (EAR) were the individual baseline risks of patients. In this cohort of 200 non-diabetic patients the mean baseline CVD risk ranged from 3.11% to 3.58%, depending on which risk estimation tool was used. Radiation exposure leads to an ERR of 11% following DIBH-RT and 17% following FB-RT. To give an order of magnitude, this corresponds to a mean 10-year EAR of 0.30%-0.37% in DIBH and 0.50%-0.60% in FB.

While the community is focusing on how to use modern RT techniques to minimize heart exposure, aim of the present study was to raise the awareness for baseline cardiac risk factors and their importance within this setting. The present study used different clinically applicable risk scores (Procam Score, Framingham Score and Reynolds Score), which all showed comparable results and can easily be integrated in daily clinical routine in radiation oncology. If we put all this effort in minimizing the radiation dose to the heart, a systematic evaluation and counselling regarding CVD risk factors appears feasible and could further impact cardiac burden. As shown in the present study, this could result in an even higher benefit as from heart-sparing irradiation techniques alone. Obviously, the authors are advocates of heart-sparing breast cancer radiotherapy techniques and recommend to routinely use them.

Smoking was one of the most important and modifiable risk factors for CVD in the present study. After estimating the baseline risks of the 28 smoking patients using the Procam score, the estimates

improved if the smoking status was set to non-smoking (5.60% vs 2.46%), which corresponds to a relative decrease of -56% (p<0.01). This effect was much more pronounced than the impact of the different radiotherapy techniques on 10-year cumulative risk (FB vs DIBH: 6.32% vs 6.05%, corresponding to a relative decrease of -4.3%). This fact is also known from several other studies, where smoking cessation significantly reduced the risk of myocardial infarction by about 65%.[20] Moreover, primary care research suggests, that simple counselling of the patient can help substantially increase smoking cessation rates.[21] Therefore, it seems advisable to make smoking cessation counselling a standard component of RT consultation, where all breast cancer patients should be screened for their smoking status, informed about the health benefits and supported with help in smoking cessation.[22]

Overall, patients with multiple cardiovascular risk factors, or patients with diabetes or metabolic syndrome are at high risk for subsequent CVD events. It is important to identify these patients prior to RT and develop a CVD risk reduction plan, accordingly. It will be necessary to educate these patients about the health benefits and importance of cardiac events prevention. Therapeutic lifestyle changes, like healthy nutrition, weight loss, smoking cessation and increased physical activity can significantly reduce cardiac toxicity after radiation exposure and the patient can actively contribute to this. In addition, adjunctive drug therapies like antihypertensive medication or statins may be appropriate measures regarding hypertension and dyslipidemia.[23,24] This detailed primary CVD prevention can be performed by the primary care providers, if elevated CVD risk scores are detected during RT screening. Moreover, young patients with multiple CVD risk factors (diabetes, hypertension, smoking) can still reach low cardiovascular risk score levels due to their young age. In these patients, it seems advisable to take preventive measures, especially if they have a good cancer prognosis. [14]

The different prediction tools were calibrated in different geographical regions and in diverse patient and population cohorts.[26] Nevertheless, our analysis showed that all three risk prediction tools report comparable results in non-diabetic patients. They showed a low individual variability and each of the scores seems feasible to assess the baseline cardiac risk of RT patients. The good news is, that the vast majority of non-diabetic patients presented with a low CVD baseline risk (45-48% had a 10-year risk ≤1%) and did not need any measures. However, 8-9% of the present 200 patient cohort did reach higher risk scores of >10% 10-year baseline CVD risk. In consequence, their relative increase through incidental heart irradiation reaches a higher absolute value. This subgroup of patients will benefit substantially from a heart-sparing irradiation technique.[14]

Patients with diabetes were analysed separately, as most CVD risk prediction tools were developed in the general population and are likely to underestimate the cardiovascular risk in patients with diabetes.[15] Usually, if diabetes is taken into account, patients are predicted with a significant 10-year risk for CVD (>10%). As shown in the present study, diabetes-specific risk estimates differed severely regarding the results of the different prediction tools, which shows the limitations of risk prediction in patients with diabetes. Both, the Procam and Reynolds scores seem to assess the cardiovascular risk similarly for diabetic patients, but the Framingham score differed widely. Indeed, the Framingham CVD model was poorly calibrated for the endpoint of major CVD, as it was developed for the broader endpoint of total CVD (coronary insufficiency, angina, peripheral artery disease, TIA).[25]

In conclusion, risk estimates of baseline cardiac risks should be included in clinical practice. In high risk patients, primary prevention with counselling or pharmacotherapy interventions could provide substantial immediate and long-term health benefits. Moreover, if these procedures are accompanied

by maximum cardiac protection during breast radiotherapy, cardiac morbidity could be substantially reduced. The approach to use clinically available risk prediction tools is a cost-effective intervention which can easily be adopted during routine patient care. It would be favourable in the near future, to include dose parameters of heart exposure to further individualize risk prediction. Nevertheless, such risk modelling calculators are not yet broadly available.[27] Key to successful implementation in clinical practice is the awareness of radiation oncologists on the importance of baseline CVD risks. It is important to minimize the burden for cardiac toxicity and radiation oncologists must come to see their role in promoting primary or secondary prevention within this setting.

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Table 1: Cardiovascular risk factors of 210 left-sided breast cancer patients. FB: free-breathing, DIBH: deep inspiration breath-hold

		Non-diabetic patients (n=200)		Diabetic patients (n=10)	
Age at diagnosis (years)	<40	16	(8.0%)	0	
	40-49	32	(16.0%)	2	(20%)
	50-59	73	(36.5%)	2	(20%)
	60-69	45	(22.5%)	5	(50%)
	70-79	33	(16.5%)	1	(10%)
	≥80	1	(0.5%)	0	
	Mean	*57*		*60*	
Smoking habit	positive	26	(13.0%)	2	(20%)
	negative	174	(87.0%)	8	(80%)
Family history	positive	27	(13.5%)	1	(10%)
	negative	173	(86.5%)	9	(90%)
LDL (mg/dL)	<100	37	(18.5%)	3	(30%)
	100-149	111	(55.5%)	6	(60%)
	150-199	43	(21.5%)	0	
	>200	9	(4.5%)	1	(10%)
	Mean	*130*		*115*	
HDL (mg/dL)	<50	20	(10%)	4	(40%)
	50-99	169	(84.5%)	6	(60%)
	>100	11	(5.5%)	0	
	Mean	*69*		*57*	
Triglycerides (mg/dL)	<50	5	(2.5%)	1	(10%)
	50-99	84	(42.0%)	2	(20%)
	100-149	62	(31.0%)	1	(10%)
	150-199	23	(11.5%)	1	(10%)
	200-249	19	(9.5%)	3	(30%)
	>250	7	(3.5%)	2	(20%)
	Mean	*122*		*171*	
Total Cholesterol (mg/dL)	100-149	3	(1.5%)	1	(10%)
	150-199	54	(27.0%)	5	(50%)
	200-249	97	(48.5%)	3	(30%)
	250-299	34	(17.0%)	1	(10%)
	>300	12	(6.0%)	0	
	Mean	*223*		*203*	
(hs)CRP (mg/dL)	<0.1	65	(32.5%)	2	(20%)
	0.1-0.5	115	(57.7%)	6	(60%)
	>0.5	20	(10.0%)	2	(20%)
	Mean	*0.23*		*0.55*	
Mean heart dose DIBH (Gy)	<1.0	37	(18.5%)	0	
	1.0-1.9	142	(71.0%)	6	(60%)
	2.0-4.9	20	(10.0%)	4	(40%)
	>5.0	1	(0.5%)	0	
	Mean	*1.42*		*1.85*	
Mean heart dose FB (Gy)	<1.0	10	(5.0%)	0	
	1.0-1.9	87	(43.5%)	1	(10%)
	2.0-4.9	97	(48.5%)	9	(90%)
	>5.0	6	(3.0%)	*0*	
	Mean	*2.33*		*2.86*	

Table 2: 10-year cardiovascular baseline risk scores of 210 left-sided breast cancer patients

10-year-CVD risk (%)	Non-Diabetic patients (n=200)		Diabetic patients (n=10)	
Procam Score				
≤1	90	(45%)	1	(10%)
1.1-4.9	76	(38%)	3	(30%)
5-9.9	16	(8%)	1	(10%)
10-19.9	15	(7.5%)	3	(30%)
>20	3	(1.5%)	2	(20%)
mean	*3.11*		*11.76*	
Framingham Score				
≤1	92	(46%)	0	
1.1-4.9	53	(26.5%)	1	(10%)
5-9.9	39	(19.5%)	2	(20%)
10-19.9	15	(7.5%)	2	(20%)
>20	1	(0.5%)	5	(50%)
mean	*3.39*		*24.23*	
Reynolds Score				
≤1	96	(48%)	1	(10%)
1.1-4.9	53	(26.5%)	4	(40%)
5-9.9	35	(17.5%)	0	
10-19.9	13	(6.5%)	3	(30%)
>20	3	(1.5%)	2	(20%)
mean	*3.58*		*10.66*	

Table 3: 10-year cardiovascular cumulative risk of 210 left-sided breast cancer patients following radiotherapy after taking into account an increase of 7.4% per Gy in mean heart dose of the individual treatment plans. FB: free-breathing, DIBH: deep inspiration breath-hold, EAR: excess absolute risk

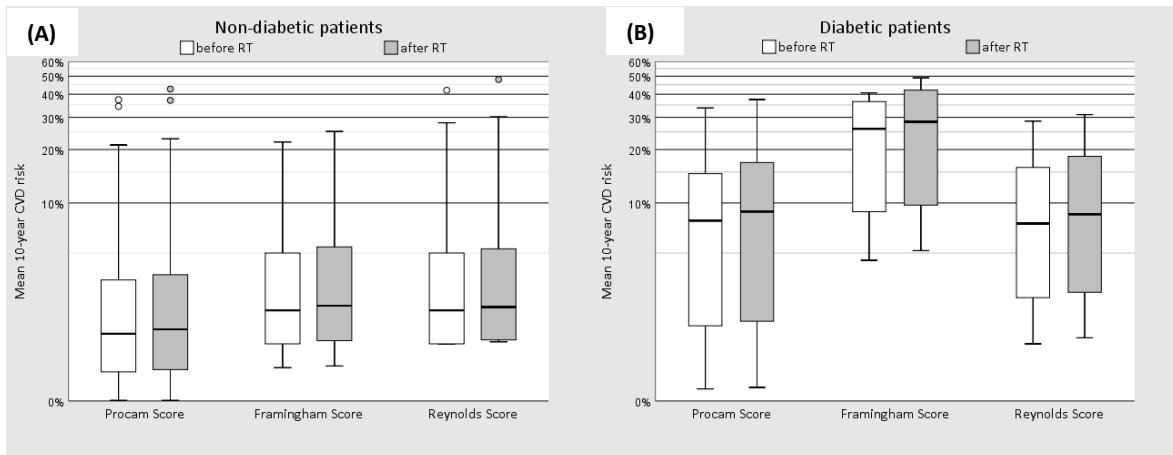|	Non-Diabetic patients (n=200)		Diabetic patients (n=10)		Entire cohort (n=210)	
	Following FB-RT	Following DIBH-RT	Following FB-RT	Following DIBH-RT	Following FB-RT	Following DIBH-RT
Procam Score						
Baseline risk	3.11 %		11.76 %		3.52%	
Mean EAR	+0.50 %	+0.30 %	+1.92 %	+1.52 %	+0.57 %	+0.36 %
Mean cumulative risk	3.61 %	3.41 %	13.68 %	13.28 %	4.09 %	3.88 %
Framingham Score						
Baseline risk	3.39 %		24.23 %		4.38 %	
Mean EAR	+0.55 %	+0.34 %	+4.64 %	+3.37 %	+0.75 %	+0.49 %
Mean cumulative risk	3.94 %	3.73 %	28.87 %	27.60 %	5.13 %	4.87 %
Reynolds Score						
Baseline risk	3.58 %		10.66 %		3.91 %	
Mean EAR	*+0.60 %*	*+0.37 %*	*+1.88 %*	*+1.47 %*	*+0.67 %*	*+0.42 %*
Mean cumulative risk	4.18 %	3.95 %	12.54 %	12.13 %	4.58 %	4.33 %

Figure 1: Mean 10-year baseline cardiovascular disease (CVD) risk of 200 non-diabetic patients (A) and 10 diabetic patients (B) as calculated by different risk estimation tools (white bars); and absolute mean 10-year cumulative CVD risk after left-sided breast radiotherapy in DIBH after taking into account a linear increase of 7.4% per Gy mean heart dose (grey bars).
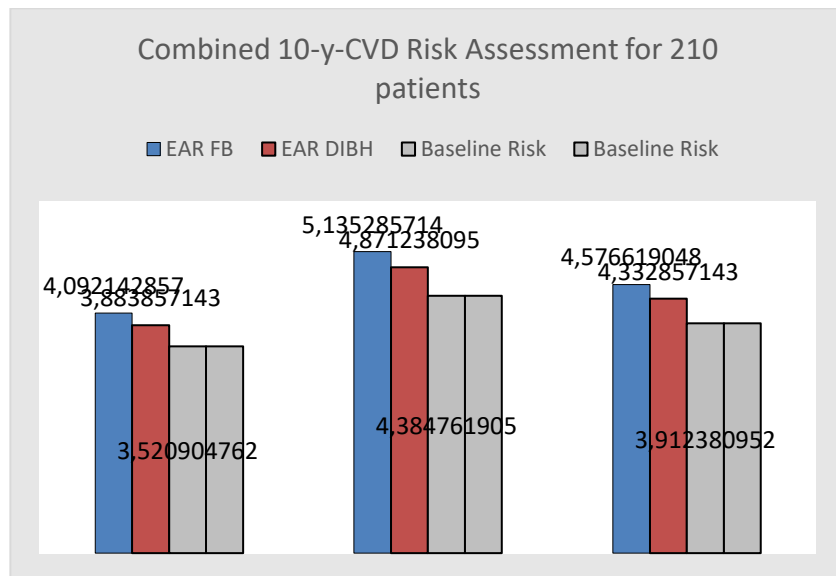

Figure 2: Absolute mean 10-year CVD risk of 210 patients after FB-/DIBH-RT as calculated by 3 different risk calculators. FB: free-breathing, DIBH: deep inspiration breath-hold, EAR: excess absolute risk
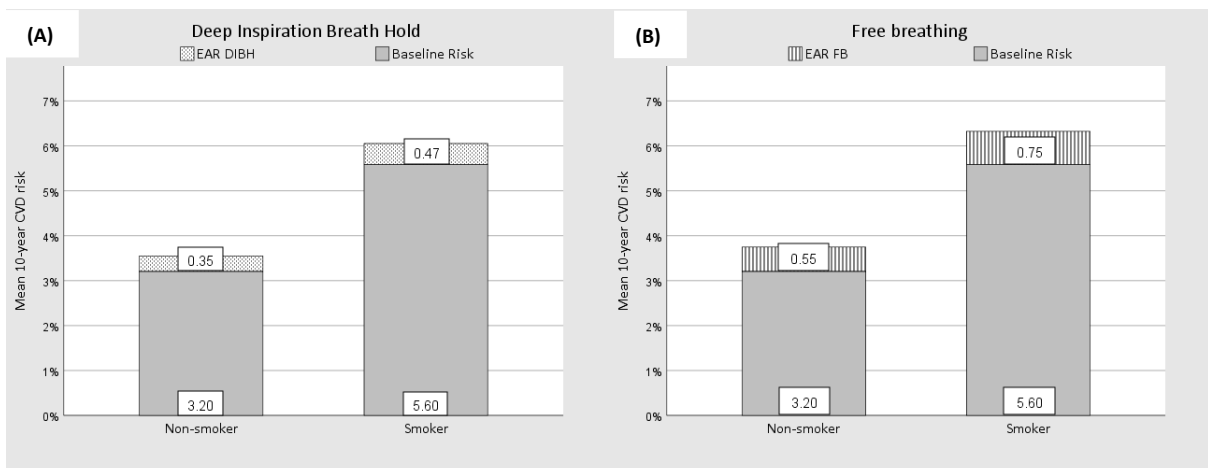

Figure 3: Mean 10-year CVD risk estimates of the entire cohort regarding their smoking habit (28 smokers, 182 non-smokers) after DIBH-RT (A) and FB-RT using Procam 10-year CVD risk score(B).