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CLINICAL INVESTIGATION

Breast Cancer Radiation Therapy and the Risk of Acute Coronary Events: Insights From a Process-Oriented Model

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Purpose: Acute coronary events (ACEs) are considered the most important side effect of radiation therapy (RT) for breast cancer, but underlying mechanisms still have to be identified. Process-oriented models mathematically describe the development of disease and provide a link between mechanisms and subsequent risk. Here, this link is exploited to learn about the underlying mechanisms from the observed age-time patterns of ACE risk.

Methods and Materials: A process-oriented model of atherosclerosis and subsequent ACEs was applied to a contemporary breast cancer cohort of 810 patients with measurements of coronary artery calcification. Patients with prior ischemic heart disease were excluded. The process-oriented model describes disease development as a series of different stages. Different variants of the model were fitted to the data. In each variant, one stage was assumed to be accelerated in relation to mean heart dose.

Results: During a mean follow-up of 9.1 years, 25 ACEs occurred. The model reproduced the prevalence and associated risk of coronary calcifications. Mean heart dose significantly improved the fit only when implemented as affecting a late stage of atherosclerosis on already-existing complicated lesions (achieving $P = .007$). This can be understood by atherosclerosis being a slowly progressing disease. Therefore, an increase in ACEs a few years after RT requires advanced atherosclerosis at the time of RT.

Conclusions: Risk of ACE increases within a few years in patients with advanced atherosclerosis at RT. Therefore, patients should be assessed for cardiovascular risk, and older patients need to be considered for heart-sparing techniques.

Introduction

Breast cancer is the most commonly diagnosed cancer worldwide.[1] In the European Union, about 1 in 11 women is affected by breast cancer before age 75.[2] Standard treatment involves radiation therapy (RT).[3] However, owing to the large case numbers and good overall survival of patients with breast cancer, late side effects of treatment become increasingly relevant. The most important late side effect of

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breast cancer RT is ischemic heart disease.[4] In the past decade, several biological pathways have been uncovered relating ionizing radiation to cardiac pathologies.[5-9] These include mitochondrial dysfunction, microvascular damage, fibrosis, inflammation, endothelial permeability, and loss of thromboresistance. However, it is unclear which are the main mechanisms that lead to increased risk. Research is complicated by the fact that depending on the dose received by different components of the cardiovascular system, different mechanisms may contribute. The present study aims for a better understanding of the mechanisms leading to acute coronary events (ACEs) after radiation exposure from breast cancer RT.

Atherosclerosis is a chronic, slowly evolving disease. Risk factors may accelerate disease related processes which may lead to an increased risk of ACEs after years or decades. Age-time patterns in risk are shaped by the way risk factors affect disease development. Recently, this relationship has been illustrated using a process oriented, mathematical model of atherosclerosis and subsequent myocardial infarction.[10,11] The model describes the incidence in the general population as a consequence of risk factors perturbing disease development.[11] Interestingly, when different model variants were implemented to describe how risk factors affect disease development, goodness-of-fit changed in support of biologically known mechanisms.[11]

In this study, we will follow the approach outlined previously. We will successively test in the process-oriented model different effects of RT on disease development and evaluate the corresponding model performance. By doing so, presumed effects of RT are tested for compatibility with the observed time pattern of risk.

In general, the time to an ACE may strongly depend on the extent of atherosclerosis present already before RT. In the model, this is considered by simulating a variety of different courses of disease development. Moreover, as a unique feature of the breast cancer cohort, some information on the individual extent of atherosclerosis is available. The presence of coronary artery calcification (CAC) is strongly associated with the risk for coronary events[12] and was determined from the planning CT-scans.[13]

Methods and Materials

Data of the patients with breast cancer

The study cohort is based on 910 patients with breast cancer treated in the period from 2005 to 2008 with postoperative RT after breast conserving surgery at the University Medical Center Groningen.[13] Patients with a history of other malignancies that required adjuvant treatment with systemic therapy or RT were not included. For each patient the mean heart dose (MHD) was acquired from the planning CT-scan, and the presence of coronary artery calcifications was noted, based on the Agatston score. For 70 patients, calcifications could not be assessed, and they were excluded. Moreover, 35 patients with a history of ischemic heart diseases were excluded for this modeling study, leaving 810 patients for analysis. Data was organized in a person-year table stratified for time since RT, age at RT (5-year categories), calcifications (positive/zero CAC score), and MHD (<1 Gy, 1-2 Gy, 2-4 Gy, 4-8 Gy, >8 Gy). The endpoint, ACEs, was defined by either myocardial infarction (International Classification of Diseases, 10th revision, codes 121-124), coronary revascularization, or death resulting from ischemic heart disease (codes 120-125) after completion of breast cancer RT. Written informed consent was obtained from the patients. For deceased patients, general practitioners were allowed to provide relevant information, because they have legal governance over deceased patients' records in the Netherlands. The aforementioned procedure was approved by the medical ethical committee of the University Medical Center Groningen. More details on the data acquisition can be found in van den Bogaard et al.[13]

Model of atherosclerosis and subsequent acute coronary events

For analysis of these data, we applied a derivative of the process-oriented model published in Simonetto et al.[10] In the model, coronary atherosclerosis is characterized by the coronary artery surface covered with fatty streaks, fibrous plaques, and complicated lesions. Lesion initiation is parameterized by rates ν_1 (fatty streaks), ν_2 (fibrous plaques) and ν_3 (complicated lesions), and lesion growth by γ_1, γ_2, and γ_3 (Fig. 1). Initiation and growth are proportional to the extent of lesions present. To reflect individual differences in susceptibility and unknown risk factors, growth parameters γ_K $(K = 1, 2, 3)$ were drawn from a random distribution. The extent of fatty streaks, fibrous plaques and complicated lesions is not known for the breast cancer cohort. Therefore, following previous studies,[10,11] model parameters were simultaneously adjusted to the breast cancer cohort and to some autopsy data.[14] The autopsy data provide age dependent extent and distribution of the aforementioned lesion types. Atherosclerosis is the main cause of coronary ischemia, and rupture, fissure, or erosion of complicated lesions may lead to myocardial infarction.[15,16] Plaque area is a strong predictor of infarction[17] and complicated lesions are supposed to be most closely related to the risk of wall ruptures and resulting thrombosis and infarction.[16] Consequently, in the model ACEs were assumed to follow complicated lesions, with some rate ν_h that connects the underlying biological processes to the hazard rate. In earlier applications of the process-oriented model[10,11] the endpoint was restricted to myocardial infarction. In the present study, it has been broadened to ACEs to increase the number of cases and to conform with earlier risk analysis in patients with breast cancer.[14,18]

Moreover, individual information on CAC was available in the breast cancer cohort and was thus included into the

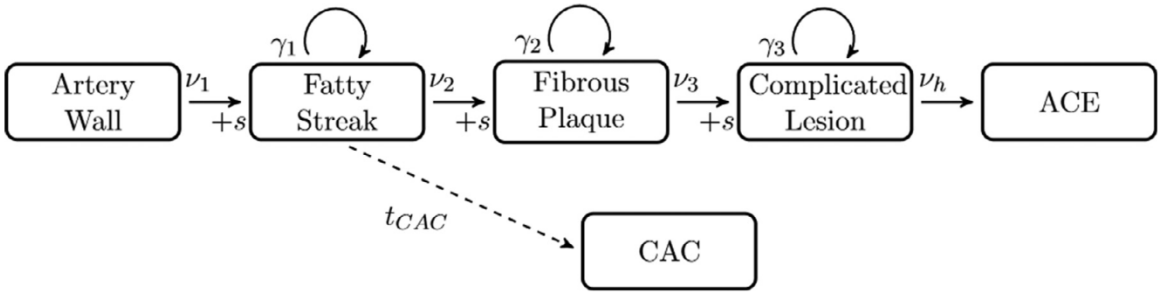

Fig. 1. Schematic representation of the applied process-oriented model. New fatty streaks (fibrous plaques and/or complicated lesions) develop stochastically with rate ν_1 (ν_2/ν_3) and initial size s, and subsequently grow with rate γ_1 (γ_2/γ_3). The risk of acute coronary events is proportional to the extent of complicated lesions. Coronary artery calcification (CAC) appears with some random latency t_{CAC} after fatty streak development. The number and size distribution of fatty streaks, fibrous plaques, and complicated lesions is fitted to data from the Pathobiological Determinants of Atherosclerosis in Youth Research Group,[26] the acute coronary event (ACE) rate, and the CAC prevalence to the data of the patients with breast cancer.

model. Calcifications are markers of atherosclerosis. Lipid cores of fibrous plaques almost always contain calcium particles, and eventually also lipid pools of earlier lesions.[19] Over years and decades, the initial particles of calcium increase in size and fuse. The amount of calcification greatly varies between individuals even when the lesions and their lipid cores look similar otherwise.[19] Calcified plaques tend to be stable and not to yield to infarction themselves.[20,21] However, calcification is associated with the extent of atherosclerotic lesions and therefore with risk. To reflect this knowledge in the model, CAC was assumed to arise from fatty streaks with a latency that varies between individuals. This is illustrated in Figure 1 by the dashed line.

For each stratum in the data defined by age at RT and MHD, the model was simulated more than 2,500,000 times, and this was repeated with varying parameters to obtain a good fit to the data. MHD was chosen as measure of dose for consistency with the bulk of epidemiologic literature. Midpoint values of the strata were applied for age and dose. Simulation and evaluation were performed with software adapted from.[10] More explanations on the model and the fitting procedure can be found in the Appendix E1.

Testing radiation effect on different disease stages

Disease development is accelerated by radiation therapy. In the model, this can be described by a radiation-dependent increase of some initiation or growth rate parameter. However, the main biological effect of radiation is unknown. Therefore, we tested multiple model variants, assuming the radiation effect on any possible disease stage. Each model variant implies a characteristic pattern in the age- and time-dependence of risk. This pattern may or may not be compatible with the observed incidence data. In this way, the incidence data are used to learn about the effect of incidental cardiac RT on atherosclerosis progression.

In each model variant, either a transition or growth rate was assumed to be affected by MHD. As transition parameters cannot be negative and growth rates could be in principle, different parameterizations were chosen. The dependence of an initiation rate ν_K ($K = 1, 2, 3, h$) on MHD d was modeled by

$$\nu_K(d) = \nu_K(0)\ exp(\beta\ d) \quad (1)$$

while a growth rate γ_K ($K = 1, 2, 3$) was parameterized by

$$\gamma_K(d) = \gamma_K(0)\ (1 + \beta\ d) \quad (2)$$

Here, $\nu_K(0)$ and $\gamma_K(0)$ denote the value before radiation therapy, $\nu_K(d)$ and $\gamma_K(d)$ the value thereafter, and β some linear coefficient. For each of the model variants, 2 extreme scenarios were implemented to allow for a different time dependence after RT. In the first scenario, the dose dependent parameter was only applied to the age at RT, that is, for 1 year. In the second, the parameter was assumed to be altered at the age at RT and kept constant at the new value thereafter. These 2 extreme scenarios may reflect acute changes on the one side, and chronic conditions or persistent tissue alterations on the other side. Each model variant was compared with a model without any radiation effect based on the likelihood ratio test. A 95% confidence level was considered for statistical significance.

Results

During a mean follow-up of 9.1 years, a total of 25 ACEs occurred. Patient characteristics are shown in Table 1. As a reference, the model was first applied without considering RT dose. The resulting modeled age-dependent prevalence of calcifications, ACE risk, and the hazard ratio associated with calcifications are shown in Figure 2. The model adequately described the data.

Next, it was systematically evaluated how best to include MHD into the model. For each parameter, an acute (1-year) and a persistent association to MHD was tested. Table 2 shows the results of likelihood ratio tests compared with the reference model. When MHD was related in any way to some parameter governing the first 2 modeled stages of

Table 1 Characteristics of the study cohort

Characteristic	Person years	Cases
Age at radiation therapy, y		
25-34	104	1
35-44	896	0
45-54	2097	2
55-64	2448	3
65-74	1556	16
75-84	277	3
Time since radiation therapy, y		
<5	3947	10
5-9	2857	12
10-14	574	3
Cardiac calcification		
No	5934	11
Yes	1444	14
Mean heart dose, Gy		
0-1	840	3
1-2	2515	6
2-4	1907	4
4-8	1883	9
8-16	234	3

atherosclerosis, that is, fatty streaks and fibrous plaques, the lowest P value achievable was .24. In contrast, parameters of the last modeled stage, complicated lesions, were significantly associated with MHD. For a persistent increase of ν_3, the initiation rate of complicated lesions, the P value was .02. In this model variant, the parameter ν_3 was increased by 1.42 (95% confidence interval [CI], 1.11-2.1) per Gy of MHD. A persistent increase of ν_3 means an accelerated transition from fibrous plaques to complicated lesions. This steadily increases the extent of complicated lesions and therefore increases ACE risk. Assuming ν_3 to be increased only for 1 year after RT, a somewhat lower significance was obtained (P = .04). The best estimate of this increase was 2.0 (95% CI, 1.2-3.9) per Gy. The same as before, this leads to a steady increase of ACE risk but only during a single year. Finally, the best fit was obtained for a model variant with persistent increase of the rate ν_h for complicated lesions to develop an ACE (P = .007). In this model variant, ν_h increased by a factor of 1.26 (95% CI, 1.06-1.49) per Gy of MHD. An increase of ν_h does not affect the lesion extents in the model but increases ACE risk.

The related modeled hazard ratios are presented in Figure 3 for 1 Gy MHD. The left panel shows the dependence on age at RT. For all 3 model variants, hazard ratios decreased with the age at RT. With higher age, the average extent of complicated lesions increases. Additional RT-induced complicated lesions thus have a smaller relative effect. This explains the decrease for the models with a radiation effect on ν_3. The decrease in models with radiation

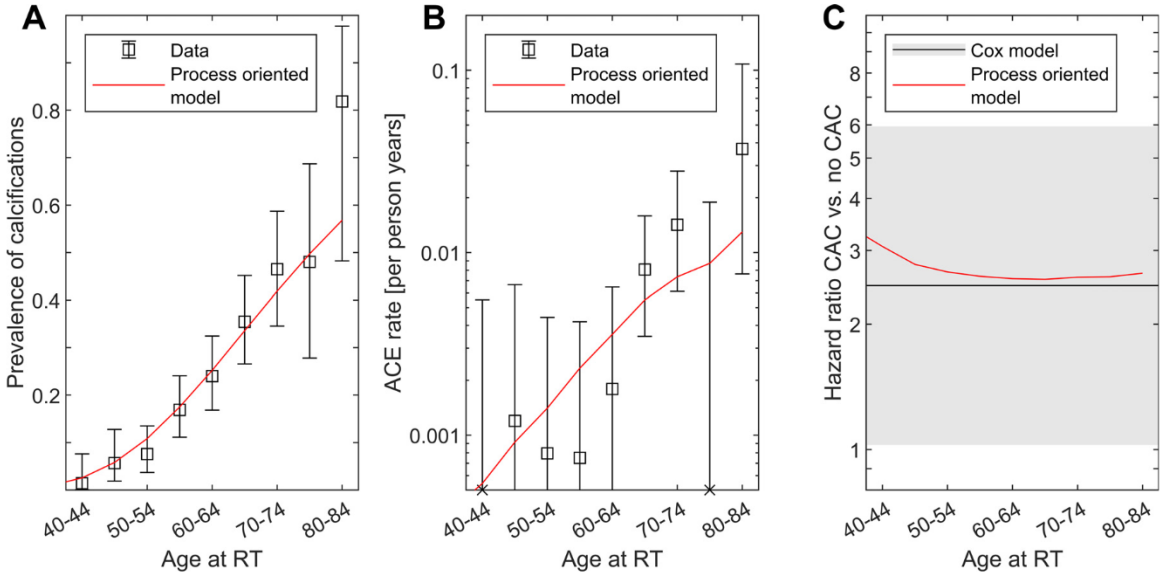

Fig. 2. Conformance of the process-oriented model to the data of the patients with breast cancer without considering radiation therapy (RT) dose. (A) Prevalence of coronary artery calcifications at the age of RT. (B) Rate of acute coronary events (ACEs). (C) ACE hazard ratio comparing patients with coronary artery calcifications (CAC) to patients without. In all panels, the red line corresponds to the model fit, black boxes to the data, and error bars to uncertainty at the 95% confidence level. In (C), the black horizontal line and the shading refer to the best estimate and 95% confidence interval from a Cox model based on age, time since radiation therapy, dose, and CAC. In the Cox model, hazard ratios are assumed constant. In contrast, the hazard ratio of CAC increases for young ages in the process-oriented model.

Table 2 ***P* values for model variants testing the effect of mean heart dose on different parameters in the model**

	ν_1 (fatty streak initiation)	γ_1 (fatty streak growth)	ν_2 (fibrous plaque initiation)	γ_2 (fibrous plaque growth)	ν_3 (complicated lesion initiation)	γ_3 (complicated lesion growth)	ν_h (incidence)
Persistent	.4	.2	.5	.4	.02*	.07	.007*
Acute	>.5	.3	>.5	.5	.04*	.2	.3

First, the model was fitted with dose-independent parameters. Next, dose dependence was included in a single parameter, and the *P* value for model improvement was calculated by the likelihood-ratio test. For each parameter, a persistent alteration after radiation therapy was tested, as well as an acute alteration, that is, a change of the parameter for 1 year before going back to the baseline value. The meaning of the parameters is illustrated in Figure 1.

Abbreviations: ACE = acute coronary events; CAC = coronary artery calcification; MHD = mean heart dose; RT = radiation therapy.

* Significant improvements.

effect in ν_h is minor. The reason for this decrease is that events occur predominantly in patients with severe atherosclerosis, thus gradually selecting high-risk patients out. This selection effect is stronger in patient groups with higher risk: those with higher dose and higher age. Therefore, the hazard ratio 5 years after RT is reduced, and this reduction increases with age. As shown in the other panels, dependence of the hazard ratio on time since RT was different between model variants: In the model variant with persistently increased ν_3, the hazard ratio increased continuously during the first decade after RT as the model predicted a steady increase of complicated lesions. In the other model variants, there was an instantaneous increase of risk after RT, either immediately or within the first year. Thereafter, the hazard ratio declined in the model with persistently increased ν_h. The reason is the same selection effect explained previously. For the model variant with an acute increase of ν_3, this effect competes with general growth of complicated lesions, and the dependence of the hazard ratio on time since RT varies with age. For all model variants, CAC had only minor effect on the hazard ratio.

Discussion

In this study, a relationship was observed between MHD and ACE risk after breast cancer RT, see Table 2. This confirms earlier findings in the same study cohort.[18] Compared with earlier studies, however, for this study only patients without history of ischemic heart disease were included. Therefore, our results show that the increase of ACE risk within the first decade after RT is not limited to patients with prior history of ischemic heart disease.

To infer about the underlying mechanism, the ACE incidence data was analyzed using a process-oriented model of atherosclerosis. The applied model describes atherosclerosis development and subsequent ACEs in a very simplified manner. Nevertheless, overall time spans should be

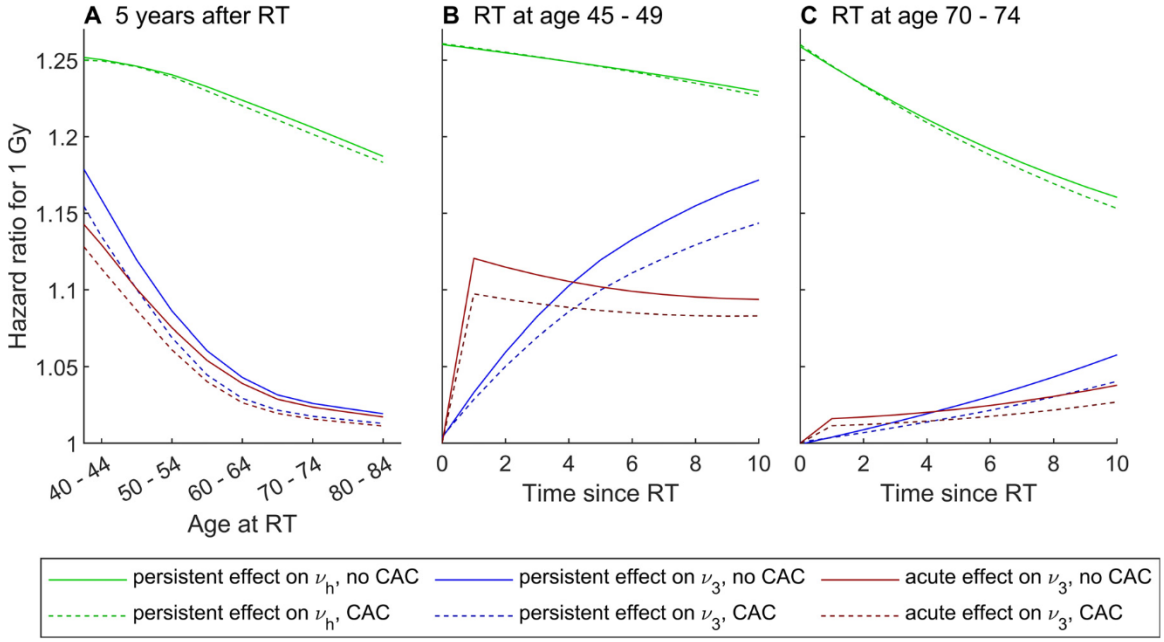

Fig. 3. Age and time dependence of the ACE hazard ratio according to the best model variants. In each model variant some parameter is altered after RT, either persistently or for 1 year (acute effect). *Abbreviations*: ACE = acute coronary event; CAC = coronary artery calcification; RT = radiation therapy.

faithfully reflected as the model was adjusted to autopsy data of atherosclerotic lesions. Moreover, model parameters relating to normal disease development were similar to previous results,[10,11] implying that overall model fits were robust. Due to the limited number of ACE cases, modeling of the radiation effect was limited to simple relationships involving a single parameter. The tested model variants may be regarded as extreme cases as they relate only to a single disease stage, and exhibit simplistic time dependence after RT. Nevertheless, the model variants coincide with respect to a minor effect of CAC on the relative radiation risk (Fig. 3). Positive CAC is thus related to high baseline[12] and thus high absolute RT risk. On the other hand, model variants differ in their predictions regarding age- and time dependence, and the true behavior may be intermediate.

Although it was not possible to discern between these different age and time dependencies, other model variants could be rejected. It turned out that RT effects on an early process of atherosclerosis did not yield an optimal description of the data, see the first 4 columns of Table 2. Instead, the model reveals the existence of a major effect of RT on established, complicated lesions. This can be understood as follows: Formation or destabilization of complicated lesions can have rapid effect on risk. In contrast, any potential perturbations of early processes would lead to alterations in risk only more than a decade later. As the present study is limited to about one decade after contemporary breast cancer RT, nothing can be concluded about potential radiation effects on early atherosclerotic stages.

In a recent study, risk was investigated in the subgroup of patients with calcification in the left anterior descending artery. In these selected patients, dose to the calcification turned out to be a better predictor of ACE than MHD or other dose metrics.[13] Given our model results, this observation can easily be interpreted: Calcifications themselves may not be causative for increased risk[20,21]; however, position of calcifications correlates with the local presence of atherosclerotic lesions. On average, a high dose to calcified areas thus means a high dose to established atherosclerotic lesions. According to our results, this is causative for an increased ACE risk during the first decade after RT. Biologically, this may be explained by high-dose radiation to predispose to an inflammatory, thrombotic plaque phenotype.[9]

An early increase of risk was also observed in a large study in Denmark and Sweden which included 963 cases and 1205 controls[17]: during the first 5 years after RT, risk was elevated with a linear excess relative risk of 16.3% (95% CI, 3.0%-64.3%)/Gy and for the next 5 years with 15.5% (2.5%-63.3%)/Gy. Similar values were found in the cohort used for the present analysis: excess risks for the first 5 and 9 years after RT of 24.6% (0.4%-49.5%)/Gy and 15.3% (0.6%-35.0%)/Gy.[18] The large case-control study provides information beyond 10 years after RT. Excess risks tended to be smaller, 1.2% (−2.2% to 8.5%)/Gy for the range 10 to 19 years after RT, and 8.2% (0.4%-26.6%)/Gy more than 20 years after exposure. In light of the present analysis, the increase of risk during the first 10 years may result from a radiation effect on a late stage of atherosclerosis such as complicated lesions. On the other hand, risk that occurs later may well be caused by biological effects on early stages of atherosclerosis.

No association with coronary artery disease within the first 10 years after RT was observed in a newly published study.[22] In fact, cardiac doses have been reduced significantly in the CT-based era for many patients, partly by the introduction of deep inspiration breath hold. Nevertheless, there will still be patients receiving higher cardiac doses, for example when the internal mammary nodes are included. In Milo et al,[22] no left-sided node positive patients were included who received RT to the internal mammary nodes as these fields were omitted between 2003 and 2014 to investigate their effect and to reduce heart dose. However, it was shown that RT including the internal mammary nodes is associated with an increased overall survival of 3.7% in right-sided patients compared with left-sided patients without these additional fields.[23]

Various mathematical models of atherosclerosis development exist describing different aspects on a lower level of biological organization.[24] This includes a study that provides a model-based estimate of the risk from low-dose radiation.[25] However, to the best of our knowledge, the applied model is the first combining observed age-dependent lesion extent with incidence data, and this study is the first applying a process-oriented model of atherosclerosis to radiation therapy. Compared with standard epidemiologic analysis, use of the process-oriented model has the advantage that the age-time patterns of risk are connected to the underlying biological processes. In the future, the process-oriented model may be refined as research on these processes is ongoing. Moreover, the model may be used to improve individual risk prediction. Effects of smoking, hypertension and dyslipidemia were already analyzed in the same model in Simonetto et al[11] and results may be combined with the radiation effect.

Conclusions

The time to an ACE may strongly depend on the extent of atherosclerosis present already before RT. Our results imply that RT on advanced atherosclerosis can result in ACE already within 5 to 10 years after radiation therapy. Therefore, we hypothesize that on average, patients with more cardiac risk factors are more prone to develop early onset radiation-induced ACE than patients with less cardiac risk factors. In other words, particularly in patients with advanced atherosclerosis, the risk of ACE may increase relatively shortly after commencing treatment. Therefore, we hypothesize that for patients with breast cancer and cardiac risk factors or preexisting atherosclerotic plaques as assessed on the planning-CT scan, the dose to these plaques should be reduced as much as possible. Cardiac risk should be assessed at baseline as part of a standard follow up program, or by a general practitioner to control atherosclerotic cardiac risk factors. Based on the limited follow-up time of the

present study, nothing can be concluded about RT induced late onset ACE which is mainly relevant for young patients. However, due to the strong increase of the extent of atherosclerosis with age and the relatively short time to an ACE, heart sparing is very important also for the elderly.

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