Radiotherapy and Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

# Does deep inspiration breath-hold prolong life? Individual risk estimates of ischaemic heart disease after breast cancer radiotherapy

Cristoforo Simonetto [a,*], Markus Eidemüller [a], Aurélie Gaasch [b], Montserrat Pazos [b], Stephan Schönecker [b], Daniel Reitz [b], Stefan Kääb [c,d], Michael Braun [e], Nadia Harbeck [f], Maximilian Niyazi [b], Claus Belka [b], Stefanie Corradini [b]

[a] Department of Radiation Sciences, Institute of Radiation Protection, Helmholtz Center Munich German Research Center for Environmental Health, 85764 Neuherberg; [b] Department of Radiation Oncology, University Hospital, LMU Munich; [c] Department of Medicine I, University Hospital, LMU Munich; [d] German Cardiovascular Research Centre (DZHK), Munich Heart Alliance; [e] Red Cross Breast Centre, Munich; and [f] Department of Obstetrics and Gynecology, Breast Centre, University Hospital, LMU Munich, Munich, Germany

ARTICLE INFO

*Article history:*
Received 3 April 2018
Received in revised form 13 July 2018
Accepted 23 July 2018
Available online xxxx

*Keywords:*
Breast cancer
3-D conformal radiotherapy
Deep inspiration breath-hold
Ischaemic heart disease
Risk model
Risk factors

ABSTRACT

*Purpose:* Aim of the current comparative modelling study was to estimate the individual radiation-induced risk for death of ischaemic heart disease (IHD) under free breathing (FB) and deep inspiration breath-hold (DIBH) in a real-world population.

*Materials and methods:* Eighty-nine patients with left-sided early breast cancer were enrolled in the prospective SAVE-HEART study. For each patient three-dimensional conformal treatment plans were created in FB and DIBH and corresponding radiation-induced risks of IHD mortality were estimated based on expected survival, individual IHD risk factors and the relative radiation-induced risk.

*Results:* With the use of DIBH, mean heart doses were reduced by 35% (interquartile range: 23–46%) as compared to FB. Mean expected years of life lost (YLL) due to radiation-induced IHD mortality were 0.11 years in FB, and 0.07 years in DIBH. YLL were remarkably independent of age at treatment in patients with a favourable tumour prognosis. DIBH led to more pronounced reductions in YLL in patients with high baseline risk (0.08 years for upper vs 0.02 years for lower quartile), with favourable tumour prognosis (0.05 years for patients without vs 0.02 years for those with lymph-node involvement), and in patients with high mean heart doses in FB (0.09 years for doses >3 Gy vs 0.02 years for doses <1.5 Gy).

*Conclusion:* Ideally, the DIBH technique should be offered to all patients with left-sided breast cancer. However, highest benefits are expected for patients with a favourable tumour prognosis, high mean heart dose or high baseline IHD risk, independent of their age.

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In the light of continuously improving long-term breast cancer (BC) survival rates [1], minimizing therapeutic morbidity has become a major topic of concern. The risk of heart disease mortality is significantly higher in women after radiotherapy as known from retrospective long-term follow-up data of randomized trials [2]. The results of a population-based case-control study of 2168 BC patients showed a linear correlation of the relative risk for major coronary events by 7.4% per Gray (Gy) increase in mean heart dose [3]. Furthermore, an analysis of standard tangential radiotherapy for left-sided breast cancer found that parts of the heart still receive significant radiation doses with three-dimensional conformal radiation techniques [4]. Therefore, decreasing the heart dose in BC patients is of fundamental importance.

As a result, advanced radiotherapy techniques, such as respiratory-gated radiotherapy using deep inspiration breath-hold (DIBH), have lately been introduced into clinical practice [5]. During DIBH the distance between the heart and the irradiated target volume (chest wall/breast) increases – which results in a

*Abbreviations:* BC, breast cancer; DIBH, deep inspiration breath-hold; FB, free breathing; IHD, ischaemic heart disease; RNI, regional nodal irradiation; YLL, expected years of life lost.

* Corresponding author at: Department of Radiation Sciences, Institute of Radiation Protection, Helmholtz Center Munich German Research Center for Environmental Health, Ingolstädter Landstraße 1, 85764 Neuherberg, Germany.

*E-mail addresses:* Cristoforo.Simonetto@helmholtz-muenchen.de (C. Simonetto), Markus.Eidemueller@helmholtz-muenchen.de (M. Eidemüller), Aurelie.Gaasch@med.uni-muenchen.de (A. Gaasch), Montserrat.Pazos@med.uni-muenchen.de (M. Pazos), Stephan.Schoenecker@med.uni-muenchen.de (S. Schönecker), Daniel.Reitz@med.uni-muenchen.de (D. Reitz), Stefan.Kaab@med.uni-muenchen.de (S. Kääb), Michael.Braun@swmbrk.de (M. Braun), Nadia.Harbeck@med.uni-muenchen.de (N. Harbeck), Maximilian.Niyazi@med.uni-muenchen.de (M. Niyazi), Claus.Belka@med.uni-muenchen.de (C. Belka), Stefanie.Corradini@med.uni-muenchen.de (S. Corradini).

https://doi.org/10.1016/j.radonc.2018.07.024
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significant reduction of cardiac dose exposure [6]. Even though, in some countries, DIBH is already routinely applied, it cannot be extensively used in most other countries. Thus, there is an important gap in the current evidence base. If the DIBH technique cannot be offered to all patients: which patients benefit most from DIBH?

Due to the slow progression of ischaemic heart disease, so far, no randomized studies have been able to quantify the clinical long-term benefit of the DIBH technique. Therefore, aim of the present comparative modelling study was to estimate individual risks of ischaemic heart disease (IHD) after BC radiotherapy in a real-world population. Individual cardiovascular risk factors, tumour stage, and age at treatment were used to estimate the impact of DIBH on lifetime risks for coronary heart disease mortality.

## Materials and methods

### *Patients*

The prospective SAVE-HEART study was performed in accordance with the Declaration of Helsinki and 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).

### *Treatment planning*

Every patient received two planning CT scans and treatment plans, one in free breathing (FB) and one in DIBH. Patients were immobilized in a supine position on a positioning device (WingSTEP®, IT-V, Austria), with both arms elevated above the head. The DIBH manoeuvre during CT simulation and treatment delivery was performed using the surface-based Catalyst™/Sentinel™ system as described elsewhere [6]. The system enables a continuous optical surface scanning with automated treatment delivery using an audio-visual patient feedback system. The gating window was set at the level of stable and reproducible deep inspiration breath-hold. The clinical target volume was delineated according to the RTOG contouring atlas [7] and ESTRO consensus guideline [1], the heart according to the CT-based atlas by Feng et al. [8]. Treatment planning was performed using the Oncentra 4.5.2 software (Elekta, AB, Stockholm). All plans consisted of two opposing tangential beams for the breast/chest wall with the addition of some subfields to increase dose homogeneity, as well as anterior/posterior fields for regional nodal irradiation (RNI). RNI included lymph node levels IV, III, Rotter lymph nodes and some parts of lymph node level II according to the ESTRO-guidelines [1]. A total dose of 50 Gy in 25 fractions was applied in cases of chest wall irradiation or RNI. Patients receiving breast radiotherapy without RNI were eligible to undergo hypofractionated radiotherapy with 40 Gy in 15 fractions.

### *Risk estimates*

Individual coronary heart disease mortality risks can be estimated by the SCORE prediction formula [9] of the European Society of Cardiology and were evaluated for "low-risk" European countries. Besides age ($a$), SCORE takes into account the following individual risk factors ($\boldsymbol{r}$): cholesterol level, systolic blood pressure and smoking. From this information, the individual baseline relative risk as compared to the general population was calculated as:

$$RR^{IHD}(e,\boldsymbol{r}) = \frac{h^{IHD}_{SCORE}(e,\boldsymbol{r})}{h^{IHD}_{pop}(e)} \tag{1}$$

Here, $h^{IHD}_{SCORE}(e,\boldsymbol{r})$ denotes the individual annual IHD mortality risk and corresponds to the negative derivative of the logarithm of the survival function as given in Eq. (3) of Ref. [9]. The baseline relative risk $RR^{IHD}$ was evaluated at the age of treatment ($e$) and was assumed to be independent of age. By this assumption, the typical age-dependent increase in risk due to worsening of risk factors is automatically taken into account. The rates of IHD for the general population, $h^{IHD}_{pop}$, were taken from Ref. [10] and interpolated within 5-year strata. It should be noted that $h^{IHD}_{SCORE}$ and $h^{IHD}_{pop}$ are derived from similar populations but there may be some residual deviation in their age dependency. For the radiation-induced risk, the results of Darby et al. [3] were applied, i.e. an excess relative risk of 7.4% per Gray mean heart dose $d$. Together with Eq. (1), the individual annual IHD mortality risk after radiation exposure was thus derived:

$$h^{IHD}(a,e,d,\boldsymbol{r}) = h^{IHD}_{pop}(a)RR^{IHD}(e,\boldsymbol{r})\left(1 + d\cdot 0.074\mathrm{Gy}^{-1}\right) \tag{2}$$

In order to calculate absolute risks, information on total survival is necessary. To estimate the total survival in BC patients, the survival of the general population $S_{pop}$ [11] was adjusted with the relative survival $RS$ of BC patients according to their TNM status [12]:

$$S(a,e,TNM) = \frac{S_{pop}(a)}{S_{pop}(e)}RS(TNM,a-e) \tag{3}$$

As data on relative survival were available only up to 15 years after radiotherapy, we extrapolated the relative survival thereafter, based on the relative reduction in relative survival within the five preceding years. To account for the individual contribution of IHD to the expected survival, the individual annual IHD mortality risk from Eq. (2) was applied:

$$S(a,e,TNM,d,\boldsymbol{r}) = S(a,e,TNM)\exp\left[\int_e^a -h^{IHD}(t,e,d,\boldsymbol{r}) + h^{IHD}_{pop}(t)\cdot\left(1+d_m\cdot 0.074\mathrm{Gy}^{-1}\right)dt\right] \tag{4}$$

The relative survival in BC patients results from many causes of death, some of which may be radiation-induced. Therefore, to compensate for the individually estimated contribution of IHD mortality $h^{IHD}(t,e,d,\boldsymbol{r})$, the average IHD mortality risk was added. It was approximated by the general population rate, $h^{IHD}_{pop}$, times a radiation dependent factor. We used $d_m = 2.5$ Gy, the average mean heart dose in the study cohort under FB. However, results are quite insensitive to this value: for example, mean years of life lost (see below) due to irradiation under FB would change by a factor of 1.03 if $d_m = 5$ Gy was assumed.

Using Eqs. (2), (4), absolute IHD mortality risks, $AR$, were calculated:

$$AR(a,e,TNM,d,\boldsymbol{r}) = \int_e^a h^{IHD}(t,e,d,\boldsymbol{r})S(t,e,TNM,d,\boldsymbol{r})dt \tag{5}$$

For $a = e + 10$ years, this corresponds to the often-encountered 10-year-risks; for $a = 80$ years, it corresponds to the cumulative risk until the age of 80. For lifetime risks $a = 100$ years was assumed. To calculate the excess risks due to radiation, the difference to $AR(a,e,TNM,d=0,\boldsymbol{r})$ was evaluated. Finally, years of life lost due to the detrimental effects of irradiation on IHD were calculated from Eq. (4):

$$YLL(e,TNM,d,\boldsymbol{r}) = \int_e^{100} S(t,e,TNM,0,\boldsymbol{r}) - S(t,e,TNM,d,\boldsymbol{r})dt \tag{6}$$

All analyses were performed with MATLAB, version R2017b. Integrals were approximated by sums. The Wilcoxon rank-sum test was applied to compare different groups if not stated otherwise.

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## Results

One hundred and seven consecutive patients with left-sided breast cancer were enrolled in the prospective SAVE-HEART study since November 2016, and were assessed for cardiovascular risk factors including cholesterol levels, blood pressure and smoking habits. For 18 patients, the SCORE prediction formula was not applicable (8 patients with diabetes, 8 younger than age 40, and 4 older than age 75) and they were excluded from the present analysis. Descriptive statistics on risk factors, tumour, and treatment characteristics in the remaining 89 patients are presented in Table 1. Application of the SCORE risk prediction formula revealed that the estimated annual IHD mortality risks were close to the general population rates on average but showed large individual variability (median of baseline relative risk $RR^{IHD}$: 1.0, range: 0.27–3.9). Moreover, there was a trend in the estimated relative risks with increasing age (mean $RR^{IHD}$ for patients below/above the age of 60 years was 1.0/1.5).

**Table 1**
Risk factors, tumour, and treatment characteristics of 89 breast cancer patients between ages 40 and 75. IQR: Interquartile range. RNI: Regional nodal irradiation.

| | |
|---|---|
| Treatment age [years] | Mean 57, range 42–73, median 57, IQR 51–62 |
| Total cholesterol [mg/dl] | Mean 223, range 137–321, median 222, IQR 198–247 |
| Systolic blood pressure [mmHg] | Mean 130, range 96–188, median 125, IQR 116–140 |
| Smoking | |
| Yes | 13 (15%) |
| No | 76 (85%) |
| Tumour size | |
| Tis (Carcinoma in situ) | 12 (13%) |
| T1 | 49 (55%) |
| T2 | 23 (26%) |
| T3 | 4 (4%) |
| T4 | 1 (1%) |
| Nodal status | |
| N0 | 65 (73%) |
| N+ | 18 (20%) |
| Nx | 6 (7%) |
| Surgery | |
| Mastectomy | 7 (8%) |
| Breast conserving surgery | 82 (92%) |
| Radiotherapy schedule | |
| Normofractionated | 39 (44%) |
| Hypofractionated | 50 (56%) |
| Radiotherapy volume | |
| Breast | 70 (79%) |
| Breast with RNI | 12 (13%) |
| Chest wall | 2 (2%) |
| Chest wall with RNI | 5 (6%) |

Mean heart doses in FB were in the range of 0.9–9.1 Gy with an average of 2.5 Gy. In DIBH, they ranged from 0.6 Gy to 5.1 Gy, with an average reduction of 0.9 Gy compared to DIBH. Relative to doses in FB, mean heart doses in DIBH decreased by 35% (interquartile range: 23% to 46%). Only in one single patient, DIBH led to an increased planned mean heart dose, with a minimal difference of 0.04 Gy. The frequencies of occurrence of mean heart doses in FB and DIBH, as well as the individual reductions are presented in Fig. 1.

For the entire patient cohort, a mean 10-year absolute radiation-induced IHD mortality risk of 0.14% was estimated for treatments in FB. This was largely driven by the 16 patients who were 65 years or older, for whom the mean 10-year absolute risk was estimated to 0.47%.

The mean radiation-induced lifetime risk for the entire cohort was estimated to 1.6% in FB, and the cumulative risk until the age of 80 years was 0.4%. Corresponding values for DIBH can be found in Table 2.

As radiation-induced IHD mortality can occur late in life, estimated years of life lost (YLL) may offer a more intuitive understanding of risks. The calculated mean of YLL due to radiation-induced IHD mortality was 0.11 years in FB, and 0.07 years in DIBH ($p < 0.001$, Wilcoxon signed-rank test). The reduction in YLL with DIBH as compared to FB was higher in patients with good prognosis (0.05 years for patients without vs 0.02 years in those with lymph node involvement, $p = 0.001$), in patients with high mean heart doses in FB (0.09 years for doses above 3 Gy vs 0.02 years

**Table 2**
Average doses and radiation-induced IHD mortality risk estimates comparing treatments under free breathing (FB) and deep inspiration breath-hold (DIBH).

| | Mean heart dose | 10-Year risk | Risk to age 80 | Lifetime risk | Years of life lost |
|---|---|---|---|---|---|
| FB | 2.5 Gy | 0.14% | 0.4% | 1.6% | 0.11 years |
| DIBH | 1.5 Gy | 0.08% | 0.2% | 1.0% | 0.07 years |

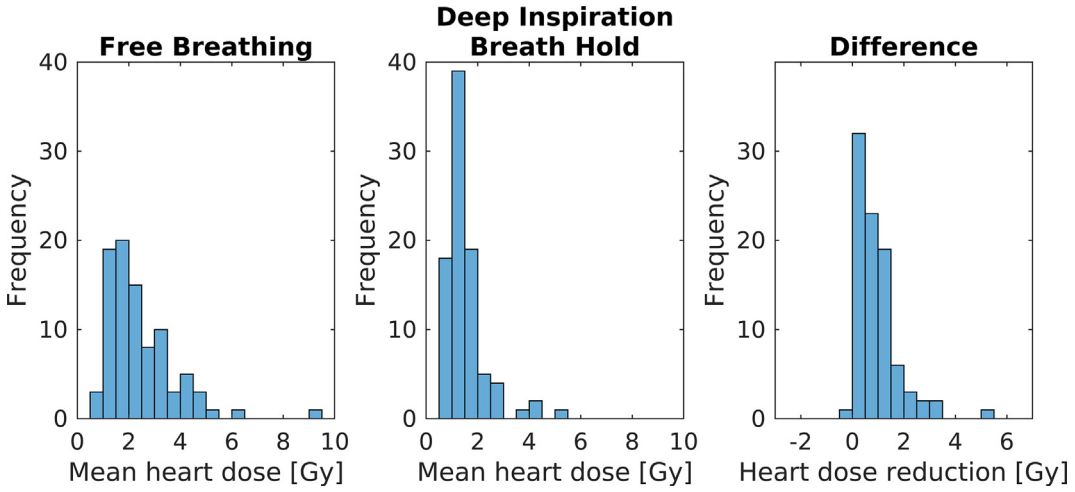


**Fig. 1.** Histograms of mean heart doses in free breathing and deep inspiration breath-hold for 89 patients with left-sided breast cancer radiotherapy. The third panel shows the absolute frequency of reductions in mean heart dose from deep inspiration breath-hold as compared to free breathing.

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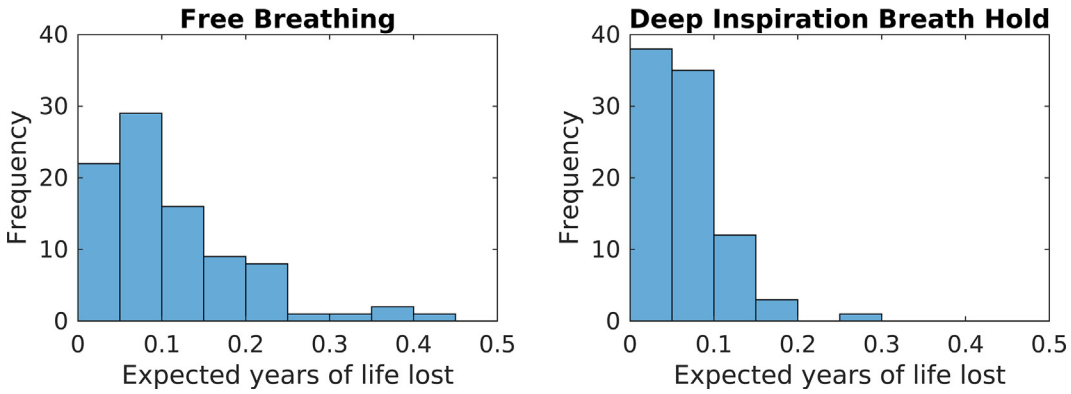


**Fig. 2.** Histograms of individually estimated years of life lost due to radiation-induced IHD mortality in free breathing and deep inspiration breath-hold for 89 patients with left-sided breast cancer. Estimates were based on age, cardiovascular risk factors, expected survival, and mean heart dose.

for doses below 1.5 Gy, $p < 0.001$) and in patients with high cardiovascular baseline relative risk (0.08 years for upper quartile vs 0.02 years for lower quartile, $p < 0.001$). Age at diagnosis was a less important predictor and – in contrast to first intuition – reduction in YLL was higher in older patients (0.05 years for patients above the age of 60 vs 0.04 years for patients below the age of 60, $p = 0.11$). The distribution of the YLL for the cohort is shown in Fig. 2.

## Discussion

In the present study, the heart received an average mean dose of 2.5 Gy when the patients were allowed to breathe freely during the treatment. In contrast, a recent review of heart doses in modern radiotherapy [13] showed typical mean heart doses in the treatment of left-sided BC, which even exceeded 5 Gy. In order to reduce the dose to the heart, respiratory gating using a breath-hold procedure has been introduced into the clinical routine. There are different strategies for implementing the DIBH technique in terms of used equipment, required accessories, intra-fractional monitoring and patient feedback systems. Several studies have confirmed the substantial impact of DIBH on dosimetric endpoints, such as mean heart or ipsilateral lung dose [6,14–16]. The dose reduction in our study (35%, interquartile range: 23–46%) was slightly lower than the range reported in the literature (38–67%). However, high reductions in the literature were in particular obtained if the mean heart dose was high in FB, e.g. for IMRT techniques [16].

As recently mentioned in a systematic review of Sardaro et al. [17], only few studies have analysed the role of cardiac baseline risk factors on lifetime risks for coronary heart disease mortality [18]. To the best of our knowledge, this is the first study addressing this issue for a "real-world" patient population. The present comparative modelling study analysed the impact of DIBH on lifetime risks for coronary heart disease mortality by taking the role of individual cardiovascular risk factors, tumour stage, and age at treatment into account. Moreover, it quantifies the expected benefit of DIBH. Finally, radiation-induced risk will be put into perspective by common risk factors below.

### *Risk dependence on treatment age and other individual risk factors*

Age at treatment is often considered a key factor regarding late health risks, and physicians may intuitively prefer young patients for selection of advanced treatment techniques. However, only minor differences in estimated years of life lost were seen comparing patients in the cohort above and below the age of 60 years. To elucidate this apparent contradiction, first, the build-up of radiation risk with age will be outlined in the following and, second, the dependence of lifetime risk on age at treatment.

Fig. 3 shows how the absolute radiation-induced IHD mortality risk accumulates with age in two exemplary patients of the cohort. As IHD mortality is overall very rare in young and middle-aged women, the first 10 years after radiotherapy contribute very little to the lifetime risk of both patients. One of the patients (patient A) has an early-staged breast cancer with good prognosis and is thus more likely to reach high ages. For higher ages, radiation-induced IHD mortality is more frequent, and adds to a lifetime risk of about 1.4%. For the second exemplary patient (patient B) with poor tumour prognosis, the estimated total survival until an age of 80 years is only about 5%. Therefore, radiation-induced IHD death is less likely to occur.

To analyse the effect of age at treatment, we analyse two fictitious patients. For better comparison, baseline risks are assumed to follow national mortality rates for both patients and radiation risks are estimated from a mean heart dose of 2 Gy. However, as

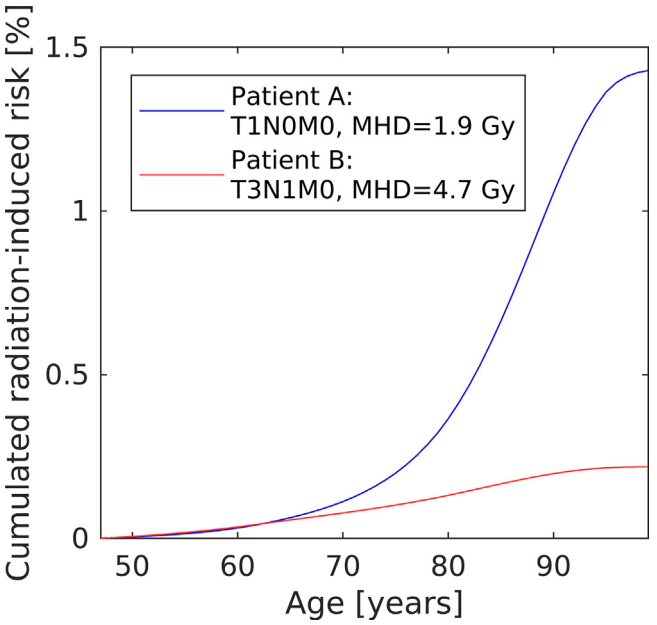


**Fig. 3.** Individual estimated radiation-induced IHD mortality risk cumulative from treatment up to a given age, exemplary for two young patients treated in free breathing. Patient A has a good prognosis and relatively low mean heart dose. On the other hand, patient B has a more advanced stage of breast cancer and a higher mean heart dose. Her shorter life expectancy leads to a lower probability of radiation-induced IHD mortality. MHD: Mean heart dose in free breathing.

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before, the two patients differ in their assumed prognosis, corresponding to tumour stages T1N0M0 and T3N+M0, respectively.

For the patient with an early-stage T1N0M0 breast cancer, the expected years of life lost are remarkably independent of age at treatment (blue curve in Fig. 4a). With increasing treatment age, the years of life lost associated with a radiation-induced IHD death decrease (Fig. 4c). However, this is largely compensated by an increase in the absolute risk for IHD mortality (Fig. 4b). This increase in absolute radiation-induced risk can be attributed to the fact that the older the patient already is, the more likely she will reach an age where IHD death is frequent. Consequently, for patients with poor prognosis and limited expected survival, this increase in the lifetime IHD risk is even more pronounced (red curve in Fig. 4b).

An important issue for the age dependence is a possible lag-time. So far, there is conflicting evidence on whether radiation-induced coronary risk sets in shortly after treatment [3] or increases with a lag-time following exposure [19]. If radiation-induced processes took e.g. 10 years before they manifest in a raised IHD risk, expected years of life lost would be substantially reduced for patients treated above ages of about 70 years, see Fig. 4a.

To summarize, treatment age is a rather weak predictor of the expected risk. For patients with poor tumour prognosis IHD risks are overall very low but increase with treatment age.

In addition to tumour prognosis, other predictors were strongly associated to YLL. There was large variation in baseline and radiation-induced risks by cardiovascular risk factors albeit patients were selected without major cardiovascular preconditions and without diabetes. For example, for two 50-year-old patients, their risks for IHD differ by a factor of 9 (smoker, 157 mmHg systolic blood pressure, 246 mg/dl cholesterol with a baseline relative risk for IHD of 3 and non-smoker, 104 mmHg, 165 mg/dl with a baseline relative risk for IHD of 0.3).

Mean heart dose may be regarded as another individual factor as it depends on the individual anatomy. The relative dose reduction by DIBH was almost independent of the mean heart dose in FB. As a consequence, DIBH led to higher absolute reductions in doses and risks in patients with higher mean heart dose in FB.

*Comparison of radiation therapy with the detriment of other risk factors*

To estimate years of life lost due to other risk factors, we also derived the expected lifetime for altered risk factors: First, if the 13 smokers in the patient group were non-smokers, their estimated life expectancy would be larger by 0.5 years on average (7 years in total for all smoking patients). Second, if the 22 patients with systolic blood pressure above 140 mmHg had a pressure of 140 mmHg, their life expectancy would be larger by 0.3 years (6 years in total). Third, if the 27 patients with cholesterol level above 240 mg/dl had a cholesterol level of 240 mg/dl, their life expectancy would be larger by 0.1 year (3 years in total). Of course, these numbers take only into account mortality due to IHD. Radiation exposure in FB was estimated to reduce years of life in the cohort by 10 years thus being the most important risk factor regarding IHD mortality when referring to the entire study cohort. With DIBH this number was reduced to 6 years.

*Limitations*

The radiation risk estimates are based on a number of assumptions, including applicability of the underlying general population and BC patient data, uncertainty in individual risk prediction [9], extrapolation of the relative survival of BC patients beyond 15 years, linearity of the dose–response relationship and use of mean heart dose, ignoring the potential impact of higher exposure to some substructures of the heart. Moreover, estimates were based on the relative-risk assumption, meaning that radiation-induced risks add multiplicatively to individual IHD risks. The relative-risk assumption is commonly used in epidemiological studies and was tested in Ref. [3]. The extent to which the relative-risk assumption may apply to patients with major cardiovascular preconditions is uncertain. Therefore, those were excluded from the study.

This study deals with IHD only, for which there is good evidence of radiation effects down to doses typically encountered in BC radiotherapy, with mean heart doses in the range 2–4 Gy [3], and even below (<1 Gy) [20,21]. Other radiation-induced heart diseases

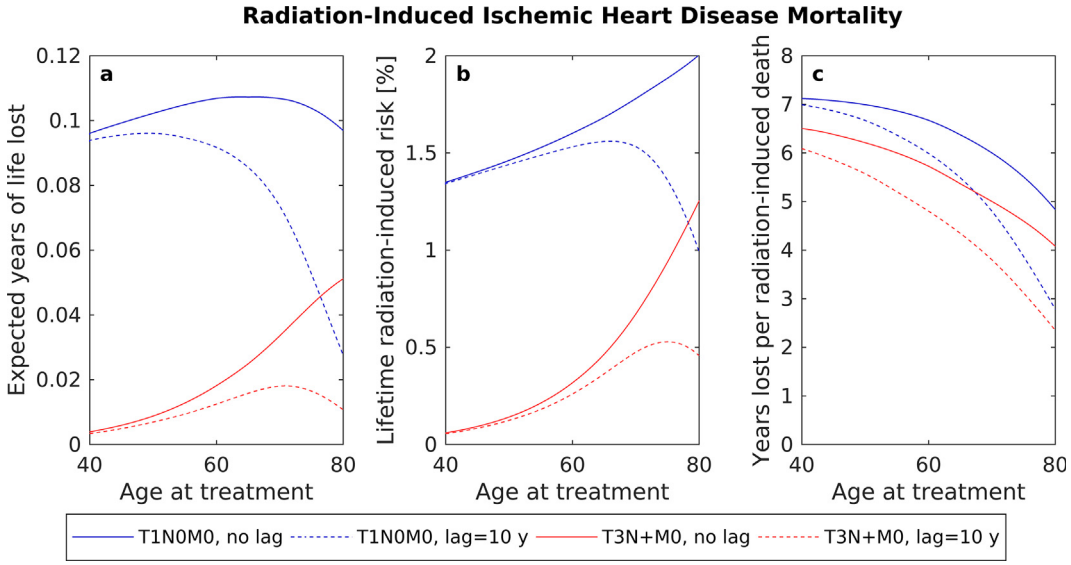


**Fig. 4.** Different risk metrics of radiation-induced IHD mortality as dependent on treatment age for two fictitious patients with normal risk factors and 2 Gy mean heart dose. The blue and red curves represent expected survivals, corresponding to tumour stages T1N0M0 (blue) and T3N+M0 (red). Immediate radiation effect was presumed for the solid lines while for the dashed lines it was assumed that radiation risk sets in 10 years after treatment. The right panel shows the average expected years of life lost per radiation-induced death. It is obtained from the ratio of expected years of life lost to the lifetime radiation-induced risk. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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[22,23] may add to the risk. Regarding exposure to the lung, an earlier study was inconclusive about a reduction of lung cancer risk with DIBH [24]. However, it can be expected that DIBH reduces the exposure and cancer risk in other organs outside the main radiation fields.

### *Conclusions*

The absolute risk of radiation-induced IHD mortality due to breast cancer radiotherapy may be regarded as modest when compared to other risks associated with cancer therapy. Nevertheless, the heart exposure is a major IHD risk factor in patients with left-sided breast cancer. The deep inspiration breath-hold technique can effectively reduce this exposure. The corresponding effect on life expectancy appears to be determined by individual prognosis and cardiovascular risk factors rather than age at treatment.

## Disclosures

CB reports grants and personal fees from C-Rad and from Elekta during the conduct of the study. SC reports grants and personal fees from C-Rad during the conduct of the study. Other authors did not report any conflicts of interest.

## Funding

This project has received funding from the Euratom research and training programme 2014–2018 under grant agreement No 755523 (MEDIRAD). The funding source had no role in study design, in the collection, analysis and interpretation of data, nor in the writing or submission of the report.

## References

[1] Offersen BV, Boersma LJ, Kirkove C, Hol S, Aznar MC, Biete Sola A, et al. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer. Radiother Oncol 2015;114:3–10.
[2] Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;366:2087–106.
[3] Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Bronnum D, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 2013;368:987–98.
[4] Taylor CW, Povall JM, McGale P, Nisbet A, Dodwell D, Smith JT, et al. Cardiac dose from tangential breast cancer radiotherapy in the year 2006. Int J Radiat Oncol Biol Phys 2008;72:501–7.
[5] Latty D, Stuart KE, Wang W, Ahern V. Review of deep inspiration breath-hold techniques for the treatment of breast cancer. J Med Radiat Sci 2015;62:74–81.
[6] Schonecker S, Walter F, Freislederer P, Marisch C, Scheithauer H, Harbeck N, et al. Treatment planning and evaluation of gated radiotherapy in left-sided breast cancer patients using the Catalyst(TM)/Sentinel(TM) system for deep inspiration breath-hold (DIBH). Radiat Oncol. 2016;11:143.
[7] Radiation Therapy Oncology Group. RTOG Breast Cancer Contouring Atlas.
[8] Feng M, Moran JM, Koelling T, Chughtai A, Chan JL, Freedman L, et al. Development and validation of a heart atlas to study cardiac exposure to radiation following treatment for breast cancer. Int J Radiat Oncol Biol Phys 2011;79:10–8.
[9] Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003;24:987–1003.
[10] German Federal Statistical Office (DESTATIS). Statistics on the causes of death. German Federal Statistical Office (DESTATIS); 2015.
[11] German Federal Statistical Office (DESTATIS). Life table 2013/2015. German Federal Statistical Office (DESTATIS); 2016.
[12] Munich Cancer Registry. ICD-10 C50: Breast cancer (women) Survival. Munich Cancer Registry; 2017.
[13] Taylor C, Correa C, Duane FK, Aznar MC, Anderson SJ, Bergh J, et al. Estimating the risks of breast cancer radiotherapy: evidence from modern radiation doses to the lungs and heart and from previous randomized trials. J Clin Oncol. 2017;35:1641–9.
[14] Swanson T, Grills IS, Ye H, Entwistle A, Teahan M, Letts N, et al. Six-year experience routinely using moderate deep inspiration breath-hold for the reduction of cardiac dose in left-sided breast irradiation for patients with early-stage or locally advanced breast cancer. Am J Clin Oncol 2013;36:24–30.
[15] Joo JH, Kim SS, Ahn SD, Kwak J, Jeong C, Ahn SH, et al. Cardiac dose reduction during tangential breast irradiation using deep inspiration breath hold: a dose comparison study based on deformable image registration. Radiat Oncol 2015;10:264.
[16] Smyth LM, Knight KA, Aarons YK, Wasiak J. The cardiac dose-sparing benefits of deep inspiration breath-hold in left breast irradiation: a systematic review. J Med Radiat Sci 2015;62:66–73.
[17] Sardaro A, Petruzzelli MF, D'Errico MP, Grimaldi L, Pili G, Portaluri M. Radiation-induced cardiac damage in early left breast cancer patients: risk factors, biological mechanisms, radiobiology, and dosimetric constraints. Radiother Oncol 2012;103:133–42.
[18] Brenner DJ, Shuryak I, Jozsef G, Dewyngaert KJ, Formenti SC. Risk and risk reduction of major coronary events associated with contemporary breast radiotherapy. JAMA Intern Med 2014;174:158–60.
[19] Henson KE, McGale P, Taylor C, Darby SC. Radiation-related mortality from heart disease and lung cancer more than 20 years after radiotherapy for breast cancer. Br J Cancer 2013;108:179–82.
[20] Little MP, Kleinerman RA, Stovall M, Smith SA, Mabuchi K. Analysis of dose response for circulatory disease after radiotherapy for benign disease. Int J Radiat Oncol Biol Phys 2012;84:1101–9.
[21] Simonetto C, Azizova TV, Grigoryeva ES, Kaiser JC, Schollnberger H, Eidemuller M. Ischemic heart disease in workers at Mayak PA: latency of incidence risk after radiation exposure. PLoS One 2014;9:e96309.
[22] Santoro F, Tarantino N, Pellegrino PL, Caivano M, Lopizzo A, Di Biase M, et al. Cardiovascular sequelae of radiation therapy. Clin Res Cardiol 2014;103:955–67.
[23] McGale P, Darby SC, Hall P, Adolfsson J, Bengtsson NO, Bennet AM, et al. Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden. Radiother Oncol 2011;100:167–75.
[24] Corradini S, Ballhausen H, Weingandt H, Freislederer P, Schonecker S, Niyazi M, et al. Left-sided breast cancer and risks of secondary lung cancer and ischemic heart disease: Effects of modern radiotherapy techniques. Strahlenther Onkol 2018;194:196–205.

Please cite this article in press as: Simonetto C et al. Does deep inspiration breath-hold prolong life? Individual risk estimates of ischaemic heart disease after breast cancer radiotherapy. Radiother Oncol (2018), https://doi.org/10.1016/j.radonc.2018.07.024