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The impact of fractionation on secondary malignancies in postoperative breast cancer irradiation

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A B S T R A C T

Purpose: Randomized studies demonstrated the oncological equivalence of (ultra-)hypofractionation compared to a 5-week schedule in postoperative radiotherapy of breast cancer. Due to the low incidence and long latency of secondary malignancies, there are currently no reliable clinical data regarding the influence of fractionation regimens on the development of secondary malignancies.

Material and methods: For 20 patients with right or left-sided breast cancer, postoperative treatment plans were created using 3D-CRT (n = 10) or VMAT (n = 10) for three different fractionation schedules: 5-week schedule with 50.4Gy in 1.8Gy (28fx), hypofractionation with 40.05Gy in 2.67Gy (15fx) and ultra-hypofractionation with 26Gy in 5.2Gy (5fx). The EARs (absolute additional cases of disease per 10,000 patient-years) for secondary malignancies in the lung, contralateral breast, esophagus, liver, thyroid, spinal cord, bones and soft tissue were calculated using a fraction-dependent dose-response model.

Results: Based on risk modulation, (ultra-)hypofractionation resulted in significantly lower EARs for lung cancer (LC), contralateral breast cancer (CBC) and soft tissue sarcoma (STS) ($p < .001$). For the ultra-hypofractionated dose concept the median EARs for LC, CBC and STS were 42.8 %, 39.4 % and 58.1 % lower compared to conventional fractionation and 31.2 %, 25.7 % and 20.3 % compared to hypofractionation. The influence of fractionation on the risk of secondary malignancies for LC and CBC was less pronounced with 3D-CRT than with VMAT. For STS, however, the influence of fractionation was greater with 3D-CRT than with VMAT.

Conclusion: Based on this simulation study (ultra-)hypofractionated postoperative breast cancer irradiation may be associated with a lower risk of secondary malignancies compared to a 5-week schedule.

1. Introduction

In recent decades, advances in early breast cancer therapy have led to longer survival rates and a permanent cure in a substantial number of patients. Hereby, postoperative radiotherapy plays an important role by improving local tumor control and overall survival in patients with non-metastatic breast cancer. After breast-conserving surgery, postoperative radiotherapy reduces the 10-year risk of any first recurrence to 50 % and breast cancer mortality by about a sixth [1].

Given the favorable oncologic prognosis of most patients with early breast cancer, long-term complications and side effects of radiotherapy are of particular importance. It is known that radiation of the breast is associated with a higher risk of secondary cancer [2,3]. Nevertheless, due to the low incidence of secondary malignancies and their long latency period, the existing data is mostly based on large cohort or case-control studies using outdated irradiation techniques, limiting our understanding of risks associated with modern approaches.

Today, various irradiation techniques are available to minimize the dose to organs at risk. Volumetric modulated arc therapy (VMAT), for example, allows precise dose distribution in complex target volumes. However, these techniques also result in larger low-dose volumes in surrounding organs such as the lung [4–6]. Simulation studies suggest that this may lead to a higher secondary cancer risk compared to 3D-CRT [7].

In recent years, the standard fractionation in breast cancer irradiation has changed from a 5-week schedule with 25–28 fractions to hypofractionated (15-16fx) or ultra-hypofractionated (5fx) schedules based on randomized trials that showed equivalent oncologic results

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[8–10]. Yet, the impact of this development on secondary cancer remains largely unknown due to the low incidence of secondary cancer and the limited follow-up time.

In the current study, we aimed to investigate the impact of fractionation on secondary cancer risk for different irradiation techniques including VMAT and 3D-CRT in breast cancer using a mathematical model derived from atomic bomb survivors as well as Hodgkin's lymphoma patients treated with radiotherapy, to estimate the excess absolute risk (EAR) of developing a secondary cancer or sarcoma which also takes fractionation into account [11].

2. Material and methods

2.1. Patients

Women with non-metastatic breast cancer (stage T1-4, N0-3, M0, n = 10 right-sided, n = 10 left-sided) who had undergone breast-conserving surgery (n = 10) or mastectomy (n = 10) receiving post-operative breast cancer irradiation between 2019 and 2023 in our institute were included in the current study. The patients were randomly selected without using a selection criterion to diversify the study group and avoid selection bias. The median age of the patients was 61 years (range 36–86 years).

2.2. CT simulation and delineation

CT for planning radiotherapy was performed in the supine position with the arms positioned above the head using a commercial immobilization system (WingSTEP). The slice thickness of the images was 3 mm. A radiation oncologist defined the target volume and organs at risk including the entire lung, contralateral breast, liver, esophagus, thyroid, spinal cord, bones, and soft tissue. The clinical target volume (CTV) included the entire breast or thoracic wall with the lymphatic drainage pathways and was defined according to the European Society for Radiotherapy and Oncology (ESTRO) guideline for delineation for elective radiotherapy for early breast cancer [12]. The planning target volume (PTV) was calculated by expanding the CTV by a margin of 5–7 mm.

2.3. Treatment planning

Three treatment plans were created for each patient: one with 5-week schedule (50.4Gy in 28fx; fraction dose 1.8Gy), one with hypofractionation (HF, 40.05Gy in 15fx; fraction dose 2.67Gy) and one with ultra-hypofractionation (UF, 26Gy in 5fx; fraction dose 5.2Gy). Patients were treated with either 3D-CRT plans (n = 30) or volumetric modulated arc therapy (n = 30) (VMAT; RapidArc, Varian Medical System, Palo Alto, CA, USA). The 3D-CRT plans consisted of 3–6 tangential beams with 6-MV or 6-/15-MV beams. Gantry angles were chosen to best cover the target and minimize dose exposure to the heart, ipsilateral lung, and contralateral breast. VMAT plans were created with two or three partial 6-MV photon arcs irradiated between gantry angles of 50/60°–181° (right side) and 179°-300/315° (left side).

All radiotherapy techniques were planned and calculated in the Eclipse treatment planning system version 16.01 (Varian Medical System, Palo Alto, CA, USA) using the Anisotropic Analytical Algorithm version 13.0.26. with the Photon Optimizer version 16.1 for RapidArc optimization. All plans were normalized to ensure that 50 % of the PTV received 100 % of the prescribed dose.

2.4. Calculation of secondary cancer risk estimates

The risk of secondary malignancies for organs in the irradiation field was calculated using a mechanistic model developed by Schneider et al. [11]. The organ doses were exported, and the organ equivalent doses (OEDs) and EARs were calculated for the representative patient group irradiated at the age of 50 years and reached age of 80 years using the following formulas for carcinomas and sarcomas:

The model uses parameters for cell killing (α) and cell repopulation (R) during fractionation resulting in a dosimetry function called risk equivalent dose (RED). The RED is derived for carcinoma risk:

$$RED_{carcinoma} = \frac{e^{-\alpha' D}}{\alpha' R}\left[1 - 2R + R^2 e^{\alpha' D} - (1-R)^2 e^{\frac{-\alpha' RD}{1-R}}\right]$$

And for sarcoma risk:

$$RED_{sarcoma} = \frac{e^{-\alpha' D}}{\alpha' R}\left[1 - 2R + R^2 e^{\alpha' D} - (1-R)^2 e^{\frac{-\alpha' RD}{1-R}} - \alpha' RD\right]$$

The cell killing parameter (α) is defined by the linear quadratic (LQ) model and represents cells killed per dose fraction. The dose per fraction is (d) and the total dose (D). D_T and d_T are prescribed dose and dose per fraction. The $\alpha/\beta = 3$ for all tissues is relevant for secondary cancer induction. This formulation allows risk assessment for different fractionation schemes.

$$\alpha' = \alpha\left[1 + \frac{d_T}{\alpha/\beta}\cdot\frac{D}{D_T}\right]$$

As tissues close to the primary field receive inhomogeneous doses, the concept of OED was applied to calculate secondary malignancy risk for an organ exposed to heterogenous doses. In this approach, RED is weighted by the corresponding subvolume $V(D_i)$. The summation of all voxel-weighted RED values divided by the organ volume (V_T) gives the OED:

$$OED = \frac{1}{V_T}\sum V(D_i)\cdot RED(D_i)$$

The excess absolute risk (EAR) for specific organs (defined as the excess cases per 10,000 person–years [PY]) is the product of OED, initial slope of the doses-response curve (β) and a population modifying function (μ) including the age at exposure (age x) and age reached (age a) variables:

$$EAR^{org} = \frac{1}{V_T}\sum V(D_i)\cdot\beta\cdot RED(D_i)\cdot\mu(age\ x, age\ a)$$

$$\mu(age\ x, age\ a) = exp\left[\gamma_e(age\ x - 30) + \gamma_a\left(age\frac{a}{70}\right)\right]$$

All organ-specific parameters for EAR calculations were used from Schneider et al. The RED model parameters α and R were obtained for different tissues using the combined secondary cancer data from atomic bomb survivors and Hodgkin's patients.

To compare the risk estimation model to clinical data we calculated the EARs for lung and contralateral breast cancer using the age at exposure of 50 years and reached age of 60 years for the 5-week schedule 3D-CRT plans. These parameters most closely correspond to the population from the prospective studies used by Taylor et al. for the systematic review of secondary cancer induced by postoperative breast irradiation [3] and Veiga et al. in a retrospective cohort study assessing secondary soft tissue sarcoma development after breast cancer irradiation [13].

2.5. Statistical analysis

Statistical analysis was performed using SPSS 29.0.2.0 software (IBM, Armonk, NY, USA). Non-parametric quantitative data were expressed as median, minimum, and maximum. Boxplots were used to visualize differences between groups. Two-factor analysis of variance for ranks according to Friedman was used to evaluate statistically significant differences between dependent samples. Mann-Whitney-U-tests was used to test statistical differences between independent samples. In all cases, differences were considered statistically significant at $p < .05$.

Table 1
EARs assuming an age of exposure at 50 years and observation period of 30 years for the 5-week schedule-(28fx), hypo-(15fx) and ultra-hypofractionation(5fx), 3D-CRT and VMAT altogether: lung cancer, contralateral breast cancer and soft tissue sarcoma. Two-factor analysis of variance for ranks according to Friedman for dependent samples to show statistically significant difference between median EARs depending on the fractionation scheme.

	5fx	15fx	28fx	Two-factor analysis of variance for ranks according to Friedman (sig.)
Lung Cancer				
median	31.3	45.4	54.6	$p < .001$
minimum	11.9	17.3	20.9	
maximum	51.5	74.3	89.1	
Contralat Breast Cancer				
median	6.7	9.5	11.1	$p < .001$
minimum	4.9	6.6	7.5	
maximum	14.7	19.9	22.5	
Soft Tissue Sarcoma				
median	.3	.6	.7	$p < .001$
minimum	.03	.3	.3	
maximum	.9	1.3	1.6	

3. Results

Based on the risk model, both ultra-hypofractionation and moderate hypofractionation resulted in significantly lower EARs for secondary malignancies compared to a 5-week schedule for all tested organs.

For an assumed age of exposure to radiation of 50 years and an observation period of 30 years (reached age of 80 years) the median EARs for lung cancer after ultra-hypofractionation was 31 % lower compared to hypofractionation and 43 % lower compared to 5-week schedule. For breast cancer the EAR after UF was 26 % lower compared to HF and 40 % lower compared to the 5-week schedule. The EAR of soft tissue sarcomas after UF was 20 % lower compared to HF and 58 % lower compared to the 5-week schedule. The ΔEAR between UF and the 5-week schedule was 23.3 for lung cancer, 4.4 for contralateral breast cancer and 0.4 for soft tissue sarcomas. The EARs for all fractionation schedules are summarized in Table 1 and Fig. 1. The EARs for all fractionation schedules assuming an age of exposure of 50 years and an observation period of 10 years (reached age of 60 years) are presented in Table 2 for lung cancer, contralateral breast cancer and soft tissue sarcoma. The EARs for the liver, thyroid, esophagus, spinal cord, and bones are included in the Supplementary Table 1.

The impact of fractionation on the development of secondary cancers, such as lung cancer and contralateral breast cancer, was observed to be less pronounced in 3D-CRT compared to VMAT. For an observation period of 30 years the median lung cancer ΔEAR for 28fx versus 5fx was 33.6 (15fx vs. 5fx: 20.4) for VMAT and 11.6 (7.0) for 3D-CRT. The median contralateral breast carcinoma-ΔEAR for 28fx versus 5fx was 6.8 (15fx vs. 5fx: 4.6) for VMAT and 2.9 (2.0) for 3D-CRT. In soft tissue sarcoma on the other hand, the impact of fractionation was greater in 3D-CRT (median ΔEAR of 28fx and 5fx: 0.6; 15fx and 5fx: 0.4) than in VMAT (median ΔEAR of 28fx and 5fx: 0.3; 15fx and 5fx: 0.2) (Fig. 2).

4. Discussion

This simulation study evaluated the impact of fractionation on secondary malignancies in postoperative breast cancer irradiation using a mechanistic model of radiation-induced cancer after fractionated radiotherapy. For most organs, including the lungs, contralateral breast and soft tissues, there was a significant decrease in the risk of developing a secondary malignancy for hypofractionated RT.

Clinical studies focusing on secondary malignancies after postoperative breast cancer irradiation are sparse. The existing studies, however, indicate an elevated risk of secondary cancer after postoperative radiotherapy in breast cancer patients: Taylor et al. observed an excess absolute risk (EAR) for contralateral breast cancer in 8.8/10,000 patient-years. The EAR for lung cancer was 8.6/10,000 patient-years with a follow-up period of 10 years and a radiation exposure of 50 years [3]. These data are in accordance with the median EARs for lung and contralateral breast cancer after 28fx in the 3D-CRT group of this study if assuming an age of exposure of 50 years and an observation period of 10 years (reached age of 60 years). It can thus be presumed that this model is suitable for the generation of realistic results regarding the correlation between the fractionation scheme and the risk of secondary malignancies.

In a retrospective study based on the Kaiser Permanente (KP) cohort, 19 (0.1 %) of 15,940 women with breast cancer developed subsequent thoracic soft tissue sarcoma. Most (18 of 19) occurred in women treated with radiotherapy, but no association could be found with the

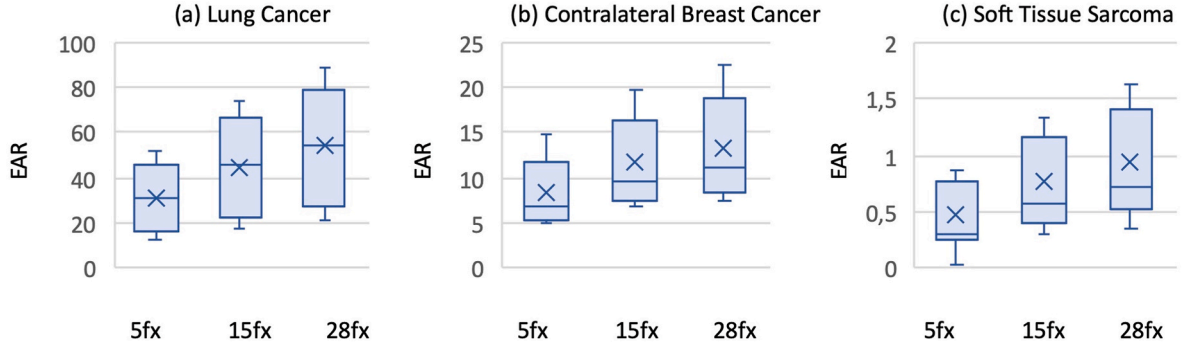

Fig. 1. EARs assuming an age of exposure at 50 years and observation period of 30 years for a 5-week schedule -(28fx), hypo-(15fx) and ultra-hypofractionation(5x), 3D-CRT and VMAT altogether: (a) lung cancer, (b) contralateral breast cancer, (c) soft tissue sarcoma.

Table 2
EARs (age of exposure at 50 years; observation period of 10 years) for a 5-week schedule-(28fx), hypo-(15fx) and ultra-hypofractionation(5fx) for 3D-CRT: lung cancer, contralateral breast cancer and soft tissue sarcoma.

	Lung Cancer			Contralateral Breast Cancer			Soft Tissue Sarcoma		
	5fx	15fx	28fx	5fx	15fx	28fx	5fx	15fx	28fx
median	4.6	6.7	8.0	3.3	4.5	5.0	.9	1.4	1.7
minimum	3.5	5.1	6.2	3.0	4.1	4.6	.0	.0	.0
maximum	6.7	9.8	11.7	4.6	4.7	5.3	1.0	1.6	1.9

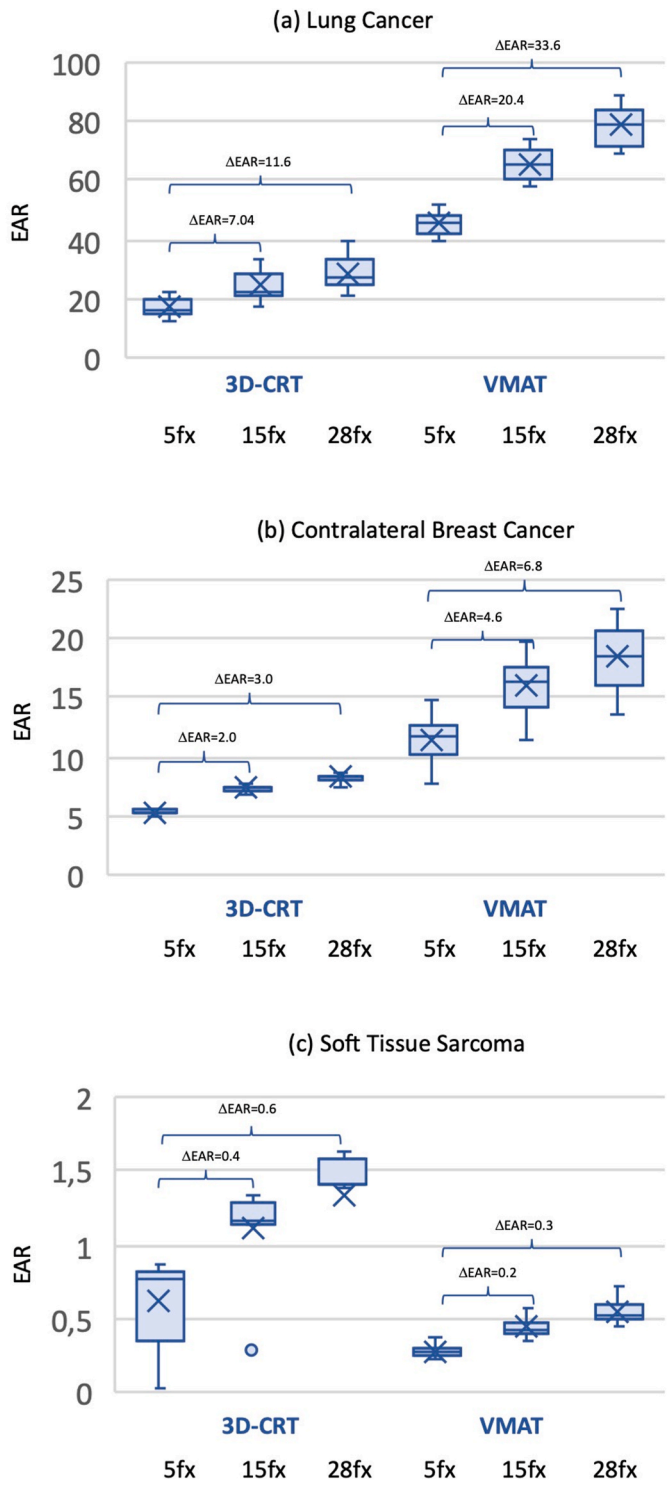

Fig. 2. Difference of EARs between 28fx and 5fx, respectively 15fx and 5fx for 3D-CRT and VMAT. EARs assuming an age of exposure at 50 years and observation period of 30 years for: (a) lung cancer, (b) contralateral breast cancer, (c) soft tissue sarcoma.

prescribed dose, fractionation, or boost. In a Surveillance, Epidemiology, and End Results (SEER) cohort, 430 (0.1 %) of 457,300 patients developed a STS and 335 of 430 cases occurred after radiotherapy. By 10 years after radiotherapy, the cumulative incidence of thoracic STS was 0.21 % in the KP cohort and 0.15 % in SEER [13]. Since the prognosis for angiosarcomas is poor [14] care must be taken to reduce the risk of occurrence even if the incidence is low.

While the overall risk for breast cancer patients to develop secondary cancer or sarcoma after radiotherapy is small, reducing the risk to 'as low as reasonably achievable' is still highly relevant, given the large number of patients with long-term survival and the potential morbidity and mortality associated with secondary malignancies [2]. Our results emphasize that the increasing use of (ultra-)hypofractionation can potentially contribute to this effort.

Moderate hypofractionation with 15–16 fractions of 2.6–2.7Gy is recognized in most countries as the standard of care for postoperative radiotherapy for invasive breast cancer [15–17]. Long-term observation confirms that appropriately dosed hypofractionated radiotherapy is safe and effective for patients with early-stage breast cancer [9]. After publication of the FAST-Forward study, some centers have already adopted a 5 fractions schedule as standard dose regimen.

In the FAST-Forward trial, data for secondary primary cancer such as contralateral breast cancer were collected: CBC was reported for 23/1,361 patients in moderate hypofractionation and 23/1,368 patients in the ultra-hypofractionated group (26Gy) [8]. The START-B trial included CBC as a secondary endpoint within 'any breast cancer-related event' and showed no evidence of a possible difference between fractionation regimens [9]. In the ONTARIO trial, CBC was also considered as a secondary endpoint, without the ability of a definitive statement [10]. Aside from BCB, secondary malignancies were adequately addressed in none of the randomized trials. Even for BCB, the follow-up period and the patient numbers are insufficient to draw definite conclusions.

The current study is to our knowledge the first study specifically addressing the impact of fractionation on the long-term (30 years) occurrence of different secondary malignancies after postoperative breast cancer irradiation. Our results suggest that the use of ultra-hypofractionation could prevent up to 23 cases of secondary lung cancer and 4 cases of secondary breast cancer in 10,000 patient-years. In a previous study, Sitathanee et al. evaluated the EARs after definitive prostate irradiation with 3D-CRT (78Gy in 2Gy), IMRT (78Gy in 2Gy) and SBRT (36.25Gy in 7.25Gy) using a risk estimation model. The risk of secondary sarcoma was reduced by more than 50 % for SBRT compared to conventional fractionation [18].

In our study, EARs for VMAT plans were significantly higher compared to 3D for all organs and bones except soft tissues. These results are consistent with recently published data from Racka et al. who used Schneider's model to compare the dose distribution and estimation of projected secondary malignancy risk after left-sided breast irradiation using 3D-CRT and VMAT (3 and 4 arcs) [19]. Biologically, this difference can be explained by the extensive low-dose exposure in VMAT. Interestingly, the influence of fractionation on the development of secondary malignancies in lung cancer and contralateral breast cancer was smaller with 3D-CRT than with VMAT. For soft tissue sarcomas, however, the influence of fractionation was greater with 3D-CRT than with VMAT.

There are certain limitations to this study. One is the relatively small number of cases. Individual anatomic features can influence organ doses and therefore the projected secondary cancer risk. The second limitation is that we mixed data from breast irradiation and thoracic wall irradiation. Another limitation is that the model for calculating the EAR by Schneider et al. uses the linear quadratic model. Hypofractionated and ultra-hypofractionated dose concepts are also calculated with this model in clinical practice for the best approximation, although different biological effects occur. In addition, secondary malignancy data from atomic bomb survivors and patients after radiation for Hodgkin's lymphoma can only be compared to a limited extent with postoperative breast cancer radiotherapy. Yet, it can be assumed that the model of Schneider et al. is adequate for the simulation of the EAR for different fractionation schemes carried out in this study.

It should be noted that the estimated risk of secondary cancers in our study did not include baseline risk because we did not consider the medical history of the patients analyzed. The risk we estimated is

therefore only based on radiation even though previous studies showed that the risk of radiation-induced lung cancer is strongly influenced by smoking status [20]. Therefore, EAR estimates should be interpreted with caution due to these uncertainties.

5. Conclusion

(Ultra-)hypofractionated radiotherapy can potentially reduce the risk of secondary malignancies after postoperative irradiation for breast cancer. The impact of fractionation on the risk of secondary malignancies in lung and contralateral breast cancer was lower with 3D-CRT compared to VMAT. These findings should be considered when selecting dose regimens for postoperative irradiation in breast cancer especially in younger breast cancer patients.

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Ethics approval

The study was approved by the local institutional review board (IRB) (2024-169-S-CB).

CRediT authorship contribution statement

Sophia Kiesl: Writing – original draft, Visualization, Validation, Supervision, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Mathias Düsberg:** Writing – review & editing, Validation, Software, Methodology, Investigation, Conceptualization. **Sophie T. Behzadi:** Writing – review & editing, Validation. **Rebecca Moser:** Writing – review & editing, Validation. **Jana Nano:** Writing – review & editing, Validation. **Thomas Huber:** Writing – review & editing, Validation, Resources. **Evelyn Klein:** Writing – review & editing, Validation, Resources. **Marion Kiechle:** Writing – review & editing, Validation, Resources. **Denise Bernhardt:** Writing – review & editing, Validation, Resources. **Stephanie E. Combs:** Writing – review & editing, Validation, Resources. **Kai J. Borm:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2024.103819.

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