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Original paper

Risk of contralateral breast and ipsilateral lung cancer induction from forward-planned IMRT for breast carcinoma

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ABSTRACT

Purpose: To assess the risk of contralateral breast and ipsilateral lung cancer induction from forward-planned IMRT for breast carcinoma.
Methods: The study group included 13 females irradiated for breast cancer with 6 MV photons. The plans were initially generated by using standard fractionated (SF) forward-planned IMRT (50 Gy at 2 Gy/fraction). Hypofractionated (HF) IMRT (42.56 Gy at 2.66 Gy/fraction) was also employed for plan creation. Differential DVHs derived from the treatment plans were used to estimate the patient-specific organ equivalent dose (OED) to the contralateral breast and ipsilateral lung and the relevant lifetime attributable risks of cancer development. These estimates were made with a non-linear mechanistic model. The radiotherapy-induced cancer risks were combined with the lifetime intrinsic risk (LIR) values for unexposed people to determine the patient- and organ-specific relative risk (RR) for second cancer induction.
Results: The OED of the contralateral breast from SF and HF forward-planned IMRT was up to 0.99 and 0.86 Gy, respectively. The corresponding values for the ipsilateral lung were 4.15 and 3.66 Gy. The patient-specific RR range for the contralateral breast and ipsilateral lung cancer induction following SF forward-planned IMRT was 1.04–1.10 and 1.60–1.81, respectively. The corresponding RRs from hypofractionated treatment were 1.03–1.09 and 1.53–1.73.
Conclusions: The treatment of primary breast carcinoma with the use of SF or HF forward-planned IMRT results in increased probabilities for developing secondary malignancies in the healthy contralateral breast or ipsilateral lung compared to the respective LIRs for an unexposed population.

1. Introduction

Breast cancer is the most common neoplasm in women of the United States of America [1] and Europe [2]. The improvements associated with the detection and the treatment of this disease have resulted in a considerable reduction of the mortality rate by 39% from 1989 to 2015 [1]. The five-year survival rate from all types of breast carcinomas reaches to 89.7% nowadays [3]. The probability for developing a breast malignancy increases exponentially up to the age of menopause [4]. Based on the most recent SEER report [3], 10.5% of the new breast cancer cases are up to 44 years old whereas 20.4% of the cases belongs to the age group of 45–54 years. These young and middle-aged patients are often worried about the complications of the applied anticancer treatment.

The use of breast-conserving surgery followed by external-beam radiotherapy is considered as the standard of care for most of the patients with early stages of this malignant disease [4]. However, breast exposure to high therapeutic doses may be associated with an excess risk for second cancer induction [5–7]. The risk magnitude is related to the patient's age at the time of breast irradiation. Young patients are subjected to a higher probability for carcinogenesis than older women [5,6]. Many of the previously reported secondary malignancies [5–7] were observed in patients subjected to conventional radiation therapy based on two-dimensional treatment planning which is no longer used in current clinical practice. The introduction of computed tomography (CT)-based treatment planning enabling the accurate determination of the target site and the subsequent sparing of the surrounding critical structures has resulted in a cancer risk reduction in breast cancer patients irradiated in recent years [6].

The intensity-modulated radiotherapy (IMRT) is a commonly applied radiation delivery method for the management of breast-conserved patients during the last decade. The IMRT for breast carcinoma

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leads to a good dose homogeneity within the target site [4,8]. This treatment method can also restrict the risk for adverse skin effects and improve the cosmetic outcome compared to the conventional radiotherapeutic techniques [8]. One of the different types of the IMRT delivery is based on the forward planning process. The forward-planned IMRT is often considered as the favored approach in female patients requiring treatment of the whole breast alone without the need for additional nodal irradiation [8].

The objective of the current study was to estimate the probability of carcinogenesis in adjacent critical organs receiving high radiation doses from forward-planned IMRT for the whole breast by using a non-linear mechanistic model and patient-specific dosimetric data.

2. Materials and methods

2.1. Study participants

Seven left-sided and six right-sided early-stage breast cancer females were included in this study. All patients had been previously subjected to breast-conserving surgery and, then, they were referred for post-operative external-beam radiotherapy in our department. Axillary, supraclavicular and/or internal mammary lymph node irradiation was not required for any of the study participants. The age of these patients ranged from 34 to 55 years. The mean patient's age was equal to 45.3 years with a standard deviation (SD) of 6.7 years. The age of each study participant is presented in Table 1.

2.2. Forward IMRT planning

The breast cancer patients initially underwent a treatment planning CT on a 16-row multidetector scanner (Somatom Sensation 16, Siemens, Forcheim, Germany). All patients were scanned supine to simulate their position during treatment. The CT slice thickness was set to 5 mm. The contouring and treatment planning procedures were carried out with the aid of the Monaco software (Elekta AB, Stockholm, Sweden). The planning target volume and the surrounding critical healthy structures such as contralateral breast, lungs and heart were manually delineated on all CT slices by a radiation oncologist experienced in breast irradiation. The contralateral and ipsilateral lungs were delineated as two different organs.

The therapy plans were created for use on an Elekta Infinity linear accelerator producing 6 MV photon beams (Elekta AB, Stockholm, Sweden). A forward-planned IMRT technique involving a pair of isocentric fields was applied for all study participants. The field arrangement consisted of two opposed medial and lateral tangential fields. Two to three segments were added to each tangential field in order to obtain a homogeneous dose distribution inside the PTV with dose values ranging from 95% to 107% of the prescribed target dose. The plans were initially based on the use of the standard fractionated (SF) radiotherapy delivering 50 Gy to the tumor site with 25 daily fractions of 2 Gy [4]. The plans were also calculated on the basis of hypofractionated (HF) irradiation delivering 42.56 Gy to the tumor site with 16 fractions of 2.66 Gy [4,9]. The dose constraints of the surrounding healthy organs, as previously reported by Dumane et al. [8], were satisfied for all patients' plans with both fractionation schemes.

Table 1
Age of the breast cancer female patients.

Patient no.	Age (years)
1	45
2	48
3	38
4	51
5	34
6	45
7	55
8	53
9	38
10	50
11	39
12	42
13	51

2.3. Organ equivalent dose calculations

Previous epidemiological studies which are related to non-modulated irradiation for breast carcinoma have reported that the ipsilateral lung and contralateral breast are subjected to an elevated risk for cancer induction [5,6]. Cumulative dose volume histograms (DVH) derived from the IMRT plans were used to find and record the average radiation dose (D_{av}) to each of the above critical structures. These DVHs showed that portions of the ipsilateral lung and contralateral breast received high doses exceeding 2.5 Gy. It is well known that the radiation-induced cancer risk increases linearly with the dose up to a level of 2.5 Gy [10]. The above linearity is debated for radiation doses exceeding the above level [10–12]. The process of cell inactivation at the high dose region is not taken into account by the linear models. The application of the simple linear models for cancer risk assessment, such as that introduced by the BEIR-VII report [13], should be limited to critical organs not receiving high therapeutic doses [14–16]. More sophisticated approaches have been proposed for estimating the probability of carcinogenesis to organs exposed to high doses during radiotherapy [11]. These approaches often ignore the dependence of the radiotherapy-induced cancer risk upon either the fractionation of the tumor dose during the entire treatment course or the cell proliferation existing in irradiated tissues between consecutive fractions [17–19].

In the current study, the breast and lung cancer risks due to forward-planned IMRT were estimated with a non-linear mechanistic model introduced by Schneider et al. [20]. This approach provides site-specific probabilities for carcinogenesis by taking into account the effects of cell-killing, dose fractionation and tissue repair between dose fractions. The parameters of the mechanistic model were defined on the basis of data obtained by A-bomb survivors and Hodgkin lymphoma patients subjected to external-beam radiation therapy. The model has been extensively employed for estimating the probability of carcinogenesis due to radiotherapy of both benign [21,22] and malignant disorders [23–26]. The application of the mechanistic model is based on the organ equivalent dose (OED) concept which is proportional to the risk of radiation carcinogenesis in a specific critical organ. The OED is related to the dose distribution within each organ of interest. The above organ dose distribution was defined with the aid of differential DVHs derived from each patient's plans. The histograms were analyzed with a dose interval of 0.01 Gy. The OED of the contralateral breast and ipsilateral lung of each patient subjected either to SF or HF forward-planned IMRT for breast cancer was calculated with the following equation:

$$\mathrm{OED} = \frac{1}{V_t}\sum_i V_{D_i}\frac{e^{-a_i' D_i}}{a_i' R}\left[1 - 2R + R^2 e^{a_i' D_i} - (1-R)^2 e^{-\frac{a_i' R}{1-R} D_i}\right] \quad (1)$$

where V_{D_i} is the volume of the ipsilateral lung or contralateral breast absorbing a dose of D_i, V_t is the total volume of each of the aforementioned organs as derived from CT scans, a_i' is the organ-specific cell-killing parameter and R is the organ-dependent cell repopulation parameter [20]. The a_i' was found as follows:

$$a_i' = a + \frac{\beta D_i}{n} \quad (2)$$

where a and β are the linear-quadratic parameters and $n$is the number of daily fractions given during breast irradiation. The values of R, a and β are summarized in Table 2 [27,28].

Table 2
Parameters of the mechanistic model employed for lung and breast cancer risk assessments. These values were defined on the basis of previously published data [20,27,28].

Parameter	Organ-at-risk	
	Lung	Female breast
R	0.84	0.62
$a(\mathrm{Gy})^{-1}$	0.061	0.067
$a/\beta(\mathrm{Gy})$	3	3
γ_e $(\mathrm{years})^{-1}$	0.002	−0.037
γ_a $(\mathrm{years})^{-1}$	4.23	1.7
β_0 $(10^4\,\mathrm{PY\,Gy})^{-1}$	8.0	8.2

2.4. Radiotherapy-induced cancer risk assessments

The excess absolute risk (EAR) for the development of secondary malignancies to contralateral breast or ipsilateral lung due to SF and HF forward-planned IMRT of primary breast carcinoma was estimated as follows:

$$\mathrm{EAR} = \beta_0 \mathrm{OED} \exp\left[\gamma_e(age_e - 30) + \gamma_a \ln\left(\frac{age_a}{70}\right)\right] \quad (3)$$

where β_0 denotes the slope of the dose-response relationship at low doses, age_e is the age of the patient during exposure, age_a is the attained patient's age and γ_e, $\gamma_a$are the age modifying factors [20]. The values of γ_e, $\gamma_a$and β_0 for both breast and lung have been previously defined [20] and they are presented in Table 2. The age_e was taken from Table 1 for each female patient. A maximum attaining age of 75 years old was considered for the EAR assessment.

The EAR values were used to estimate the patient-specific lifetime attributable risk (LAR) for developing secondary malignancies to the contralateral breast and ipsilateral lung with the formula:

$$\mathrm{LAR} = \sum_{age_e+L}^{75} EAR(OED, age_e, age_a)\frac{S(age_a)}{S(age_e)} \quad (4)$$

where L is a free cancer risk time interval of 5 years [13] and $S(age_a)/S(age_e)$ is the probability of a healthy female to survive fromage_e to age_a. The above probability was obtained from the already published United States life tables [29].

The patient-specific relative risk (RR) for the appearance of malignancies in the contralateral breast and ipsilateral lung was estimated as follows:

$$\mathrm{RR} = \frac{\mathrm{LAR} + \mathrm{LIR}}{\mathrm{LIR}} \quad (5)$$

where LIR is the organ- gender- and age-dependent lifetime intrinsic risk for developing a malignancy in the above radiosensitive structures of interest. The LIR values for unexposed cancer-free people were taken by the most recent report of the SEER Cancer Statistics Review [3]. The LIR for developing breast cancer in healthy 30-, 40-, 50- and 60-year-old females was 12.59%, 12.28%, 11.15% and 9.41%, respectively. The corresponding LIRs for the appearance of lung malignancies were 5.96%, 5.99%, 5.98% and 5.68%.

A Wilcoxon signed rank test was employed to find statistical differences between the LAR and RR values related to the development of lung or breast malignancies from HF forward-planned IMRT and the respective organ-specific cancer risks from SF treatment. A P-value of less than 0.05 was taken as statistically significant in the above tests. The statistical analysis was carried out with the use of Graph Pad package version 4.00 (Graph Pad Software Inc., CA, USA).

Table 3
Organ equivalent dose (OED) of the ipsilateral lung and contralateral breast from standard fractionated (SF) and hypofractionated (HF) forward-planned IMRT for primary breast carcinoma.

Patient no.	OED (Gy)			
	Ipsilateral lung		Contralateral breast	
	SF	HF	SF	HF
1	3.69	3.25	0.83	0.71
2	3.23	2.83	0.94	0.81
3	3.26	2.89	0.64	0.55
4	4.01	3.54	0.76	0.65
5	3.61	3.19	0.76	0.66
6	3.03	2.69	0.88	0.75
7	4.06	3.59	0.99	0.86
8	3.20	2.82	0.82	0.71
9	3.23	2.84	0.79	0.68
10	3.74	3.43	0.98	0.85
11	3.48	3.05	0.59	0.52
12	2.99	2.64	0.86	0.75
13	4.15	3.66	0.90	0.78

3. Results

3.1. OED calculations

The median D_{av} of the contralateral breast from SF and HF irradiation for breast carcinoma was 0.94 Gy and 0.80 Gy, respectively. The corresponding median values for the ipsilateral lung were 9.64 Gy and 8.20 Gy. The patient- and organ-specific OED calculations due to forward-planned IMRT for primary breast cancer are summarized in Table 3. The OED of the contralateral breast attributable to SF radiation therapy varied from 0.59 Gy to 0.99 Gy for the female patients under investigation. The corresponding variation associated with the use of HF treatment was found to be 0.52–0.86 Gy. The OED ranges for the ipsilateral lung due to SF and HF treatment for breast carcinoma were equal to 2.99–4.15 Gy and 2.64–3.66 Gy, respectively.

3.2. Radiotherapy-induced cancer risk assessments

The patient-dependent lifetime risks related to the development of secondary malignancies following the forward-planned IMRT of primary breast cancer are presented in Fig. 1. The LARs related to the contralateral breast cancer risk after SF IMRT were estimated to be 0.44–1.30%. The above risk range was reduced to 0.38–1.11% following HF IMRT for breast carcinoma. The lifetime risks for the appearance of a malignancy in the ipsilateral lung after SF and HF treatment for breast carcinoma were equal to 3.59–4.94% and 3.16–4.37%, respectively. The LARs for developing lung or breast malignancies due to HF forward-planned IMRT were significantly different from the respective risks associated with the SF approach ($P = 0.0002$). The median reduction of the probability for lung and breast cancer induction with the use of HF instead of SF treatment was 12.4% and 14.8%, respectively.

The RR assessments for each female patient subjected to forward-planned IMRT for breast carcinoma are shown in Fig. 2. The range of the RR values associated with the development of contralateral breast and ipsilateral lung malignancies from SF irradiation was 1.04–1.10 (median: 1.06) and 1.60–1.81 (median: 1.75), respectively. The corresponding RR ranges due to HF treatment were reduced to 1.03–1.09 (median: 1.05) and 1.53–1.73 (median: 1.67). The differences between the RRs of lung and breast cancer induction attributable to HF treatment and those associated with SF irradiation were statistically significant ($P = 0.0002$).

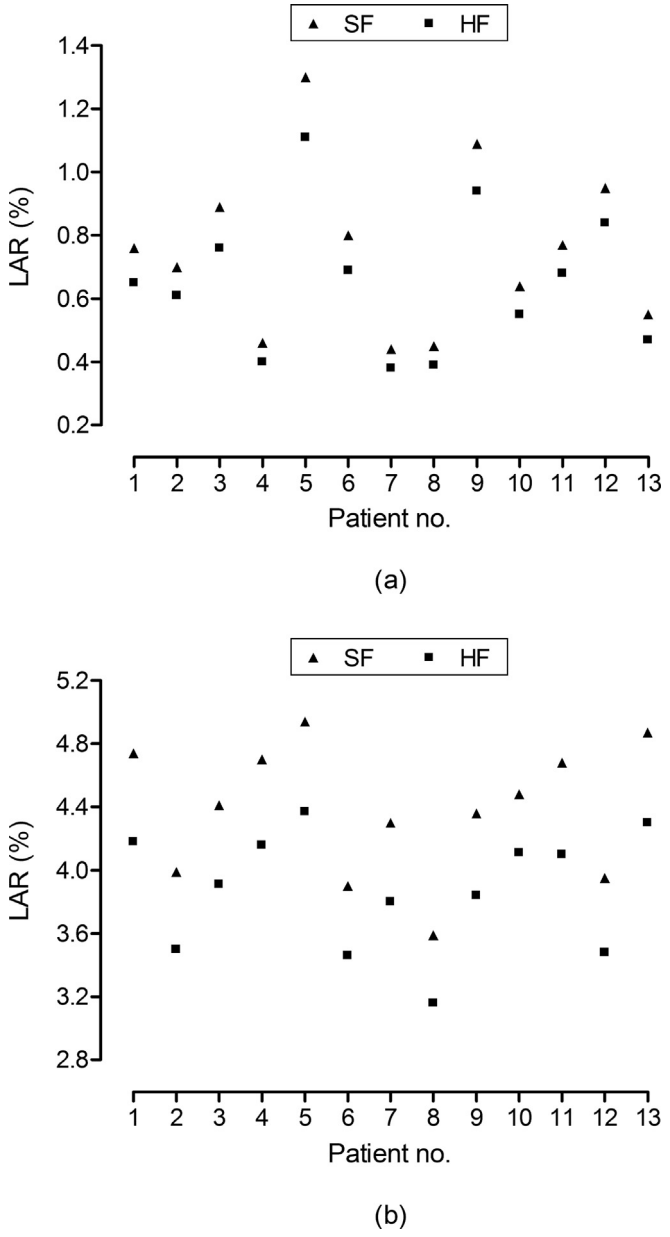

Fig. 1. Patient-specific lifetime attributable risk (LAR) for the development of secondary malignancies in the (a) contralateral breast and (b) ipsilateral lung from standard fractionated (SF) and hypofractionated (HF) forward-planned IMRT for primary breast carcinoma.

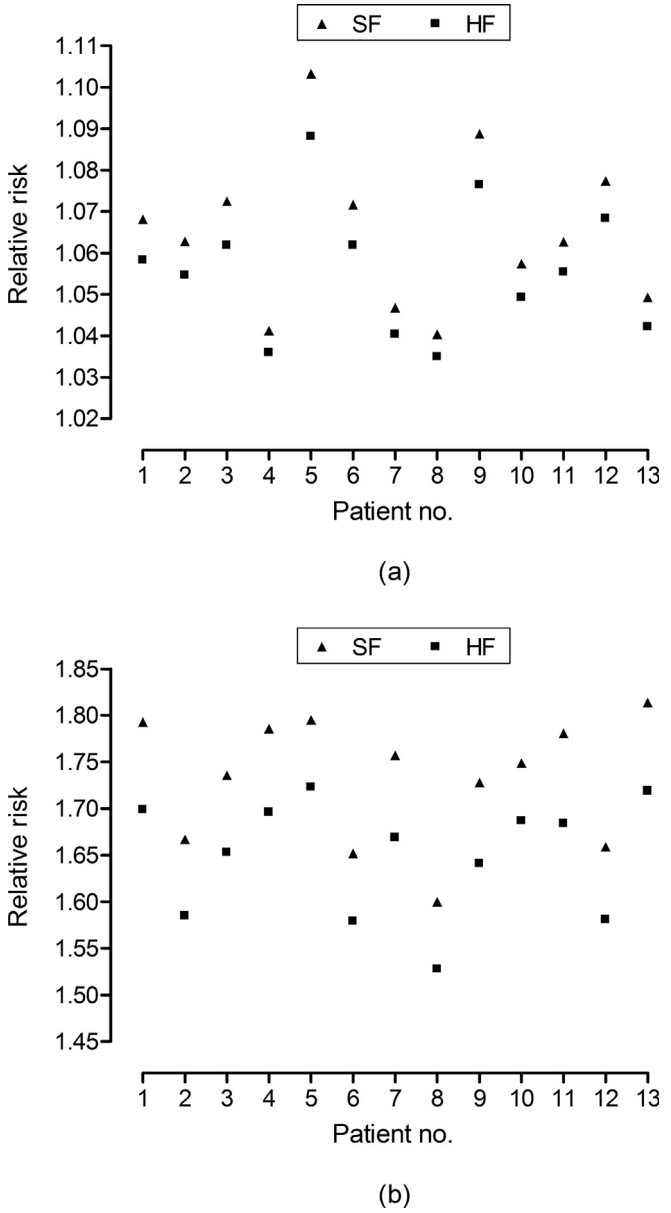

Fig. 2. Patient-specific relative risk for the development of secondary malignancies in the (a) contralateral breast and (b) ipsilateral lung from standard fractionated (SF) and hypofractionated (HF) forward-planned IMRT for primary breast carcinoma.

4. Discussion

The HF whole-breast irradiation has been considered as an effective treatment option and not inferior to the SF radiotherapy [8,9]. It should be noticed that none of the previous dosimetric studies [30–32] dealing with the probability of carcinogenesis after forward-planned IMRT for breast carcinoma investigated the impact of the fractionation scheme on the relevant second cancer risk. In the present study the lifetime second cancer risks after HF IMRT were compared with the respective risks associated with SF irradiation. The HF treatment resulted in a lower LAR of contralateral and ipsilateral lung cancer development than that associated with the conventional fractionated treatment. The above cancer risk reduction was systematically observed in all patients. The variation in the probability of breast or lung cancer induction among the study participants should be attributed to differences in the distribution of the absorbed dose within each organ of interest and to differences in the patient's age at the time of irradiation.

The LAR estimates were used together with the organ- age- and sex-specific LIRs to determine the RR for the development of secondary malignancies. The patient-specific RR for contralateral breast cancer induction was 1.04–1.10 when the SF forward planned IMRT was applied. The above risks imply that the baseline probability for the appearance of breast malignancies of unexposed people may increase by 4–10% following standard fractionated radiation therapy. The maximum LIR elevation with the use of HF irradiation was 9%. The RR values for the development of ipsilateral lung cancer were much higher than those related to the healthy contralateral breast. The use of SF forward-planned IMRT was estimated to result in a LIR increase of 60–81% whereas the hypofractionated treatment may lead to an elevation of 53–73%.

Only a few studies have used dosimetric data to estimate the second cancer risk from SF forward-planned IMRT for breast cancer [30–32]. Two of the above reports provided a single EAR value without giving

any data about the organ-specific lifetime risk of carcinogenesis [30,31]. Han et al. [32] reported that the mean LAR (± SD) for the appearance of secondary malignancies in the ipsilateral lung and contralateral breast is $(1511 \pm 263) \times 10^{-5}$ and $(104 \pm 38) \times 10^{-5}$, respectively. These risks corresponded to a 30-year-old female receiving a tumor dose of 50.4 Gy in 28 fractions and they were defined with the aid of a plateau model. This model ignores the fractionation effects on the radiotherapy-induced cancer risk. The LARs presented in the Fig. 1 of our study refer to patients aged 34 to 55 years old irradiated with 50 Gy in 25 fractions and they were derived from the use of a mechanistic model. This model accounts for the fractionation of the tumor dose and the organ-dependent ability for repopulation. The differences in the patient's age, fractionation scheme and dose-response model make the comparison of our results with the LARs given by Han et al. [32] to be discordant. The mechanistic model was previously employed for estimating the second cancer risks of three breast cancer patients subjected to SF three-dimensional conformal radiation therapy [33]. They reported similar lifetime contralateral breast cancer risks of 0.71% to 1.04% with those presented here for SF irradiation. They also gave a total LAR for cancer development in both lungs which can not compared with our results presenting the probability of carcinogenesis only to the highly exposed ipsilateral lung.

Previous epidemiological studies have provided data about the second cancer risks following radiotherapy for breast carcinoma [5–7]. These data were derived from patients irradiated with various techniques based on a variety of treatment planning methods during previous decades. Berrington de Gonzalez et al. [6] reported that the RR for the appearance of contralateral breast and ipsilateral lung cancer in patients subjected to radiotherapy for breast cancer is 1.09 and 1.54, respectively. The median follow-up in the above report was 13 years. Stovall et al. [5] studied patients diagnosed with primary breast cancer between 1985 and 1999. They found that irradiated females have 1.2 times greater risk for developing contralateral breast malignancies than unirradiated patients. Grantzau et al. [7] estimated a mean RR of 1.66 for the appearance of lung malignant diseases in exposed breast cancer patients after 15 or more years from treatment.

Our analysis showed that the median RR for lung cancer induction due to SF and HF forward-planned IIMRT for breast carcinoma is 1.75 and 1.67, respectively. The corresponding median values for the appearance of secondary contralateral breast malignancies were 1.06 and 1.05. The above RRs refer to the lifetime probability for second cancer development relative to that for unexposed and cancer-free females. The RRs in previous epidemiological reports [5–7] present the risk of carcinogenesis in respect to that of breast cancer patients not allocated for radiation therapy and they were mainly derived from the patients' follow up for certain periods not covering the entire lifetime. Despite the above differences in the RR assessment, the median RRs for lung cancer induction from SF and HF IMRT as estimated in our study are comparable with those obtained by epidemiological data [6,7]. The median RRs for developing contralateral breast cancer due to forward planned IMRT are lower than those given in previous reports [5,6] dealing with less advanced irradiation techniques.

The small number of breast cancer patients participating in this work constitutes a study limitation. The presented results may be limited by the uncertainties of the mechanistic model [20] employed in the current study. Inaccuracies in the calculation of the OED of lung and breast mainly arise from the errors in the determination of the organ-dependent model parameters R, a and β. The OED calculations were also relied on the approach that the a/β ratio equals to 3 irrespective of the organ under investigation as previously proposed by Schneider et al. [20]. It has been mentioned that the differences in the probability for breast cancer induction following exposure to high doses are not significant by assuming a/β values from 1 to 5 Gy [28]. Similar results have not been published for different organs characterized by the predisposition for carcinogenesis including the lung. The uncertainty of the LAR estimations is affected by the inaccuracy in the calculated OEDs and the error in the definition of the parameter β_0 expressing the initial slope for radiation-induced lung or breast cancer at the region of low doses. The aforementioned uncertainties need to be taken into account whenever the model-based absolute cancer risk assessments are to be used in clinical practice.

5. Conclusions

The findings of this study derived from a relatively small number of patients showed that the forward-planned IMRT for breast carcinoma results in an increased probability for developing secondary malignancies in the healthy contralateral breast or ipsilateral lung compared to the respective baseline risks of the unexposed population. The application of HF instead of SF breast irradiation may lead to a small reduction of the model-estimated cancer risks. The presented lifetime cancer risk estimates may be useful in the treatment planning and follow-up of female patients irradiated for primary breast cancer.

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