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The risk for developing a secondary cancer after breast radiation therapy: Comparison of photon and proton techniques

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Abstract

Background and purpose: To compare secondary malignancy risks of modern proton and photon therapy techniques for locally advanced breast cancer.

Methods and materials: We utilized dosimetric data from 34 [10 photon-VMAT, 10 photon-3DCRT, 14 pencil beam scanning proton (PBS)] breast cancer patients who received comprehensive nodal irradiation. Employing a model based on organ equivalent dose to account for both inhomogeneous organ dose distributions and non-linear functional dose relationships, we estimated excess absolute risk, excess relative risk, and lifetime attributable risk (LAR) for secondary malignancies. The model uses dose distribution, number of fractions, age at exposure, attained age, the linear-quadratic dose response relationship for cell survival, repopulation factor, as well as gender specific age dependencies, and initial slopes of dose response curves.

Results: The LAR for carcinoma at age 70 was estimated to be up to 3.64% for esophagus with an advantage of 3DCRT over PBS and VMAT. For the ipsilateral lung, risks were lowest for PBS (up to 5.56%), followed by 3DCRT (up to 6.54%) and VMAT (up to 7.7%). For the contralateral lung, there is a clear advantage of 3DCRT and PBS techniques (risk <0.86%) over VMAT (up to 4.4%). The risk for the contralateral breast is negligible for 3DCRT and PBS but was estimated as up to 1.2% for VMAT. Risks for the thyroid are overall negligible. Independently performed comparative treatment plans on 10 patients revealed that the risk for the contralateral lung and breast using VMAT can be more than an order of magnitude higher compared to PBS. Sarcoma risks were estimated as well showing similar trends but were overall lower compared to carcinoma.

Conclusion: Conventional (3DCRT) techniques led to the lowest estimated risks of, thyroid and esophageal secondary cancers while PBS demonstrated a benefit for secondary lung and contralateral breast cancer risks, with the highest risks overall associated with VMAT techniques.

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Conflict of interest

The authors have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2020.05.035.

Keywords

Secondary malignancies; Outcome modelling; Breast cancer

The use of a specific treatment technique in radiation therapy is mainly motivated by the achievable dose conformity to the target and the overall integral dose. Proton therapy offers a highly conformal and comprehensive treatment option with a lower integral dose (reduced low-dose bath) to organs at risk (OARs). Consequently, given the proximity of cardiopulmonary structures, proton therapy has been discussed as a treatment alternative for breast cancer patients [1–3]. Treatment planning studies, comparing 3DCRT, IMRT, and proton therapy when irradiating the breast and regional nodes showed advantages of using proton therapy particularly in terms of dose to the heart [4–6].

Considering the good prognosis and long life expectancy of breast cancer patients, late toxicities such as cardiac toxicities or secondary cancers are of concern [7–15]. While there are many factors impacting the risk for developing a secondary cancer, such as smoking status or chemotherapy [12,16,17], it has been estimated that ~9% of the secondary cancers among breast cancer patients are attributable to radiation exposure [18,19]. Several observational population-based studies have assessed secondary cancer risks [9,12,17–26]. None of these studies have included proton therapy patients.

The aim of this study was to compare secondary cancer risks between 3DCRT, VMAT and PBS. In dosimetric planning studies comparing different modalities, the outcome might depend on the treatment planning consideration for each modality. Selecting patients that were previously treated using 3DCRT, VMAT or proton therapy might introduce a bias because patients might have been selected for specific modalities due to confounding factors and different constraints might have been used depending on the treatment modality. On the other hand, using a cohort of patients and subsequently planning each patient for all three modalities also might introduce a bias as specific patients might not have been selected for a specific modality due to confounding factors or dosimetric considerations. Consequently, this study did both, comparing secondary cancer risks based on a retrospective analysis of treatment plans for a cohort of patients treated with the three modalities as well as re-planning a cohort of patients with all three different modalities to compare risks of different treatment options for the same patient.

Methods

Modelling approach

Classical models to estimate the risk (excess relative risk (*ERR*) or excess absolute risk (*EAR* in risk per 10,000 Person Years (PY))) for a secondary cancer are based on the atomic bomb survivors [27–29]. In order to apply them to radiation therapy conditions with inhomogeneous and higher doses, these models have been expanded beyond a purely linear dose–response relationship [28,30–34]. Using a repopulation parameter, the number of fractions, and a cell kill parameter obtained from the tissue-dependent parameters of the linear quadratic model, an organ equivalent dose (*OED*) can be defined. The *OED*

replaces the homogeneous low dose D in risk formalisms for low dose exposure [29]. The complete model to estimate ERR and EAR for a specific organ also includes gender and age specific parameters obtained from low dose data. In addition to ERR and EAR, the Lifetime Attributable Risk (LAR; percentage likelihood in excess of the baseline risk of secondary malignancy happening during one's lifetime) can be estimated as an integral of excess risk for all attained ages up to a maximum age. The LAR can be calculated based on either the ERR or the EAR formalism. For details on the formalism, the reader is referred to the Supplementary Material.

Model parameters

We applied model parameters based on the analysis of Hodgkin's patients published by Schneider et al. (Supplementary Material Table S3) [34]. While this might lead to an overestimation of cancer incidences due to the genetic susceptibility of the Hodgkin patient population with regard to cancer, estimated relative risks (photons versus protons) are less affected. In a study on radiation induced lung cancer in Hodgkin's disease patients, Gilbert et al [35] found similar dose–response relationships as in breast cancer patients with an ERR of 15% per Gy. For comparison, we also applied parameters published in the BEIR VII report (Supplementary Material Table S4) [29]. The LAR was calculated based on EAR alone when using the Schneider et al. parameters. When using the BEIR VII parameters for ERR and EAR, we did estimate LAR using a log weighted average of the ERR and EAR based formalisms.

Patient cohort

After approval by the institutional review board a cohort of 34 patients was analyzed, 20 treated with photon techniques (10 3DCRT and 10 VMAT) and 14 treated with proton therapy (using pencil beam scanning (PBS)). The average age was 47.3 years,41.9 years, and 45.8 years for the 3DCRT, VMAT, and PBS cohort, respectively. All patients were treated at our institution and 10 for each modality were randomly selected. We then added 4 patients in the proton arm in order to reach a similar average age at exposure for the three groups. In addition, in order to allow for a one-to-one comparison between modalities for the same patient characteristics, 10 of the PBS patients (average age 38.9 years, range 20–54) were re-planned using both 3DCRT and VMAT techniques. The dose distribution for one of these patients is shown in Fig. 1

Of the total cohort of 34 patients who received treatment by modality, 3/14 (21%) had intact breast with PBS, 3/10 (30%) had intact breast with 3D, and 2/10 (20%) had intact breast with VMAT. Of the 10 patients selected for direct comparison planning between PBS, VMAT, and 3D, 8 patients received mastectomy and 2 had intact breasts (2/10, 20%), in keeping with the approximately percentages observed in the larger cohort by modality.

Treatment planning

For the purposes of this study, all treatment plans utilized institutional constraints for acceptability to OARs. These constraints vary by virtue of treatment modality. The RTOG breast and RadCOMP contouring atlases were used for delineation of both target structures and OARs. Target structures included the breast/chest wall (excluding ribs), supraclavicular

(SCV), and internal mammary (IMN) lymph nodes, and axilla. For patients with breast reconstruction, the prosthesis and overlying skin were included in the chest wall target. OARs included the esophagus, thyroid, bilateral lungs, contralateral breast, and heart.

Across PBS, VMAT, and 3DCRT plans, the doses prescribed to each target were the same. Specifically, the chest wall and IMN dose was either 50 Gy in 25 daily fractions of 2.0 Gy, or 50.4 Gy in 28 daily fractions of 1.8 Gy, 5 days per week. The SCV and axilla received either 45 Gy or 50.4 Gy in 25 or 28 daily fractions of 1.8 Gy, 5 days per week. For patients with intact breasts, the whole breast was prescribed 45.0 Gy in 25 daily fractions of 1.8 Gy, 5 days per week, followed by a 14.4 Gy boost in 1.8 Gy per day to the lumpectomy cavity. In the case of PBS, Gy(RBE) were prescribed using an RBE (relative biological effectiveness) of 1.1. Target coverage was maximized while meeting the below normal tissue constraints.

For PBS, normal tissue constraints included a maximum esophageal dose of 40 Gy(RBE), a maximum thyroid dose of 50.4 Gy(RBE), a maximum mean heart dose of 1.5 Gy(RBE), and an ipsilateral lung volume of <20% receiving 20 Gy(RBE). The contralateral lung and breast dose is not designated with specific constraints for PBS, given the low overall exposure.

For VMAT, normal tissue constraints included a maximum esophageal dose of 40 Gy, a maximum thyroid dose of 50.4 Gy, a maximum mean heart dose of 5 Gy, the ipsilateral lung volume of <65% receiving 5 Gy and <30% receiving 20 Gy, and the contralateral breast volume of <5% receiving 10 Gy, and a mean contralateral breast dose maximum of 7 Gy. The contralateral lung is not designated with specific constraints.

For 3DCRT, normal tissue constraints include a maximum mean heart dose of 2.5 Gy and an ipsilateral lung volume of <35% receiving 20 Gy. For 3DCRT, we do not typically designate a maximum esophageal or thyroid dose as a traditional MAO field borders typically limit esophageal and thyroid exposure. We also do not typically designate a maximum contralateral breast or contralateral lung dose for 3DCRT as cardiac dose constraints typically limits contralateral organ exposure.

The planning process was homogeneous across patients. Please see Supplementary Material for more details.

Results

The three modalities considered in this study differ mainly in the distribution of dose in OARs and the total energy deposited in the patient (“integral dose”). Table 1 shows the average mean dose to the organ at risk and the correlation of the mean dose with LAR at an attained age of 70 (LAR_{70}). The risks for the contralateral lung and contralateral breast scale very well with integral dose whereas the dose distribution combined with the patient’s age plays a bigger role for the other organs. The mean dose to the esophagus and the thyroid is lowest for 3DCRT. For the lungs, there is a clear advantage for PBS and a clear disadvantage for VMAT.

Fig. 2 shows the *LAR* and *EAR* values for esophagus, thyroid, contralateral breast, ipsilateral lung, contralateral lung and whole lung using parameters from Table S3 (from Schneider et al. [36] and Santos et al. [13]). Curves for the parameter sets from Table S4 (from the BEIR VII report [29]) are not shown here as the two data sets show similar trends albeit different absolute values. This is shown in Tables 2 and 3 listing *EAR* and *LAR* at an attained age of 70 for both parameter sets. Values for *LAR* for lung and breast are very similar (within 20%) while *LAR* values for esophagus are a factor of two higher when using the BEIR parameters, which is mainly driven by *EAR* values predicted to be a factor of 10 higher for BEIR. For the ipsilateral and contralateral lung, the BEIR parameters predict an *LAR* 10% and 20% lower than with the Schneider parameter set, respectively.

Even though differences between modalities are driven also by differences in patient age, overall there is a clear disadvantage for VMAT mainly due to the higher mean dose. The *LAR* for VMAT reaches up to 11 and 6 per 100 patients per year in the ipsilateral and contralateral lung, respectively. The risk for the contralateral breast is also significantly higher when using VMAT. The risk for PBS is on average lower than for 3DCRT and VMAT for the lungs as well as contralateral breast. For the esophagus, 3DCRT shows an advantage even over PBS but the overall risk is quite low. The risk for sarcoma is overall lower than for carcinoma and negligible except for the ipsilateral lung where the *LAR* for sarcoma reaches about 1/3 of the carcinoma risk.

The range of values for the 34 patients in Tables 2 and 3 not only demonstrates differences between modalities but also patient specific differences due to age and dosimetric factors. To allow a one-to-one comparison we re-planned 10 of the PBS patients for 3DCRT and VMAT delivery carcinoma (Fig. S1 in the Supplementary Material shows average dose-volume histograms (DVH) for the 3DCRT, VMAT and PBS plans). We then calculated *EAR*, *ERR* and *LAR* values. Fig. 3 shows the ratios of LAR_{70} for the patients planned with all three modalities. For esophagus and thyroid 3DCRT offers an advantage over PBS while the risks are very similar between PBS and VMAT. For the ipsilateral lung an advantage is seen for PBS over both 3DCRT and VMAT. The most striking differences are for the contralateral lung and contralateral breast with a slight advantage of PBS over 3DCRT but a significantly higher risk compared to PBS when VMAT is used. The risk for the contralateral lung and breast using VMAT is on average about an order of magnitude higher compared to PBS.

Discussion

This dose modeling study was pragmatic in that it utilized patient treatment plans using different institutional constraints by modality. In order to minimize bias in the patient selection we not only retrospectively analyzed treatment plans from 3DCRT, VMAT and proton therapy patients but also compared treatment plans for all three modalities for the same cohort of patients. Both methods resulted in consistent findings regarding the relative differences between these three modalities with respect to secondary cancer risks.

One would expect varying degrees of both target coverage and dose to OAR across modalities for the same patient. The resulting secondary cancer risk estimates reflect modern planning constraints, but do not compare secondary cancer risks assuming the same degree

of target coverage across modalities. It should be noted that further refinements to normal tissue constraints across treatment modalities could alter the estimates of secondary cancer risk modeled in this study. Furthermore, as in any treatment planning study, be it to simply compare dosimetric indices or risk indices, institutional guidelines as well as the experience of individual treatment planners can impact results. All patients considered in this study were planned and treated at the same institution under the same institutional guidelines and planned by experienced planners. However, we can't rule out that other institutions or planners might have chosen different plan parameters. Furthermore, the plan quality certainly also depends on the treatment planning system, which could potentially impact secondary cancer risks. Nevertheless, we don't expect our relative comparison between modalities and the drawn conclusions to be affected significantly.

This study focuses entirely on the risk for a secondary malignancy when comparing three modalities. This risk has to be interpreted in the context of other potential side effects as well as potential differences in tumor control [37,38]. This is beyond the scope of this study.

The dosimetric parameters used in the analysis assume a proton RBE of 1.1 based on current clinical practice. The RBE depends on physical as well as biological parameters and could potentially be higher especially at lower doses which would increase the risk from protons [39]. For the OED this increase could potentially be on the order of ~10–20%. Note that secondary radiation from neutrons is negligible in PBS [40].

One might expect large uncertainties in the model parameters and consequently the risk estimation. Quantification of these uncertainties is difficult as discussed in detail by Preston et al. [41]. The initial slope of the dose–response curve is obtained from the atomic bomb survivor data with uncertainties in terms of radiation field and location of the person during the incident. Furthermore, the high-dose risk parameters are mostly obtained from cancer incidences of Hodgkin's patients, which might cause an overestimation of the risks. Shuryak et al. [42] have questioned their applicability in adult cancer induction estimates and concluded that excess relative risks for adults could be much higher compared to the risk after childhood irradiation. On the other hand, adults might have a negligible thyroid cancer risk after radiation therapy. Our results based on 2 different parameter sets provide some insight into potential modeling uncertainties. Furthermore, relative quantities when comparing proton versus photon radiations as done in this study will be associated with smaller uncertainties [43,44].

Only one previously published modeling study includes proton therapy [45]. Using the same formalism as used in this work (albeit with slightly different values for the high dose parameters α and R) the authors compare the risk for breast and lung cancer when treating breast cancer patients with VMAT and PBS. The results agree well with our results with EAR per 100-PY about one order of magnitude higher for VMAT than for PBS for contralateral structures (breast (0.1 versus 0.01); lung (0.14 versus 0.02)) and a factor of ~2 higher for the ipsilateral lung (0.35 versus 0.2). Also, our photon results agree well with other studies on photon techniques [7,8,10,11,13,46–49] (see Tables S6 and S7 in the Supplementary Material).

Doses were measured in anthropomorphic phantoms and then used in the BEIR formalism (with published parameters for esophagus [50]) by Hoekstra et al. [8]. The *LAR* values for women exposed at 40 were 0.04%, 0.03%, and 0.004% for thyroid using different photon radiation techniques (Whole Breast Irradiation, 3D conformal Accelerated Partial Breast Irradiation, VMAT). For the lung, the respective values were 3.69%, 2.09%, and 3.32%. For breast, *LAR* values of 0.52%, 0.08%, and 0.17%, respectively, were determined. Santos et al. [13] used the same formalism and model parameters as used in our study to estimate secondary cancer risk after different external beam photon breast radiation therapy. The *LAR* was between 0.20% and 0.54% for right sided and between 0.19% and 0.53% for left-sided targets for the contralateral lung. For the ipsilateral lung the ranges were 2.92% to 4.66% and 1.83% to 3.03%, respectively. For the contralateral breast and right-sided target, the *LAR* values were between 0.1% and 0.14% and for left sided target the risks were between 0.08% and 0.18%. Fogliata et al. [7] modeled the secondary cancer risk for breast and lung cancer after breast radiation therapy with VMAT using the same methodology as used in our study with model parameters based on Hodgkin's patient cohorts deduced previously [51] from studies by Preston et al. [52], Travis et al. [53], Gilbert et al. [35] as well as Schneider et al. [28,31,36,54]. Accordingly, they determined *EAR* for contralateral breast cancer of 0.17, 0.02 and 0.08 per 100-PY for 3D-CRT, partial VMAT and full VMAT, respectively. For the contralateral lung, the *EAR* per 100-PY was estimated to be 0.01, 0.02 and 0.07, respectively. In another modeling study using the same formalism and parameters as in our work treatment plans for VMAT used to treat left breast carcinoma were evaluated [10]. 50 patients at around 50 years of age were assessed. The mean *EAR* values were 0.45, 0.11, for left lung and right lung, respectively, for IMRT treatments and 0.55, 0.30 for VMAT treatments in units of 1/100-PY. Respective values for contralateral breast were obtained as 0.05 and 0.14 for IMRT and VMAT, respectively. The BEIR VII model in combination with dosimetric measurements in phantoms were used by Donovan et al. [46] to assess the secondary cancer risk after 5 different photon treatment techniques. For an age at exposure of 40, the investigators determined *LAR* values between 0.02% and 0.04% for thyroid cancer, between 0.07% and 1.09% for contralateral lung, between 0.14% and 0.82% for contralateral breast, and between 0.02% and 0.41% for esophagus. Haciislamoglu et al. [47] also applied the OED formalism in combination with the *EAR* concept, using the same parameter set as used in our work. The *EAR* values were reported as 0.04 and 0.20 (contralateral breast), 0.04 and 0.22 (contralateral lung), 0.28 and 0.65 (ipsilateral lung), for 3DCRT and VMAT per 100-PY, respectively. Abo-Madyan et al. [11] reported *EAR* values for lung cancer as 0.27 and 0.31 per 100-PY for 3D-CRT and VMAT, respectively.

In summary, identifying the optimal treatment technique for each patient should incorporate consideration of cancer risks by patient age. Our methodology could be implemented to do so in routine planning. For our cohort, we conclude that 3DCRT leads to the lowest estimated risks of thyroid and esophageal secondary cancers while PBS demonstrated a benefit for secondary lung and breast cancer risks, with the highest secondary cancer risks overall associated with VMAT techniques. The risk values shown with VMAT were concerning and therefore VMAT plans should attempt to constrain dose to the lungs as much as possible.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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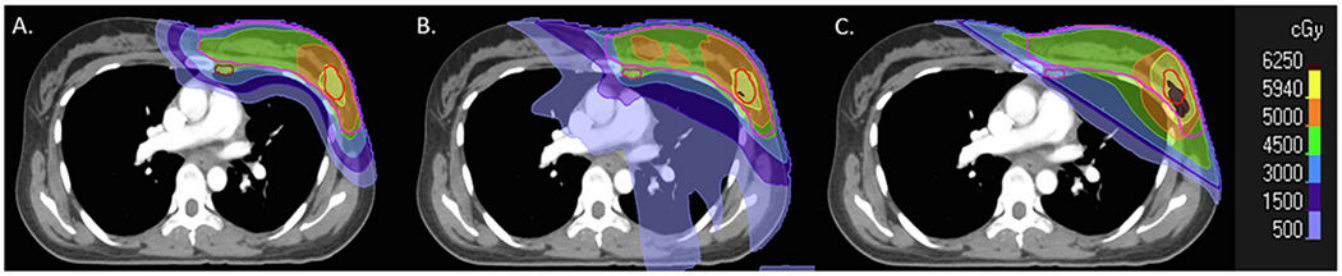

Fig. 1.
Treatment plans for a breast cancer patient using PBS (A), VMAT (B), and 3DCRT (C).

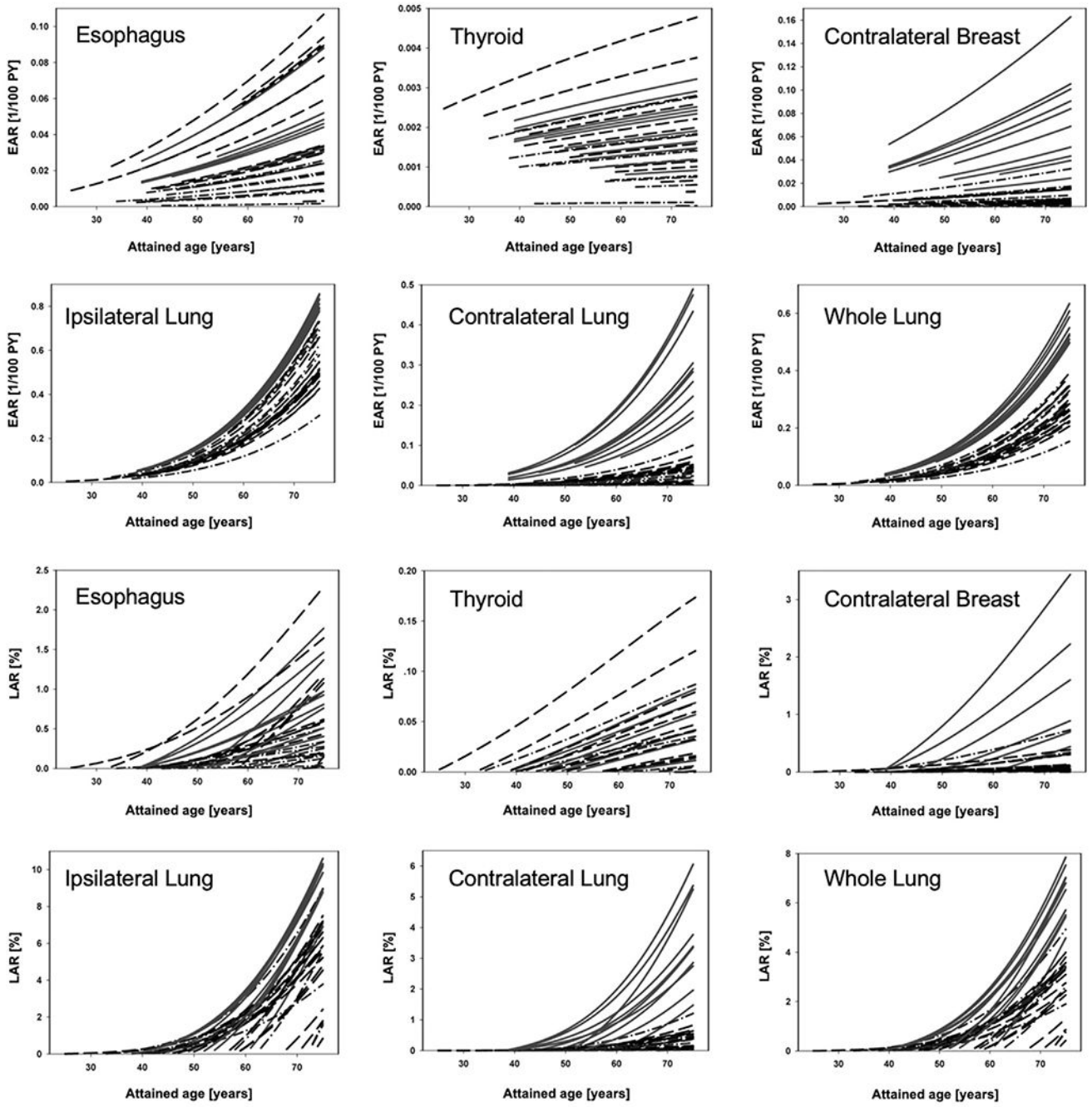

Fig. 2.

Upper panels: Excess absolute risk (*EAR;* carcinoma) for esophagus, thyroid, contralateral breast, ipsilateral lung, contralateral lung, and whole lung (right). Lower panels: Respective Lifetime attributable risk (*LAR*) as a function of attained age. The starting point for each curve is the patient's age at the time of treatment plus a latency period of 5 years. Solid lines: VMAT; Dashed lines: PBS; Dashed-dotted lines: 3DCRT.

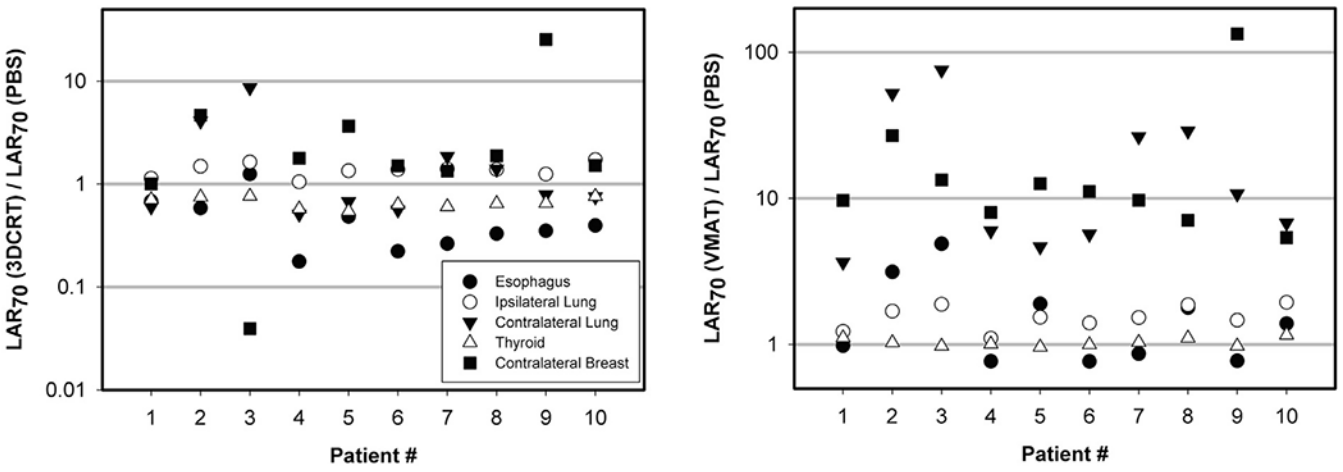

Fig. 3.

Ratio of LAR_{70} (carcinoma) for 3DCRT vs. PBS (left) and for VMAT vs. PBS (right).

Table 1

Average mean dose to different organs from different modalities for the patient cohort studied. Also shown is the linear correlation to LAR_{70} for carcinoma (using Table S3 (Schneider et al. parameters)/Table S4 (BEIR parameters), respectively).

	Average mean dose [Gy] 3DCRT	**Average mean dose [Gy] VMAT**	**Average mean dose [Gy(RBE)] PBS**	**linear correlation (slope) of LAR_{70} as a function of mean dose**
Ipsilateral Lung	11.86	13.57	8.22	0.45/0.44
Contralateral Lung	0.30	3.08	0.34	0.98/0.98
Whole Lung	5.80	8.22	4.17	0.67/0.67
Esophagus	2.18	9.50	10.91	0.77/0.80
Thyroid	9.15	21.21	19.72	0.01/0.24
Contralateral breast	0.52	5.16	0.40	0.89/0.86

Table 2

Average excess absolute risk for second carcinoma and sarcoma at age 70 and range in brackets for the patient cohort considered.

	Table S3 parameters (Schneider et al.)			Table S4 parameters (BEIR)		
	EAR_{70} [1/100 PY] 3DCRT	**EAR_{70} [1/100 PY] VMAT**	**EAR_{70} [1/100 PY] PBS**	**EAR_{70} [1/100 PY] 3DCRT**	**EAR_{70} [1/100 PY] VMAT**	**EAR_{70} [1/100 PY] PBS**
CARCINOMA						
Esophagus	0.01 [0.0–0.03]	0.05 [0.02–0.08]	0.05 [0.01–0.09]	0.10 [0.10–0.19]	0.39 [0.18–0.65]	0.44 [0.07–0.85]
Ipsilateral Lung	0.46 [0.23–0.55]	0.61 [0.58–0.64]	0.39 [0.32–0.55]	0.19 [0.10–0.24]	0.26 [0.25–0.27]	0.17 [0.13–0.24]
Contralateral Lung	0.03 [0.0–0.08]	0.23 [0.13–0.37]	0.03 [0.00–0.05]	0.01 [0.0–0.03]	0.10 [0.01–0.16]	0.01 [0.00–0.02]
Whole Lung	0.23 [0.11–0.29]	0.42 [0.37–0.47]	0.20 [0.15–0.28]	0.10 [0.05–0.13]	0.18 [0.16–0.21]	0.09 [0.07–0.12]
Thyroid	<0.005	<0.005	<0.005	0.04 [0.0–0.18]	0.04 [0.0–0.14]	0.10 [0.00–0.50]
Contralateral Breast	0.01 [0.0–0.03]	0.07 [0.02–0.14]	0.01 [0.0–0.01]	0.01 [0.0–0.01]	0.04 [0.0–0.10]	<0.005
SARCOMA						
Esophagus	<0.005	<0.005	0.01 [0.0–0.03]	<0.005	0.04 [0.0–0.14]	0.07 [0.0–0.26]
Ipsilateral Lung	0.16 [0.11–0.27]	0.21 [0.19–0.22]	0.13 [0.10–0.18]	0.07 [0.05–0.12]	0.09 [0.08–0.09]	0.06 [0.04–0.09]
Contralateral Lung	<0.005	0.01 [0.0–0.04]	<0.005	<0.005	0.01 [0.0–0.02]	<0.005
Whole Lung	0.08 [0.05–0.13]	0.11 [0.09–0.13]	0.07 [0.05–0.09]	0.03 [0.02–0.06]	0.05 [0.04–0.05]	0.03 [0.02–0.04]
Thyroid	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005
Contralateral Breast	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005

Table 3

Lifetime attributable risk in % for secondary carcinoma and sarcoma at age 70 and range in brackets for the patient cohort considered.

	Table S3 parameters (Schneider et al.)			Table S4 parameters (BEIR)		
	£LAR_{70} 3DCRT	**£LAR_{70} VMAT**	**£LAR_{70} PBS**	**£LAR_{70} 3DCRT**	**£LAR_{70} VMAT**	**£LAR_{70} PBS**
CARCINOMA						
Esophagus	0.18 [0.03–0.42]	0.74 [0.22–1.45]	0.70 [0.08–1.90]	0.36 [0.05–0.79]	1.46 [0.51–2.71]	1.49 [0.20–3.64]
Ipsilateral Lung	4.58 [2.75–6.54]	6.56 [4.10–7.70]	3.95 [0.82–5.23]	3.92 [2.27–5.57]	5.57 [3.73–6.37]	3.50 [0.72–5.56]
Contralateral Lung	0.28 [0.01–0.87]	2.56 [0.87–4.40]	0.26 [0.01–0.57]	0.24 [0.01–0.73]	2.16 [0.80–3.63]	0.23 [0.01–0.49]
Whole Lung	2.33 [1.38–3.60]	4.49 [2.71–5.70]	2.06 [0.44–2.78]	2.01 [1.14–3.07]	3.82 [2.47–4.80]	1.83 [0.40–2.74]
Thyroid	0.03 [0.00–0.08]	0.04 [0.01–0.07]	0.05 [0.00–0.16]	0.05 [0.00–0.18]	0.07 [0.01–0.11]	0.10 [0.00–0.50]
Contralateral Breast	0.18 [0.0–0.61]	1.20 [0.28–2.84]	0.09 [0.01–0.33]	0.14 [0.0–0.55]	0.92 [0.16–2.33]	0.08 [0.0–0.35]
SARCOMA						
Esophagus	<0.005	0.08 [0.0–0.32]	0.12 [0.0–0.57]	<0.005	0.15 [0.01–0.60]	0.25 [0.0–1.09]
Ipsilateral Lung	1.61 [1.28–3.14]	2.26 [1.55–2.55]	1.32 [0.30–1.77]	1.38 [1.07–2.67]	1.92 [1.40–2.17]	1.18 [0.27–1.85]
Contralateral Lung	<0.005	0.15 [0.02–0.44]	0.02 [0.0–0.06]	<0.005	0.12 [0.02–0.36]	0.02 [0.0–0.05]
Whole Lung	0.77 [0.61–1.65]	1.17 [0.89–1.42]	0.66 [0.17–0.84]	0.66 [0.55–1.40]	0.99 [0.81–1.20]	0.59 [0.15–0.89]
Thyroid	<0.005	0.01 [0.0–0.03]	0.01 [0.00–0.05]	0.01 [0.00–0.01]	0.02 [0.01–0.06]	0.03 [0.00–0.15]
Contralateral Breast	<0.005	0.02 [0.0–0.09]	<0.005	<0.005	0.02 [0.0–0.07]	<0.005