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WHAT ANATOMIC FEATURES GOVERN PERSONAL LONG-TERM HEALTH RISKS FROM BREAST CANCER RADIOTHERAPY?

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Breast cancer radiotherapy may in the long term lead to radiation-induced secondary cancer or heart disease. These health risks hugely vary among patients, partially due to anatomy-driven differences in doses deposited to the heart, ipsilateral lung and contralateral breast. We identify four anatomic features that largely cover these dosimetric variations to enable personalized risk estimates. For three exemplary, very different risk scenarios, the given parameter set reproduces 63–74% of the individual risk variability for left-sided breast cancer patients. These anatomic features will be used in the PASSOS software to support decision processes in breast-cancer therapy.

INTRODUCTION

To reduce local recurrence and mortality rates in breast cancer patients, breast-conserving surgery is commonly complemented by adjuvant whole-breast radiotherapy. However, breast cancer radiotherapy also increases the incidence of secondary cancers, in particular in the lung and contralateral breast, and heart disease mortality, mainly for patients with left-sided breast tumours.[1, 2] While the benefits of radiotherapy outweigh its risks,[3] the long-term risks become increasingly important with improved cure rates and prolonged patient survival.

The risks largely differ among patients. They vary with age, generally increase with tobacco smoking or alcohol consumption, and depend on genetic factors.[3] The risks are largely governed by radiation doses to which critical organs were exposed. Patient-specific, anatomy-dependent dose distributions in nearby organs are routinely available from treatment planning systems (TPS). Complementing TPS with organ-specific risk models accounting for non-dosimetry factors thus represents a promising strategy to incorporate long-term risks as an additional endpoint into clinical decision processes.[4] However, individual variability in doses to critical nearby organs can be largely explained by a few anatomic measures taken from planning CT images.[5, 6] Personalized risk estimates could thus be derived already before performing the actual TPS calculations, though with a reduced accuracy. This may be of added value when discussing the benefits and risks of adjuvant radiotherapy for the particular patient. It may also help optimize treatment strategies by identifying patients most benefiting from advanced irradiation techniques.[7] Making use of anatomic information to estimate individual doses may also improve retrospective analyses of radiotherapy cohorts.

Thus, to assess long-term risks from breast cancer radiotherapy on a personalized basis, in the PASSOS project,[8] methods were developed[6, 9] to estimate anatomy-dependent doses to nearby organs prior to TPS calculations. Exposures of distant organs were assessed too.[10] Organ-specific risk models were used that accounted for non-dosimetric risk factors such as age, smoking and other factors. A dedicated software tool is under development to facilitate the application of the project results in clinics.[8]

In this work, we address in detail the risk-motivated selection of anatomic features to estimate person-specific organ doses. Previously, we proposed using three anatomic features to estimate mean doses to the heart, lungs and contralateral breast.[9] The feature selection aimed at best predicting doses to these organs simultaneously. This may, however, be suboptimal with respect to assessing personal risk, since different organs hardly contribute to the overall risks equally per unit dose. Unfortunately, there is no single, general risk model that could be used as the basis for selecting most informative anatomic features, due to the mentioned dependence on age, smoking and other factors and differences between low- and high-dose data.[11] Hence, here

we update our previous paper[9] by analysing the feature selection for several risk-motivated scenarios. Complementing the previously proposed triplet by a fourth anatomic feature, we show that the quartet provides dose models almost as informative as features selected specifically for a given scenario or even for single organs. This quartet is thus robust with respect to alternative risk models and will be used in the PASSOS software.[8]

METHODS

The most pertinent aspects of the methods are described below; details can be found elsewhere.[6–9]

Treatment planning data

Whole-breast irradiations with 50.4 Gy in 28 fractions using 3D conformal radiotherapy with field-in-field technique (no physical or virtual wedges) were planned for 128 early-stage breast cancer patients (72 with left- and 56 with right-sided tumours) in two major radiotherapy centres. The inclusion criteria were as follows: pT1–2, tumour size < 3 cm, pN0, G1–3, R0. The plans were generated for 6–10 MV photons using Oncentra Masterplan system's collapsed cone algorithm. All plans met the requirements on target coverage (95% of the target covered by 95% of the prescribed dose), plan conformity (mainly keeping hot spots below 110% of the prescribed dose) and organ-at-risk dose constraints. Data for two patients with right-sided tumours whose anatomies were highly atypical were excluded from the analysis.

Anatomic features

In addition to tumour laterality and location in (or between) breast quadrants, numerous parameters on thorax anatomy were assessed from CT images[6]: maximum heart distance (MHD), i.e. the extent of the heart covered by the tangential breast field (or, for MHD < 0, the distance of the heart from the tangent); central lung distance (CLD) and contralateral lung distance (CoLD), analogous measures for the ipsilateral and contralateral lungs; contralateral lung maximum distance, given by the farthest point from the tangent; minimum breast distance (MBD), the distance of contralateral breast from the tangent; directly measured breast-to-breast distance (BBD); the thickness and width of the treated breast (BTh, BW); mid-plane lung distance (MLD), the extent of lung beyond the tangent to the treated breast in the mid-breast (isocentre) CT slice; mid-plane lung width (MLW) as the section length of this tangent; the sternal cage section length (SCL) and rib-cage section length; maximum heart length, central lung length and breast length as craniocaudal analogues of MHD, CLD and BTh; heart contour height parallel to the collimator leave opening.

Risk-motivated organ weighting

Personal radiation-induced risk R can be calculated from dose-volume distributions $D_{\mathrm{org}}(V)$ in diverse organs and their risks $\rho_{\mathrm{org}}(D)$ per unit dose (including non-dosimetric factors and potentially depending on dose), or to the first approximation from organ mean doses D_{org} and (mean) risks per unit dose ρ_{org},

$$R = \sum\nolimits_{\mathrm{org}} \int_V D_{\mathrm{org}}(V)\rho_{\mathrm{org}}(D)\mathrm{d}V/V \approx \sum\nolimits_{\mathrm{org}} \rho_{\mathrm{org}} D_{\mathrm{org}} \quad (1)$$

We focus on the heart, ipsilateral lung and contralateral breast, since they show the highest (absolute) risks.[1, 12, 13] We neglect the contribution from the contralateral lung, since it is exposed to much lower doses than the ipsilateral lung.[9]

Risk models possess large uncertainties. The selection of anatomic features is not affected by uncertainty on the absolute magnitude of the risk. For the feature selection, we neglect potential differences in relative contributions from low vs. high doses and use the mean-dose approximation in Equation (1). The needed input is thus reduced to relative contributions to the risk from diverse organs, which unfortunately are subject to uncertainty as well. Therefore, alternative feature selections based on the following exemplary risk scenarios were studied:

Scenario 1, used in our previous work,[9] treats the heart, ipsilateral lung and contralateral breast equally, i.e. with organ risk coefficients ρ_{org} in the ratio of 1:1:1. This looks for anatomic features that best predict doses to the three organs simultaneously.

In Scenario 2, organ doses contribute to the risk in the ratio of 4:2:1, so that features related to heart doses are favoured. This scenario is motivated by the BEIR VII report[12] on radiation-induced cancer, based on atomic bomb survivors data. According to this report, for a woman treated at the age of 50 years, the lifetime attributable risk of contralateral breast cancer is about 0.5–1% per Gy and that of lung cancer about 2% per Gy (considering both lungs separately). For mortality from heart disease,[14] similar calculations based on German mortality rates lead to a lifetime attributable risk of about 4% per Gy heart dose.

Scenario 3 weighs organ doses in the ratio of 5:1:15, emphasizing features related to the contralateral breast. It follows from the reported excess cases of heart disease and secondary cancer of the lung or contralateral breast in breast cancer patients,[1] assuming that the ratios of organ doses were identical to the present study.

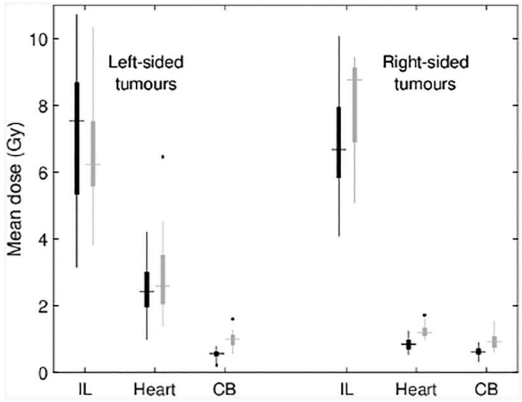

Figure 1. Mean doses to the ipsilateral lung (IL), heart and contralateral breast (CB) from whole-breast irradiations in left- or right-sided breast cancer patients treated in centres 1 (black) and 2 (grey). Boxplots depict the individual variability (mid line: median; box: 25th–75th percentile; whiskers: values not considered outliers; points: outliers).

In addition to these exemplary, intentionally very different risk scenarios, single organs were considered as extreme weighting scenarios (1,0:0, 0:1:0, 0:0:1).

Risk-motivated selection of anatomic features

To select optimal features for alternative scenarios, TPS-calculated mean organ doses were fitted by generalized linear models with logit link function,

$$D = D_{\max} / \left(1 + \exp\left(-\beta_0 - \sum_i \beta_i X_i\right)\right) \approx D_0 \exp\left(\sum_i \beta_i X_i\right). \quad (2)$$

The logit function fulfils $0 < D < D_{\max}$; $D_{\max}$ was taken as 110% of the prescribed dose. The exponential approximation holds for $D << D_{\max}$; D_0 is given by $D_{\max}$ and β_0 and denotes the dose extrapolated to all anatomic features $X_i = 0$. With model coefficients β_i, the most influential (and statistically significant, $p < 0.05$) features X_i were added gradually, using the sum-of-squared errors fitting criterion for the three organs weighted with the given scenario. This procedure thus looks for features optimal with respect to risk modelling under the studied scenario. The model performance was quantified by the coefficient of determination, i.e. the fraction of inter-individual variability in risk covered by the model; this equals the square of Pearson's correlation coefficient between model predictions and TPS data-derived risk.

RESULTS

Mean doses to the heart, both lungs and contralateral breast from the analysed whole-breast irradiations are depicted in Figure 1. The highest and most variable doses occur in the ipsilateral lung (3.1–10.7 Gy), followed by the heart for left-sided breast cancer patients (1.0–4.5 Gy). Heart doses in right-sided cases as well as doses to the contralateral breast are lower and, hence, less variable. The inter-centre differences below 1 Gy exceed the individual variability but are largely artefacts due to TPS inaccuracy.[6]

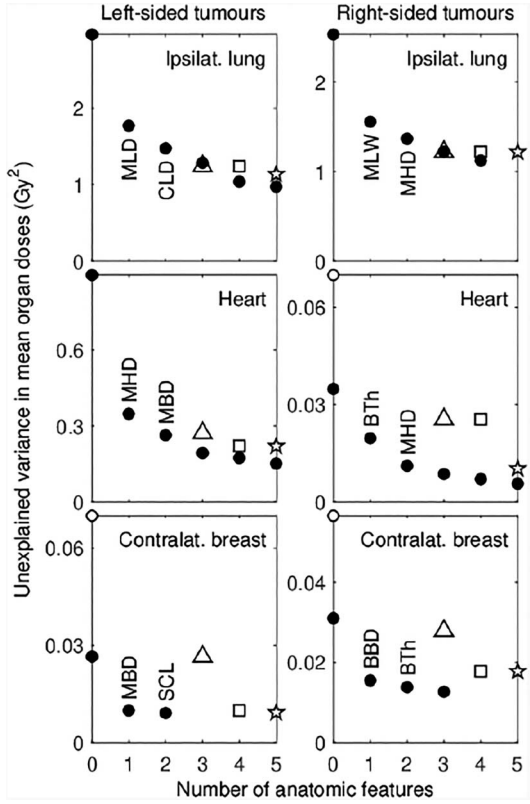

Figure 2. Residual variability in mean organ doses for models with features selected specifically for the given organ (filled circles; first two features per organ labelled). Inter-centre differences at low doses were accounted for (empty vs. filled circles at null anatomic features). The performance of models with globally selected 3–5 anatomic features (triangles, squares and pentagrams) is also shown.

The individual variability in mean doses to the analysed nearby organs can be largely explained by variations in a few anatomic measures (Figure 2). Using single-organ scenarios (filled circles), one finds that anatomic features such as CLD, MLD or MLW alone or in combination with further features such as MHD or BW explain half to two thirds of the variability in doses to ipsilateral lung (top panels). CLD, MLD and MLW are mutually highly correlated and hence largely interchangeable as predictors

Table 1. Anatomy-dependent models of mean organ doses from whole-breast irradiation.

Tumour laterality	Organ	D_0 (Gy)		β CLD (cm^{-1})	β MLW (cm^{-1})	β MHD (cm^{-1})	β MBD (cm^{-1})
		Centre 1	Centre 2				
Left	Ipsilateral lung	2.75		0.21	0.07	0.12	
	Heart	2.45		−0.20		0.64	−0.07
	Contralateral breast	0.85	1.30				−0.16
Right	Ipsilateral lung	3.38		0.18	0.08	0.08	
	Heart	1.16	1.60			0.12	
	Contralateral breast	0.86	1.30				−0.14

Table 2. Individual risk variability explained by the universal or scenario-specific anatomic features.

Tumour laterality	Scenario	Scenario-specific		Universal
		Features	Explained variance (%)	Explained variance (%)
Left	1:1:1	CLD, MHD, MLW, MBD	73	73
	4:2:1	MHD, MLW, CLD, MBD	69	69
	5:1:15	MHD, MBD, MLW, BTh	76	74
Right	1:1:1	CLD, MHD, BW, BBD	48	46
	4:2:1	CLD, MHD, BW, BTh	49	45
	5:1:15	BBD, CLD, BTh, MHD	56	42

(not shown). For the heart for left-sided cases (mid-left panel), more than half of individual variability in mean doses is explained by MHD as a single feature, and the unexplained variance drops below 20% when four additional features (MBD, BTh, BW and CLD) are considered. For the heart in right-sided cases (mid-right panel) and for contralateral breast (bottom panels), inter-centre differences were statistically significant. They were accounted for by different D_0 values; this reduces the variability (empty vs. filled circles at null features). After this correction, anatomic features were added: BTh, MHD, BW, CLD and CoLD for the heart and MBD and SCL (or BBD, BTh and MHD) for the contralateral breast in left- (or right-) sided cases.

For clinical applications, ideally a global set of a few anatomic features shall be identified that could serve as predictors of personal risk, i.e. reflect individual risk variability for alternative risk scenarios. This is feasible since features such as CLD, MLD, MLW, MHD, MBD, BW and BTh are highly influential and often correlated also to doses in organs other than for which they were initially introduced. Indeed, using the 1:1:1 organ weighting, particularly informative parameter sets were identified: the triplet CLD, MHD, MLW (triangles in Figure 2); quartet CLD, MHD, MLW, MBD (squares) and quintet CLD, MHD, MLW, MBD, BW (pentagrams). Models using these globally selected features as predictors of organ doses work almost equally well as those using organ-specific features (filled symbols). Hence, these global sets are quite robust with respect to alternative risk scenarios, even those not studied in this work. Given that BW notably improves dose estimates only for the heart for right-sided irradiations, while the inclusion of MBD is crucial for the contralateral breast, we selected the quartet. The resulting dose models are listed in Table 1. The fractions of individual risk variability covered by the universal quartet are compared with scenario-specific features in Table 2. For instance for the 4:2:1 scenario in left-sided patients, the scenario-specific set merely re-orders the global quartet. Notable differences are seen only for the 5:1:15 scenario and right-sided breast cancer patients, for whom however the risks are lower than for left-sided ones.

DISCUSSION

Breast cancer radiotherapy induces considerable long-term health risks, in particular due to exposure of the heart, ipsilateral lung and contralateral breast. Doses to these organs largely vary between patients. A few anatomic features available from planning CT images were identified that explain the major part of the variability in organ doses and subsequent risks.

There are a number of limitations to the present study. The individual variability was assessed from TPS calculations, which are inaccurate at low doses[6, 10]; the inter-centre differences largely follow from this inaccuracy.[6] Further, the considered risk scenarios combine in a simplistic way cancer incidence in diverse organs and mortality from heart disease, endpoints of very different severity. In addition, all the scenarios assume that organ contributions to long-term risks are given by mean organ doses only. If dose–risk relationships were not linear,[15] further dose–volume metrics would have to be considered. Such a generalization might alter the optimal set of anatomic features. For instance, the risk per unit dose in the lung may be higher at low than at high doses.[15] While CLD is highly informative regarding only the high-dose exposure of ipsilateral lung, BW affects its low-dose burden. The optimal set of anatomic features may also be modified by non-dosimetric risk factors, since e.g. smoking or existing cardiovascular risk factors may modulate the relative contribution of different organs to the risk and hence their weighting in the feature selection procedure. However, having to score different features, e.g. for smokers than for non-smokers, may be impractical.

CONCLUSION

The quartet CLD, MHD, MLW and MBD is a universal set of anatomic features that enables individual estimates of doses to the heart, ipsilateral lung and contralateral breast, the most critical nearby organs in breast cancer radiotherapy. Since this feature set is largely robust with respect to the choice of risk models, it will be employed for personalized risk estimates in the PASSOS software.

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