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LONG-TERM HEALTH RISK AFTER BREAST CANCER RADIOTHERAPY: OVERVIEW OF PASSOS METHODOLOGY AND SOFTWARE

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Breast-cancer radiotherapy reduces the recurrence rates and improves patient survival. However, it also increases the incidence of second cancers and of heart disease. These radiation-induced long-term health risks become increasingly important with improved cure rates and prolonged patient survival. Radiation doses to nearby as well as distant organs strongly vary between different irradiation techniques and among individual patients. To provide personalized lifetime risk estimates, the German national project PASSOS combines individual anatomy, dosimetric estimates, organ-specific low- and high-dose risk models and personal risk factors such as smoking. A dedicated software tool is under development to assist clinical decision-making processes.

INTRODUCTION

Breast cancer is the most frequent female cancer worldwide. The treatment usually consists of a multidisciplinary approach that involves surgery, radiation therapy (RT), and medical oncology. Adjuvant RT following breast-conserving surgery improves breast cancer-specific and overall survival rates[(1)]. However, breast-cancer RT also inevitably leads to high radiation burden especially to nearby organs such as the heart, lung, and contralateral breast. Organ doses differ among alternative irradiation techniques, and exhibit a large individual variability due to anatomic factors. Long after RT, these unwanted exposures may lead to radiation-induced second primary cancer or heart disease[(1)]. These long-term health effects become more and more important as the cure rates improve and patient survival gets prolonged, in particular for early-stage breast cancer. Estimating long-term health risks following breast-cancer RT on a personalized basis thus represents an important step towards optimizing RT.

Providing personalized risk estimates for modern treatment techniques is a challenging task, for several reasons: Due to the long lag times, existing risk estimates[(2-4)] are derived from long-term follow-up studies of old techniques; however, present RT techniques can lead to considerably lower exposures of healthy tissues[(5)]. Compared to conventional 3D conformal radiotherapy (3D-CRT), more modern multi-field techniques such as e.g. intensity-modulated radiotherapy (IMRT) become increasingly popular and can induce different dose distributions throughout the body. Distant organs are exposed to low or medium doses. Organ-specific risk estimates in this dose range can be obtained from radioepidemiological studies, in particular the Japanese atomic bomb survivor study (Life Span Study, LSS)[(6)]. However, organs close to the tumour receive highly non-uniform irradiations with high dose gradients; while some organ parts are exposed to doses comparable to the prescribed tumour dose, other parts see only low or medium dose levels. In addition to the huge inter-individual variability, the key challenge here is how to merge existing evidence on low-dose and high-dose risks, since risk estimates per unit dose from high-dose RT studies e.g. for lung and breast cancer are considerably lower than those from low-dose studies[(4,7)]. This also implies that the risk may depend on dose-volume pattern rather than on the mean organ dose only, and may show non-linear dose dependencies.

This paper first provides an overview of the general methodology to estimate personalized estimates of long-term health risks following breast-cancer RT, as developed within the German national project PASSOS[(8)]. Second, assessment of doses for alternative RT techniques are presented in more detail.

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METHODOLOGY FOR ASSESSING PERSONALIZED RISK AFTER BREAST CANCER RADIOTHERAPY IN THE PASSOS PROJECT

Dose assessment

In breast cancer RT, usually the whole breast is irradiated uniformly, and an additional boost to the tumour bed is applied. Organs close to the treated breast, in particular heart and lung receive very high doses with steep dose gradients. Dose distributions in these organs can depend strongly on the applied method, but can also strongly differ among individuals depending on anatomic properties. In addition, also distant organs experience substantial radiation exposures that are dependent on the treatment method and poorly classified. Within the project a systematic characterization of exposures for close and distant organs was performed and is described in more detail below.

Risk models

Developing models to assess radiation-induced late health risks of second primary cancer and heart disease for radiotherapy patients is a complex task. Radiation fields, in particular for close organs, cover an extreme dose range and are very organ-specific.

A number of (mostly case-control) studies on late health risks exist from medical therapeutic applications. For relevant organs, these were reviewed and meta-analyses were performed to provide estimates of excess relative risk. However, these studies give little information on risk in the low- and intermediate dose range (below about 1-4 Gy). More distant organs are not exposed at all to high doses, and even for the near organs a large part of the volume is usually in the lower dose range. For these lower doses, by far the statistically most powerful source of information on organ-specific risk is the LSS data of the atomic bomb survivors of Hiroshima and Nagasaki. Therefore, organ-specific risk analyses of the LSS data were performed. Risk models were developed for the most frequent cancer sites; less frequent sites were described by grouped risk models.

If possible, personal risk factors were included in the models; of particular relevance is smoking behaviour for assessment of lung cancer risk. The risk was transferred from previous Japanese to current German population by a combination of additive and multiplicative transfer, taking into account the change of population cancer rates with calendar year.

To provide both excess and absolute risk prediction for the entire relevant dose range, low- and high-dose risk models were merged for lung cancer, contralateral breast cancer and for leukemia. The considered endpoint was cancer incidence. Carcinogenesis was assumed to be a local process, so that dose-volume histograms could be integrated with dose-dependent risk estimates.

For the heart, ischemic heart disease mortality was chosen as endpoint since it is defined less ambiguously than incidence of heart diseases and national rates are available. The meta-analysis of heart disease did not reveal any differences between mortality and other major coronary events and was consistent with the LSS result in the intermediate dose range[9]. Currently only the meta-analysis is used in PASSOS.

Details on the methodology and the results for organ-specific risk models for breast cancer therapy applications are provided elsewhere.

Personalized risk evaluation and software development

To provide personalized estimates of long-term health risks from medical applications of ionizing radiation, the person-specific dosimetric information together with individual risk factors have to be combined with population-based estimates of spontaneous and radiation-induced risk of second primary cancer and heart disease.

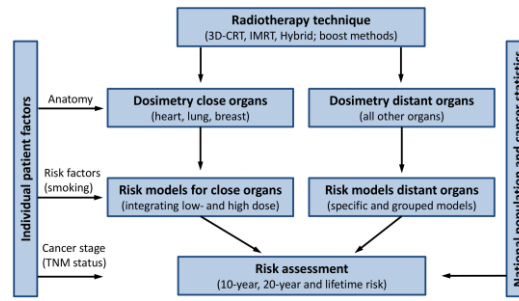

Figure 1. Scheme illustrating the methodology approach implemented in PASSOS to provide personalized estimates of long-term health risks from breast-cancer radiotherapy.

This is done in PASSOS as illustrated in Figure 1. A software tool is under development that can calculate long-term spontaneous and radiation-induced risk for various cancer sites and heart disease. Important input parameters are the employed whole-breast and/or boost irradiation technique, age at treatment, stage of breast cancer, and personal factors such as e.g. smoking or anatomy. Doses to nearby and distant organs are estimated. Risk models are implemented as discussed above. German population and disease statistics are taken from national databases. Reduced survival of RT patients compared to the general population is accounted for, explicitly considering its dependence on the breast-cancer stage (TNM status) and on the time after RT. Lifetime risk is reported together with the risk

after specified times after treatment, e.g. after 10 or 20 years.

An important element of the calculations are the associated uncertainties. Monte Carlo simulations of important sources of uncertainty, e.g. from dose distributions, risk models, or risk transfer to the German population provide uncertainty estimates of lifetime risk and constitute an integral part of the software tool. In the following we present a summary of the doses in organs at risk, which forms the basis for the risk assessment.

DOSE ASSESSMENT FOR ALTERNATIVE RADIOTHERAPY TECHNIQUES

Treatment planning study

To assess doses to critical nearby organs and their individual variability, a treatment planning study was performed with 128 early-stage female breast-cancer patients (TNM-classification pT1-2, tumour size < 3 cm, pN0, G1-3, R0) from two major radiotherapy centres (45 left- and 33 right-sided breast-cancer patients in centre 1, and 27 left- and 23 right-sided patients in centre 2). For each patient, 3D-conformal tangential whole-breast radiotherapy without wedges (3D-w) was planned as the standard technique. In centre 1, in addition all the patients were planned for a similar technique with wedges (3D+w) and for hybrid techniques in which the same tangential fields were used to deliver about 70% of the prescribed dose, complemented by inversely planned fields, flattened (FF) or flattening filter-free (FFF). In centre 2, multi-field intensity-modulated radiotherapy (IMRT) was planned for each patient in addition to 3D-w. In both centres, boost irradiations to tumour bed were also planned, alternatively with 3D-w, IMRT or ^{192}Ir brachytherapy. The prescribed whole-breast dose was 50.4 Gy in 28 fractions; the boost dose was 16 Gy in 8 fractions for external boosts and for brachytherapy 12 Gy in 2 fractions. The dose calculations were based on the collapsed cone algorithm (using Oncentra Masterplan 4.3), and for brachytherapy on the TG-43 algorithm. All plans were subject to acceptance criteria as normally used in the clinics.

The following organs were manually contoured for each patient: the treated breast, heart, lungs, contralateral breast, thyroid, spinal cord, and oesophagus. In addition, the liver was contoured in the planning CT in centre 1, and stomach in centre 2. Dose-volume histograms were generated for each patient, each organ, and each technique planned. For the liver some extrapolation was applied since minor parts lay outside the planning CT.

In addition, numerous anatomic features were assessed for each patient from the CT data. These parameters were then used to capture the individual variability in dose-volume characteristics, as discussed in detail elsewhere[10].

Monte Carlo dose calculations on whole-body CT

The CT data for patients in the planning study were limited to the upper trunk region. Furthermore, treatment planning systems are subject to large uncertainties for distant organs. Therefore, doses to distant organs were estimated using a 'whole body' (WB) CT scan available in center 2 for a single female patient with cancer in the left lung; the WB scan included the whole body except parts of the extremities. For this particular person, hypothetical breast-cancer radiotherapy plans were generated, separately for each laterality, using the voxel Monte Carlo algorithm[11] (using IPLAN 4.5.4) that provides a more accurate dose calculation than the collapsed cone algorithm.

Dose-volume histograms of brain, kidneys, bladder, ovaries and uterus were directly derived from the treatment planning system. The dose-volume histogram for bone marrow was estimated based on the dose-volume histograms of different parts of the skeleton, each weighted with its content of bone marrow[12].

Organ doses

Mean organ doses and doses to the most exposed 10% of the organ ($D_{10\%}$) from the 3D-w whole-breast irradiation technique are presented in Figure 2; for the treatment planning study, values are averaged over the patient group. The mean organ doses as well as the $D_{10\%}$ values rapidly decreased with increasing distance from the treatment fields. The lungs received the highest mean dose (about 4 Gy), as considerable parts are exposed to therapeutic dose. The tumour laterality strongly impacted doses to the heart, liver and stomach. Depending on the laterality, either the heart or the liver was the second most exposed organ. The contralateral breast, thyroid, stomach and oesophagus received mean doses below 1 Gy (Figure 2).

The results for the single person planned with Monte Carlo (WB) differed from the mean of the planning cohort (Figure 2); presumably, this was mainly due to individual variation, with some contribution from differences in the calculation algorithms. Notably, the mean bone marrow dose was higher than its $D_{10\%}$. This follows from bone marrow exposure being focused to a very small proportion of its total volume; in the given 3D-w plan, about 2% of bone marrow receive more than 10 Gy (not shown). In contrast, for IMRT practically no fraction of bone marrow receives doses above 10 Gy (not shown). Nevertheless, the mean bone marrow dose from 3D-w (0.9 Gy) is lower than that from IMRT (1.4 Gy). This is a specific example of the known IMRT feature: it reduces the volumes exposed to high doses at the expense of increased low-dose

wash and hence increased mean doses to practically all organs at risk (Figure 3). Comparing the different tangential techniques, 3D+w showed higher and FFF lower exposure than 3D-w and FF which were almost indistinguishable (Figure 3).

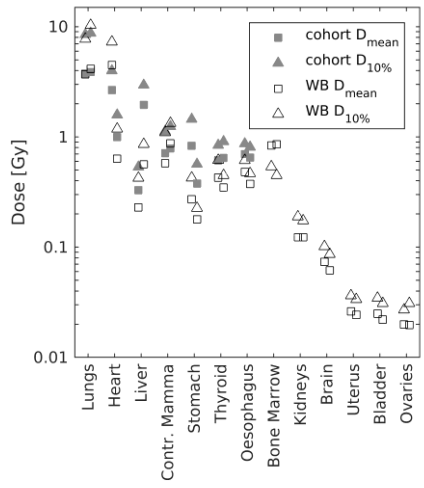

Figure 2. Mean doses D_{mean} and $D_{10\%}$ percentile of dose-volume histograms of organs at risk from whole-breast 3D conformal radiotherapy without wedges. Filled symbols refer to cohort-mean values, empty symbols present results for a single person's whole-body CT dataset. The results for left-sided/right-sided treatment are shifted to the left/right.

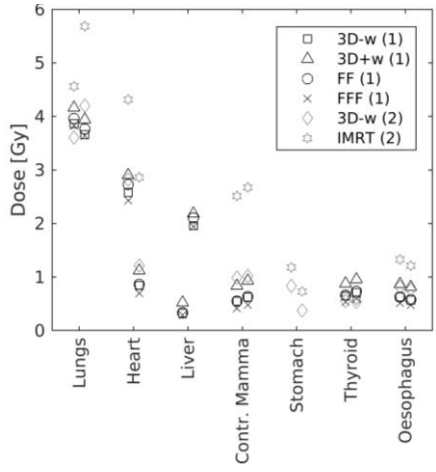

Figure 3. Mean doses to nearby organs from alternative whole-breast irradiation techniques, averaged separately for patients of each centre. The results for left-sided/right-sided treatment are shifted to the left/right.

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