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Comparison of Radiation Dose Reconstruction Methods to Investigate Late Adverse Effects of Radiotherapy for Childhood Cancer: A Report from the Childhood Cancer Survivor Study

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Abstract

Quantification of radiation dose to normal tissue during radiotherapy is critical for assessing risk for radiotherapy-related late effects, including subsequent neoplasms (SNs). Case-control studies of SNs typically reconstruct absorbed radiation dose to the specific SN location using individual treatment parameters. A simplified method estimates the maximum prescribed target dose to the

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body region in which the SN arises. We compared doses and risk estimates from these methods using data from case-control studies of subsequent brain tumors (64 cases, 244 controls) and breast cancer (94 cases, 358 controls) nested within the Childhood Cancer Survivor Study (5-year survivors of childhood cancer diagnosed 1970–1986). The weighted kappa statistic [95% confidence interval (CI)] evaluating agreement between categorical (>0–9.9/10–19.9/20–29.9/30 Gy) body-region and tumor location-specific doses was 0.95 (0.91–0.98) for brain and 0.76 (0.69–0.82) for breast. The body-region and location-specific doses were assigned to the same dose category for a smaller proportion of patients treated with fields delivering a heterogeneous dose across the tissue of interest (e.g., partial brain field = 57.1%; mantle field = 61.3%) than patients treated with fields delivering a more homogeneous dose (e.g., whole brain field = 100%). Excess odds ratios per Gy (95% CI) from conditional logistic regression were 1.25 (0.33–6.33) and 1.20 (0.31–6.14) for brain tumors and 0.21 (0.05–0.77) and 0.10 (0.02–0.44) for breast cancer, using location-specific and body-region doses, respectively. We observed that body-region doses can approximate location-specific doses when the tissue of interest is clearly in the radiation field or outside the treated body region. Agreement is lower when there is greater ambiguity of SN location relative to the treatment field.

Editor's note.

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INTRODUCTION

Survival after childhood cancer diagnosis has improved dramatically over recent decades due to treatment improvements (1); however, long-term survivors of childhood cancer are at risk for a range of late adverse treatment effects. Radiotherapy substantially increases the risk of numerous adverse outcomes, including subsequent neoplasms (SNs), cardiotoxicity, endocrine dysfunction and certain pulmonary conditions, which together account for a considerable fraction of morbidity and mortality among childhood cancer survivors (2–10).

Quantification of dose to normal tissue during radiotherapy is critical for evaluating the association between radiotherapy and late effects. This is particularly challenging due to marked dose heterogeneity across an organ for certain radiotherapy field configurations (11). Subsequent neoplasm risks have been investigated primarily in case-control studies (12), most of which have used detailed, individual-level treatment parameters, including field configurations and normal tissue blocking, to reconstruct radiation dose to the specific SN location (11).

Detailed dose reconstruction for many patients is resource intensive, often requiring several hours per radiotherapy treatment record for data abstraction alone (13). Particularly resource-intensive cases include those where patients were treated with multiple fields and/or received multiple boost/cone down treatments, as well as when the SN is near the border of the radiotherapy field (or beam blocking) used to treat the first primary cancer. More recently, a simplified approach was developed that estimates the maximum prescribed target dose to specific body regions. This “body-region” dosimetry method (13) uses fewer

treatment parameters than the detailed method, and data abstraction generally requires 30 min per radiotherapy record. This method therefore may enable dose reconstruction for a large number of patients, with potential widespread utility for studies of late effects, since it can also be applied to cohort studies for absolute and relative risk estimation and risk prediction [see Howell *et al.* (13) for examples of studies that used body-region doses]. However, previously published studies have not quantified the agreement between doses and accompanying risk estimates from these different methods. The goals of this study were to compare: 1. body-region and tumor location-specific doses, overall and by treatment fields received for the first primary cancer; and 2. risk estimates from radiation dose-response models using these different doses, utilizing data derived from two previously published nested case-control studies of subsequent brain tumors and breast cancer (14, 15) within the Childhood Cancer Survivor Study (CCSS) (16).

MATERIALS AND METHODS

Human subjects committee approval was obtained for the CCSS from participating institutions prior to participant recruitment, and participants, or parents of minor children (<18 years), provided informed consent.

Patients and Controls

Selection of cases and controls (matched by age at- and time since diagnosis of first primary cancer and sex) from the CCSS cohort has been described elsewhere (14, 15). For all analyses, we excluded patients who received radiotherapy that was not systematically ascertained within five years after first primary cancer diagnosis, and cases (and their matched controls) who had an intervening malignancy between the first primary cancer and subsequent brain tumor or breast cancer. We also excluded CNS cases outside the brain (and their matched controls). Exclusions are presented in greater detail in Supplementary Table S1 (<https://doi.org/10.1667/RR15308.1.S1>).

For the dose comparison analyses only, we excluded individuals who did not receive radiotherapy as well as individuals for whom tumor location-specific and/or body-region doses could not be estimated. For these analyses, individuals included in multiple matched sets were included only once, in order to have independent observations, resulting in 280 (56 cases, 224 controls) and 276 (70 cases, 206 controls) unique patients for the brain and breast dose comparison analyses, respectively (Supplementary Table S1).

Risk comparison analyses excluded controls whose matched case had been excluded and a set of supplemental controls in the breast cancer study matched to cases on first primary cancer type, resulting in 64 brain tumor cases with 244 controls, and 94 breast cancer cases with 358 controls (Supplementary Table S1; <https://doi.org/10.1667/RR15308.1.S1>).

Radiation Dose Reconstruction

The methods for reconstructing doses from conventional (2D and 3D conformal) external beam radiotherapy, described in detail elsewhere (11, 13), are summarized below and in Table 1 and Fig. 1.

For both dose reconstruction methods, radiotherapy records were reviewed to ascertain individual treatment information. For the full CCSS cohort, radiotherapy records were collected for all treatments received within five years after the first primary cancer diagnosis. The case-control studies had collected additional radiotherapy records for treatments that were self-reported for the period up to five years before the date of the SN (and corresponding date for controls), but the current analyses did not include information from treatments beyond five years as this information is not accounted for in the body-region doses (14, 15).

Tumor location-specific doses.—We used the tumor location-specific doses estimated for the original case-control studies of subsequent brain tumors and breast cancers (14, 15). For these studies, patient records were reviewed to determine, as precisely as possible, the location of the subsequent brain tumor or breast cancer. The mean dose to this location (matched location for controls) was estimated using individual-level treatment field parameters including prescribed dose, beam energy, field type, field size and blocking of normal tissue (Table 1). Figure 1 shows examples of subsequent brain and breast tumor locations relative to treatment fields.

Body-region doses.—The body-region dosimetry method estimates the maximum prescribed target dose (maxTD) to specific body regions (brain, other head, neck, chest, abdomen, pelvis, arm or leg; Supplementary Fig. S1; <https://doi.org/10.1667/RR15308.1.S1>). For the full CCSS cohort (including the subset included in the nested case-control studies), information was ascertained from radiotherapy records for all treatments received during the first five years after diagnosis of the first primary cancer. For each region that was directly treated (i.e., at least 10% of the region was in the treatment field), the maxTD was calculated by summing prescribed treatment doses from all overlapping fields in the region, for each course of treatment. If <10% of the region was in the treatment field, a classification of “stray-high” was made if the region was directly adjacent to a treated region (with doses ranging from 0.5–5 Gy or 1–10% of the maxTD) or “stray-low” if the region was not directly adjacent to the treated region (with doses ranging from 0.001–1 Gy or <1% of the maxTD), to account for stray dose from scatter and leakage radiation. Regions directly adjacent to the chest include arm, neck and abdomen, while for the brain, other head and neck are directly-adjacent. Because there is a range for stray-high and stray-low doses and the more precise dose within that range cannot be determined by the information collected for the body-region dosimetry, we used the approximate midpoint of the dose ranges (which were based on the detailed dosimetry efforts and the prescribed treatment doses in this cohort) in each category, and quantified stray-high and stray-low doses as 2.5 and 0.1 Gy, respectively, for analyses. Notably, in categorical analyses described below, individuals with stray-high and low doses are assigned to our lowest non-zero dose category and this would not change if we selected a different value within the estimated ranges listed above.

We assigned body-region doses to the region in which the second brain or breast tumor occurred in two stages. For stage 1, we used the brain or chest body-region doses (maxTD, stray-high dose or stray-low dose). For stage 2, we divided the brain into four segments and

the breast into five regions (four quadrants plus central/nipple area) and modified the stage 1 dose to incorporate more specific information about tumor location within the brain or breast. For brain stage 2 body-region doses, we used the maxTD (if 50% of the segment was in the primary beam), stray-high or stray-low to the brain segment (Fig. 1A) in which the SN occurred (matched location for controls) (13). For breast stage 2 body-region doses, we modified the chest maxTD to estimate dose to the quadrant or nipple/central region (Fig. 1B) in which the SN was located for females treated with: 1. mantle or T-mantle field radiation for Hodgkin lymphoma (HL) or non-Hodgkin lymphoma (NHL); or 2. mediastinal or spinal radiation, without other chest-directed radiotherapy (see detailed methods in Table 1 and Supplementary Table S2; <https://doi.org/10.1667/RR15308.1.S1>). Assumptions about tumor location relative to the treatment field (i.e., in the unblocked beam, the edge of the field or block, under the block, near the beam edge or out of beam) were based on the patterns in the case-control study. For all other females, breast stage 1 body-region doses were used.

Statistical Analysis

Dose comparisons.—We plotted the body-region doses (stages 1 and 2) against the tumor location-specific dose (scatter plots) and computed the concordance between continuous measures of dose using Lin's concordance correlation coefficient with corresponding asymptotic 95% confidence intervals (CI; Stata 15 "concord" program, College Station, TX) (17–19). We compared categories (>0–9.9, 10–19.9, 20–29.9 and 30 Gy) of body-region doses (stages 1 and 2) against the tumor location-specific dose using a weighted kappa statistic (kappa) with linear weights [FREQ procedure in SAS version 9.4 (Cary, NC)], overall and by groups defined by radiotherapy fields received for treatment of the first primary cancer (field groups). The overall kappas for stage 1 vs. 2 body region were compared using the R multiagree package (20). We also calculated the percentage of patients for whom the body-region and tumor location-specific dose categories agree (percentage agreement; using the categories above), to describe agreement overall and by field groups as well as other patient and treatment characteristics.

Risk comparisons.—Odds ratios (ORs) from conditional logistic regression analyses (Stata 15) (21) estimated the relative risk of developing a second brain tumor or breast cancer for each dose category (>0–9.9, 10–19.9, 20–29.9, 30 Gy, radiotherapy with unknown dose, and unknown radiotherapy status) relative to the referent category of zero dose, adjusted for first primary cancer type. We estimated the excess OR per Gy (EOR/Gy) adjusted for first primary cancer type using the model $OR = \exp(\sum_j \alpha_j x_j)(1 + \beta_1 D + \beta_2 M)$, where D is continuous radiation dose in Gy, M is an indicator for missing dose, β_1 is a measure of the EOR/Gy, and x_j indicates covariates (e.g., first primary cancer). Departure from linearity was assessed by fitting linear-quadratic $[OR = \exp(\sum_j \alpha_j x_j)(1 + \beta_1 D + \beta_2 D^2 + \beta_3 M)]$ and linear-exponential $[OR = \exp(\sum_j \alpha_j x_j)(1 + [\beta_1 D \times \exp(\beta_2 D)] + \beta_3 M)]$ models, and comparing the fit of these models to the linear model using likelihood ratio tests (LRT). Two-sided P values and 95% CIs for the EORs were based on maximum likelihood methods. ORs and EORs were estimated separately using body-region (stages 1 and 2) and tumor location-specific doses.

EOR models were fitted using the PECAN module of Epicure, version 2.0 (Risk Sciences International, Ottawa, Canada) (22). Akaike information criterion (AIC) values were used to compare model fit using the body-region doses against the tumor location-specific doses.

RESULTS

Patient characteristics were similar for the dose- and risk comparison analyses, for both the subsequent brain tumor and breast cancer studies (Supplementary Tables S3 and S4, respectively; <https://doi.org/10.1667/RR15308.1.S1>). Percentages reported below are from the risk comparison subsets.

Subsequent Brain Tumors

The most common first primary cancers were leukemia (44%) and CNS cancer (41%) among cases and leukemia (35%) and HL (14%) among controls. More cases (94%) than controls (67%) received radiotherapy within five years of first primary cancer diagnosis. Among cases who had received radiotherapy, 77% received whole-brain radiotherapy and 18% received partial-brain radiotherapy. Among controls, 42% received whole-brain radiotherapy and 49% received only fields outside of the brain and head.

There was good agreement between stage 1 body-region dose and tumor location-specific dose ($\kappa = 0.91$; 95% CI 0.86–0.96; Table 2), although body-region doses tended to be higher than tumor location-specific doses (Fig. 2A and Supplementary Table S5; <https://doi.org/10.1667/RR15308.1.S1>). Incorporating information on dose to specific brain segments (stage 2 body-region dose) improved agreement ($\kappa = 0.95$; 95% CI 0.91–0.98; $P_{\text{heterogeneity of kappas}} = 0.01$). However, the modifications applied for stage 2 body-region doses resulted in underestimation of tumor location-specific dose for some individuals. The concordance between continuous tumor location-specific dose and body-region dose was 0.84 (95% CI 0.81–0.88; Fig. 2A, Supplementary Table S5) for stage 1 and 0.91 (95% CI 0.90–0.93) for stage 2.

In further examination by treatment field groups, the lack of agreement between body-region stage 2 and tumor location-specific dose categories was concentrated among individuals who had received partial-brain radiotherapy (percentage agreement = 57.1%) or radiotherapy to other parts of the head/neck (85.7%; Table 2). Categorical agreement between stage 2 body-region doses and tumor location-specific doses was generally high across strata of the patient and tumor characteristics examined (Supplementary Table S6; <https://doi.org/10.1667/RR15308.1.S1>).

The estimated EOR/Gy was 1.25 (95% CI 0.33–6.33; $P_{\text{LRT}} < 0.001$) using tumor location-specific doses, 1.34 (95% CI 0.34–7.19; $P_{\text{LRT}} < 0.001$) using stage 1 body-region doses, and 1.20 (95% CI 0.31–6.14; $P_{\text{LRT}} < 0.001$) using stage 2 body-region doses (Fig. 3A). The data were consistent with a linear dose response irrespective of the doses used ($P_{\text{LRT}} > 0.10$ for all tests of non-linearity; Supplementary Table S7; <https://doi.org/10.1667/RR15308.1.S1>). The AIC values from the linear models were higher (indicating less good fit) using stage 1 (120.7) and stage 2 (119.8) body-region doses than that obtained using the tumor location-

specific dose (116.6). The patterns of ORs were similar based on tumor location-specific doses and the two stages of body-region dose (Supplementary Table S8).

Subsequent Breast Cancers

The most common first primary cancers were HL (66%) and bone sarcoma (14%) among cases and HL (41%) followed by leukemia (16%) and bone sarcoma (15%) among controls (Supplementary Table S4; <https://doi.org/10.1667/RR15308.1.S1>). Cases (87%) were more likely than controls (68%) to have received radiation within five years after the first primary cancer, with the mantle field most commonly received.

Stage 1 body-region doses generally were higher than the tumor location-specific doses (Table 3, Fig. 2B, Supplementary Table S9; <https://doi.org/10.1667/RR15308.1.S1>). Using stage 1 body-region doses, the kappa was 0.56 (95% CI 0.49–0.64; Table 3). Categorical agreement was significantly improved with the stage 2 body-region doses (kappa = 0.76; 95% CI 0.69–0.82; $P_{\text{heterogeneity of kappas}} < 0.001$). The concordance between tumor location-specific dose and body-region dose was 0.64 (0.58–0.70) for stage 1 and 0.83 (95% CI 0.79–0.86) for stage 2 (Fig. 2B). As with the brain doses, the modifications applied for stage 2 body-region doses resulted in underestimation of tumor location-specific doses for some individuals.

In subsequent examination of agreement between categories of stage 2 body-region doses with tumor location-specific doses, there was complete agreement among individuals who had not received any radiotherapy to the chest or abdomen as well as the group of females whose only radiotherapy in the chest region was from selected spine fields (Table 3). In the large group ($n = 119$) of females who had received mantle field radiation and the smaller ($n = 29$) group of females who received breast, chest (not whole), the percentage agreement was 61.3% and 62.1%, respectively. Patterns of agreement by other factors reflected the underlying treatment field groups. For example, agreement was 64% among females treated for HL (the majority of whom had received mantle field radiotherapy) and similar in the higher body-region dose groups (Supplementary Table S10; <https://doi.org/10.1667/RR15308.1.S1>).

For breast cancer, the estimated EOR/Gy using the tumor location-specific doses was 0.21 (95% CI 0.05–0.77; $P_{\text{LRT}} < 0.001$), 0.11 using stage 1 body-region doses (95% CI 0.02–0.37; $P_{\text{LRT}} = 0.002$) and 0.10 using stage 2 body-region doses (95% CI 0.02–0.44; $P_{\text{LRT}} = 0.004$) (Fig. 3B). The data were consistent with a linear dose-response using tumor location-specific and stage 1 body-region doses ($P_{\text{LRT}} > 0.10$ for tests of non-linearity; Supplementary Table S7; <https://doi.org/10.1667/RR15308.1.S1>), whereas there was some indication of a non-linear dose-response using the stage 2 body-region doses, based on both a linear-quadratic ($P_{\text{LRT}} = 0.059$ for test of non-linearity) and linear-exponential model ($P_{\text{LRT}} = 0.031$ for test of non-linearity). Using stage 2 body-region doses, these models suggested downward curvature in the dose-response above 20–35 Gy. The AIC values from the linear models were higher (indicating less good fit) using stage 1 (277.3) and stage 2 (278.7) body-region doses than that obtained using the tumor location-specific dose (270.5). Whereas the ORs using tumor location-specific doses showed elevated risks for all dose

categories ≥ 10 Gy, the largest ORs were observed in the 10–19.9 Gy group using each stage of body-region dose, albeit with wide confidence intervals (Supplementary Table S8).

DISCUSSION

Due to marked dose heterogeneity across normal tissues from radiotherapy, the preferred method of dose reconstruction in case-control studies of SNs estimates the absorbed radiation dose to the specific location of the SN using detailed information on tumor location, radiotherapy field configurations and blocking of normal tissue (11). Our study compared tumor location-specific doses and corresponding risk estimates to those from two versions of a simplified dose reconstruction approach which estimates the maximum prescribed target dose to specific body regions. Overall, agreement between body-region (stages 1 and 2) and tumor location-specific doses was higher in the subsequent brain tumor study than the breast cancer study, but in both studies, agreement depended on the radiation fields received. We also found that the agreement between body-region and tumor location-specific doses improved when we estimated body-region doses to a component of the brain or breast, and (for the breast) incorporated assumptions about the position of the breast tumor relative to radiotherapy field blocking. Nonetheless, using body-region doses, the EORs/Gy were generally lower, particularly for breast SNs, than tumor location-specific doses, the confidence intervals tended to be narrower, and the body-region doses (stages 1 and 2) provided less good fit to the data than the tumor location-specific doses.

The exact magnitude of our quantitative results is specific to the study characteristics, including the specific treatment fields received as well as types of first primary cancer and ages at diagnosis. Notably, use of different (finer or broader) dose categories would also change the agreement. Nonetheless, the overall findings provide a framework for considering the use of body-region doses in other studies. We observed that body-region doses provide a good approximation of tumor location-specific doses when the tissue of interest is clearly in the radiation field (e.g., brain tumors after whole-brain radiotherapy) or outside the treated body region (e.g., breast cancers among females who did not receive chest-directed radiotherapy). In contrast, our findings suggest that when the dose is highly heterogeneous because the field borders and/or blocking overlap the tissue of interest (e.g., brain tumors after partial-brain radiotherapy or breast cancers after mantle field radiotherapy), it is more difficult to approximate the tumor location-specific dose without detailed treatment field data, even after incorporating minimal information about tumor location in stage 2. As the conditions under which we observe good agreement are also the ones in which it is less complicated to determine the location of the second primary tumor relative to the treatment field for the first primary cancer, a main advantage to using the body-region dosimetry would be the time savings associated with using the simplified data coding form.

The overall lower agreement between doses and risk estimates in the breast cancer study compared to the brain tumor study reflects the underlying distribution of treatment fields in the two studies. A substantial proportion of females in the breast cancer study received mantle field radiotherapy, which results in ~ 10 -fold variation in radiation exposure across the breast (23), largely because of lung blocking, which is highly individualized to fit the

patient's extent of primary disease (11). After incorporating assumptions about dose by breast quadrant, agreement remained at only 61% in this group. Patients treated for HL more recently are less likely to have received full mantle field radiation and more likely to have received less-standardized involved-field or involved-node radiotherapy, which may make it even more difficult to develop assumptions about blocking and field borders (24). In contrast to the breast cancer study, a substantial proportion of survivors in the brain tumor study received whole-brain radiotherapy or radiotherapy only to regions outside of the head, both of which result in relatively homogeneous dose to the brain (high or very low, respectively). Similarly, agreement among the smaller proportion of individuals who received partial-brain radiotherapy (largely for first primary CNS cancers) was 57%. Consequently, agreement would likely be lower in studies of more recently treated individuals, since partial-brain radiotherapy has increasingly replaced whole-brain radiotherapy for treatment of first primary CNS cancer (25) as well as leukemia with CNS involvement (26).

The analytic goals of a study may also inform the decision to use body-region dosimetry in lieu of tumor location-specific doses. Body-region doses, like tumor location-specific doses, clearly showed an association between radiation dose and second primary brain and breast cancers. However, measurement error, indicated by differences between body-region and the more precise tumor location-specific doses, can bias the magnitude and shape of a dose-response relationship (27, 28), a key focus of epidemiologic studies investigating the main effect of radiotherapy and SN risk. For example, the modest indication of downward curvature in the dose-response relationship above 20–35 Gy using stage 2 body-region breast doses could reflect dose misclassification (agreement was <65% in the higher body-region dose categories). However, this may also be a chance finding, since small numbers, particularly in the 10–<19 Gy dose range, resulted in unstable risk estimates (shown in Supplementary Table S8; <https://doi.org/10.1667/RR15308.1.S1>). Furthermore, the EORs/Gy using body-region doses were generally lower, particularly for breast SNs, than tumor location-specific doses, and the confidence intervals tended to be narrower. This suggests that for detailed dose-response analyses, body-region doses are not a substitute for estimating the mean absorbed dose to the tumor location, which, in principle, would provide unbiased estimates of the magnitude and shape of the radiation dose-response relationship. Misclassification of tumor location-specific doses when using body-region doses also has implications for radiation dose as a covariate in analyses of chemotherapy or other factors, by failing to provide adequate adjustment for confounding (27, 28) or as a potential effect modifier (e.g., in genetic studies), by potentially biasing effect estimates and increasing the sample size needed to detect an interaction (29). Given the paucity of studies with long-term follow-up, available treatment data and available DNA, reduced statistical power for studies of gene-radiotherapy interactions is particularly challenging (30, 31). Beyond the case-control setting, comparison of stage 1 body-region doses with mean organ doses (which were not available for the current study) could inform the application of body-region doses for absolute as well as relative risk estimation (32), and risk prediction (33).

The detailed treatment and tumor location data collected for earlier case-control studies (14, 15) is a key strength of this study, enabling direct comparison of body-region doses and corresponding risk estimates with tumor location-specific doses, and providing the additional treatment information used to modify stage 2 body-region breast doses and

evaluate agreement by treatment fields received. Nonetheless, the tumor location-specific doses are also subject to limitations related to the availability and quality of individual treatment data records (11). We sought to maximize the comparability across dose reconstruction methods by excluding cases diagnosed with an intervening malignancy before the date of the second breast cancer or brain tumor, as well as individuals known to have received radiotherapy after five years due to concerns of incomplete treatment ascertainment. Body-region doses in the CCSS are currently based on treatments within the first five years of first primary cancer diagnosis. For studies including large proportions of first primary cancers that are more likely to relapse after five years (e.g., HL), extending the period of time for which radiotherapy records are collected may be warranted. Importantly, we acknowledge that the ORs and EORs/Gy are not intended to replace those from the detailed dose-response literature. The earlier study of subsequent CNS tumors reported an EOR/Gy of 0.69 (95% CI 0.25 to 2.23) for all CNS tumors (15), which is lower than our estimate of 1.25 (95% CI 0.33 to 6.33) using tumor location-specific dose. Similarly, the earlier study of subsequent breast tumors reported an EOR/Gy of 0.27 (95% CI 0.10 to 0.67) (14), compared to our estimate of 0.21 (95% CI 0.05–0.77). Certain exclusion criteria for the population considered for this methodologic work fundamentally changed the distribution of cases and controls and therefore the risk estimates from the original case-control studies (14, 15), such as the higher proportion of subsequent meningioma cases in this analysis compared with the original study.

CONCLUSIONS

As the science of cancer survivorship expands and the population of cancer survivors continues to grow (34), so will the need for efficient alternatives to the resource-intensive, tumor location-specific dose reconstruction method. Our results demonstrate that tumor location-specific doses can be approximated using maximum prescribed treatment doses to body regions (defined with varying degrees of specificity) when the tissue of interest is clearly in the radiation field for the first primary cancer or outside the treated body region, but that agreement is lower when there is greater ambiguity of SN location relative to the treatment field for the first primary cancer. With the stage 2 body-region doses, we demonstrate how body-region doses may be tailored to better approximate tumor location-specific doses by estimating doses to a component of the brain or breast (although less detailed than the location information used for tumor location-specific doses), and (for the breast) by incorporating assumptions about the position of the breast tumor relative to radiotherapy field blocking. The specific modifications needed will depend, however, on the tissue of interest and relevant treatment fields. Our comparison of risk estimates suggests that body-region doses may provide an efficient basis for preliminary SN risk analyses but may not be a suitable substitute for tumor location-specific doses for purposes of quantifying and describing the dose-response relationship, due to the challenges associated with dose heterogeneity across an organ.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIG. 1.

Tumor location-specific and body-region dose reconstruction methods. Panel A: Three hypothetical subsequent brain tumor locations (X, Y, Z) relative to a whole brain field (solid line) and two partial brain fields (dashed lines), where X = within whole brain field, Y = within whole brain and one partial brain field and Z = within all three fields using tumor location-specific doses. Stage 1 body-region doses use the maximum prescribed target dose (maxTD) to anywhere in the brain. Stage 2 body-region doses use the maxTD to anywhere in the brain segment (1, 2, 3, 4) of the case's subsequent tumor and matched location in controls. Panel B: Three hypothetical subsequent breast tumor locations relative to mantle-field blocking, where X = in-beam, Y = under a block and Z = at block edge using tumor location-specific doses. Stage 1 body-region doses use the maxTD to any part of the chest. For women who received Mantle or selected other chest-directed radiotherapy fields, stage 2 body-region doses use the chest maxTD scaled based on quadrant- and age-specific blocking assumptions to assign dose to the quadrant (1, 2, 3, 4) or central/nipple area) of the case's subsequent neoplasm and matched location in controls. For all other women, the chest maxTD is used, as in stage 1. See Materials and Methods and Table 1 for additional details for defining body-region doses.

FIG. 2.

Agreement between tumor location-specific and body-region doses for brain (panel A) and breast (panel B) dose comparison studies. See Materials and Methods and Table 1 for definitions of stages 1 and 2 body-region doses.

FIG. 3. Radiation-related risk estimates for brain (panel A) and breast (panel B) subsequent neoplasm studies. Panels show the categorical odds ratios (circle with 95% CIs) and fitted linear dose response excess odds ratio (EOR)/Gy (solid line with shaded area representing 95% CI) from conditional logistic regression. See Materials and Methods and Table 1 for definitions of stages 1 and 2 body-region doses.

TABLE 1

Description and Comparison of Tumor Location-Specific and Body-Region Doses

Tumor location-specific doses		Body-region doses
Ascertainment period of radiotherapy for first primary cancer:	First 5 years after first primary cancer diagnosis with pursuit of additional records often made for case-control studies based on self-reported RT from follow up surveys.	First 5 years after first primary cancer diagnosis
Treatment characteristics	Sources: individual radiotherapy records	Sources: individual radiotherapy records
Prescribed dose	*	*
Beam energy	*	
Field type	*	*
Field size and blocking of normal tissue	*	Only used for breast stage 2 body-region doses; applied assumptions about second breast tumor location (i.e., in the unblocked beam, the edge of the field or block, under the block, near the beam edge, or out of beam) for select fields based on data collected for earlier case-control study ^a
Contributions to dose estimate		
In-beam	*	*
Scatter and leakage	*	Regions not directly treated classified as “stray-high” if adjacent to treated regions or “stray-low” if not adjacent to treated regions.
Dose for risk analysis	Mean absorbed dose to SN location and corresponding location in matched controls.	MaxTD, stray-high, or stray-low to: Stage 1: Entire region (brain or chest). Stage 2: Brain segment ^a or breast region ^b (quadrant or central/nipple area) in which the SN was located and corresponding location in matched controls.

^aFor breast stage 2 body-region doses, we divided the breast into four quadrants plus the central/nipple area and assigned dose to the specific region in which the tumor was located, incorporating typical treatment information on certain radiotherapy fields to scale the chest maxTD for women who received mantle (treatment involving mediastinal, supraclavicular and axillary areas) or T-mantle (mantle field without treatment of the axillas) and no other chest-directed (i.e., whole or partial chest, breast) radiotherapy for Hodgkin or non-Hodgkin lymphoma as well as women who received mediastinal or spinal field radiation and no other chest fields as follows. 1. Full mantle radiotherapy at ages <11 years or T-mantle field and no full mantle; the breast is assumed to have been under the lung block and a dose of 0.12*maxTD is assigned. 2. Full mantle radiotherapy at ages 11 years (a. upper and lower inner quadrants assumed to be under the lung block and assigned 0.12*maxTD; b. central/nipple area and lower outer quadrant assumed to be at field-edge and assigned 0.60*maxTD; and c. upper outer quadrant assumed to be in-field and assigned maxTD). 3. Mediastinal field with no other chest-directed fields at any age (a. outer upper and lower quadrants assumed to be out-of-field and assigned 0.05*maxTD; b. inner upper and lower quadrants and central breast/nipple area assumed to be in-field and assigned maxTD). 4. Total or upper spine, sanctuary or banjo fields and no other chest-directed fields; full breast assumed to be out-of-field and assigned 0.05*maxTD. The scaling factors are also presented in Supplementary Table 2. If quadrant was unknown, the maximum quadrant dose was applied. For women who did not receive these fields, the breast stage 1 body-region dose was used.

^bThe body-region dosimetry method classifies brain segments as in the treatment field (and assigned maxTD) if at least 50% of the segment was in the primary beam [see (13)]. For tumors overlapping multiple segments, we used the maximum of the involved segment doses. For tumors with unknown segment, we used the maximum segment dose.

SN = subsequence neoplasm; maxTD = maximum prescribed target dose.

TABLE 2
Categorical Agreement between Brain Tumor Location-Specific and Body-Region Doses

Field group ^a	Tumor location-specific dose (Gy)	Stage 1 body-region dose ^b (Gy) (brain)					Stage 2 body-region dose ^b (Gy) (brain segment)				
		>0–9.9	10–19.9	20–29.9	30	Total	>0–9.9	10–19.9	20–29.9	30	Total
Any	>0–9.9 ^c	112	0	0	6	118	115	0	0	3	118
	10–19.9	0	34	0	5	39	4	34	0	1	39
	20–29.9	0	0	80	4	84	1	0	82	1	84
	30	0	0	0	39	39	0	0	0	39	39
	Total	112	34	80	54	280	120	34	82	44	280
	Agreement %	94.6%					96.4%				
	Kappa ^d	0.91 (0.86–0.96)					0.95 (0.91–0.98)				
Whole brain	>0–9.9 ^c	0	0	0	0	0	0	0	0	0	0
	10–19.9	0	34	0	0	34	0	34	0	0	34
	20–29.9	0	0	80	2	82	0	0	82	0	82
	30	0	0	0	30	30	0	0	0	30	30
	Total	0	34	80	32	146	0	34	82	30	146
	Agreement %	98.6%					100.0%				
	Kappa ^d	0.98 (0.95–1.00)					1.00				
Partial brain ^e	>0–9.9 ^c	0	0	0	5	5	3	0	0	2	5
	10–19.9	0	0	0	5	5	4	0	0	1	5
	20–29.9	0	0	0	2	2	1	0	0	1	2
	30	0	0	0	9	9	0	0	0	9	9
	Total	0	0	0	21	21	8	0	0	13	21
	Agreement %	42.9%					57.1%				
	Kappa ^d	–					0.51 (0.23–0.78)				
Other head ^f	>0–9.9 ^c	6	0	0	1	7	6	0	0	1	7
	10–19.9	0	0	0	0	0	0	0	0	0	0
	20–29.9	0	0	0	0	0	0	0	0	0	0
	30	0	0	0	0	0	0	0	0	0	0

Field group ^a	Tumor location-specific dose (Gy)	Stage 1 body-region dose ^b (Gy) (brain)					Stage 2 body-region dose ^b (Gy) (brain segment)				
		>0-9.9	10-19.9	20-29.9	30	Total	>0-9.9	10-19.9	20-29.9	30	Total
Total		6	0	0	1	7	6	0	0	1	7
Agreement %		85.7%					85.7%				
Kappa ^d		–					–				
Other ^e											
>0-9.9 ^c		106	0	0	0	106	106	0	0	0	106
10-19.9		0	0	0	0	0	0	0	0	0	0
20-29.9		0	0	0	0	0	0	0	0	0	0
30		0	0	0	0	0	0	0	0	0	0
Total		106	0	0	0	106	106	0	0	0	106
Agreement %		100%					100%				
Kappa ^d		–					–				

^aField types were grouped according to the typical dose level to brain (high vs. low) and the degree of dose heterogeneity generally observed within and across patients. Field groups were defined hierarchically to create mutually exclusive categories. Patients receiving a combination of fields were assigned to the first applicable group, beginning with whole brain.

^bStage 1 body-region dose uses the maximum prescribed target dose (maxTD) to any segment of the brain. Stage 2 body-region dose uses the maxTD to the segment of the brain in which the tumor occurred (matched location in controls).

^cIncludes three individuals with tumor location-specific dose of 0.

^dWeighted kappa statistic (linear weights) to assess the agreement between tumor location-specific and body-region dose categories. Kappas were not calculated when one or both methods assigned 90% of individuals to the same dose category.

^eIncludes posterior fossa, banjo (posterior brain and full spine) and other brain fields.

^fIncludes other head (nasopharynx, face, mandible, nose, etc.), Waldeyer's ring (other head ± neck) and eye/orbit fields.

^gIncludes all field types to regions other than brain or other head.

Boldface text is indicated along the diagonal where there is agreement between the tumor location-specific and body-region dose categories.

TABLE 3

Categorical Agreement between Breast Tumor Location-Specific and Body-Region Doses

Field group ^a	Tumor location-specific dose (Gy)	Stage 1 body-region dose ^b (Gy) (chest)				Stage 2 body-region dose ^b (Gy) (breast region)				
		>0-9.9				>0-9.9				
		99	6	8	151	134	2	6	9	151
Any	>0-9.9	1	7	3	13	3	7	3	0	13
	10-19.9	0	0	6	41	6	0	14	27	47
	20-29.9	0	0	1	64	2	0	3	60	65
	30	100	13	18	145	145	9	26	96	276
	Total	63.8%				77.9%				
Whole chest	Agreement %	0.56 (0.49-0.64)				0.76 (0.69-0.82)				
	Kappa ^c									
	>0-9.9	1	0	0	1	1	0	0	0	1
	10-19.9	0	2	1	3	0	2	1	0	3
	20-29.9	0	0	1	1	0	0	1	0	1
Breast, chest (not whole)	30	0	0	0	0	0	0	0	0	0
	Total	1	2	2	5	1	2	2	0	5
	Agreement %	80.0%				80.0%				
	Kappa ^c	0.74 (0.27-1.00)				0.74 (0.27-1.00)				
	>0-9.9	1	1	1	9	1	1	1	6	9
Mantle ^d	10-19.9	0	5	0	5	0	5	0	0	5
	20-29.9	0	0	1	4	0	0	1	3	4
	30	0	0	0	11	0	0	0	11	11
	Total	1	6	2	29	1	6	2	20	29
	Agreement %	62.1%				62.1%				
Mantle ^d	Kappa ^c	0.39 (0.16-0.63)				0.39 (0.16-0.63)				
	>0-9.9	0	0	0	19	12	0	4	3	19
	10-19.9	0	0	2	4	2	0	2	0	4
	20-29.9	0	0	4	42	6	0	12	24	42
	30	0	0	1	53	2	0	3	49	54
	Total	0	0	7	119	22	0	21	76	119

Field group ^a	Tumor location-specific dose (Gy)	Stage 1 body-region dose ^b (Gy) (chest)					Stage 2 body-region dose ^b (Gy) (breast region)				
		>0-9.9	10-19.9	20-29.9	30	Total	>0-9.9	10-19.9	20-29.9	30	Total
Agreement %											
47.9%											
T-mantle ^e	Kappa ^c	-					0.50 (0.37-0.63)				
	>0-9.9	0	0	2	7	9	9	0	0	0	9
	10-19.9	0	0	0	0	0	0	0	0	0	0
	20-29.9	0	0	0	0	0	0	0	0	0	0
	30	0	0	0	0	0	0	0	0	0	0
	Total	0	0	2	7	9	9	0	0	0	9
Agreement %											
100%											
Mediastinum	Kappa ^c	-					-				
	<10	0	0	1	1	2	2	0	0	0	2
	10-19.9	0	0	0	0	0	0	0	0	0	0
	20-29.9	0	0	0	0	0	0	0	0	0	0
	30	0	0	0	0	0	0	0	0	0	0
	Total	0	0	1	1	2	0	0	0	2	2
Agreement %											
100%											
Selected spine fields ^f	Kappa ^c	-					-				
	>0-9.9	0	4	3	5	12	12	0	0	0	12
	10-19.9	0	0	0	0	0	0	0	0	0	0
	20-29.9	0	0	0	0	0	0	0	0	0	0
	30	0	0	0	0	0	0	0	0	0	0
	Total	0	4	3	0	7	12	0	0	0	12
Agreement %											
100%											
Supraclavicular ± neck	Kappa ^c	-					-				
	>0-9.9	2	0	1	0	3	2	0	1	0	3
	10-19.9	0	0	0	0	0	0	0	0	0	0
	20-29.9	0	0	0	0	0	0	0	0	0	0
	30	0	0	0	0	0	0	0	0	0	0
	Total	2	0	1	0	3	2	0	1	0	3
Agreement %											
66.7%											

Field group ^a	Tumor location-specific dose (Gy)	Stage 1 body-region dose ^b (Gy) (chest)					Stage 2 body-region dose ^b (Gy) (breast region)				
		>0-9.9	10-19.9	20-29.9	30	Total	>0-9.9	10-19.9	20-29.9	30	Total
Abdomen ^g	Kappa ^c	–					–				
	>0-9.9	13	1	0	0	14	13	1	0	0	14
	10-19.9	1	0	0	0	1	1	0	0	0	1
	20-29.9	0	0	0	0	0	0	0	0	0	0
	30	0	0	0	0	0	0	0	0	0	0
	Total	14	1	0	0	15	14	1	0	0	15
	Agreement %	86.7%					86.7%				
Other ^h	Kappa ^c	–					–				
	>0-9.9	82	0	0	0	82	82	0	0	0	82
	10-19.9	0	0	0	0	0	0	0	0	0	0
	20-29.9	0	0	0	0	0	0	0	0	0	0
	30	0	0	0	0	0	0	0	0	0	0
	Total	82	0	0	0	82	82	0	0	0	82
	Agreement %	100%					100%				
	Kappa ^c	–					–				

^aField types were grouped according to the typical dose level to the breast (high vs. low) and the degree of dose heterogeneity generally observed within and across patients. Field groups were defined hierarchically to create mutually exclusive categories. Women receiving a combination of fields were assigned to the first applicable group, beginning with whole chest.

^bStage 1 body-region dose uses the maximum prescribed target dose (maxTD) to any part of the chest. Stage 2 body-region dose uses a scaled maxTD to the specific region (quadrant or central/nipple area) of the breast in which the tumor occurred (matched location in controls) for women who received mantle or T-mantle radiotherapy fields for Hodgkin lymphoma and non-Hodgkin lymphoma, as well as women who received mediastinal or spinal field radiation and no other chest fields (See Table 1 and Supplementary Table S2). For women who did not receive these fields, the stage 1 body-region dose was used.

^cWeighted kappa statistic (linear weights) to assess the agreement between tumor location-specific and body-region dose categories. Kappas were not calculated when one or both methods assigned 90% of individuals to the same dose category.

^dTreatment involving mediastinal, supraclavicular and axillary areas.

^eMantle field without treatment of the axillas.

^fIncludes total spine, upper spine, sanctuary, and banjo (posterior brain and full spine) fields.

^gIncludes whole abdomen, other abdomen, abdomen with para-aortic, and abdomen (whole or other) with pelvis fields.

^hIncludes all other field types not specified above.

Boldface text is indicated along the diagonal where there is agreement between the tumor location-specific and body-region dose categories.

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