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PENTEC ORGAN SYSTEM REVIEW

Risk of Subsequent Neoplasms in Childhood Cancer Survivors After Radiation Therapy: A PENTEC Comprehensive Review

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Purpose: A Pediatric Normal Tissue Effects in the Clinic (PENTEC) analysis of published investigations of central nervous system (CNS) subsequent neoplasms (SNs), subsequent sarcomas, and subsequent lung cancers in childhood cancer survivors who received radiation therapy (RT) was performed to estimate the effect of RT dose on the risk of SNs and the modification of this risk by host and treatment factors.

Methods and Materials: A systematic literature review was performed to identify data published from 1975 to 2022 on SNs after prior RT in childhood cancer survivors. After abstract review, usable quantitative and qualitative data were extracted from 83 studies for CNS SNs, 118 for subsequent sarcomas, and 10 for lung SNs with 4 additional studies (3 for CNS SNs and 1 for lung SNs) later added. The incidences of SNs, RT dose, age, sex, primary cancer diagnosis, chemotherapy exposure, and latent time from primary diagnosis to SNs were extracted to assess the factors influencing risk for SNs. The excess relative ratio (ERR) for developing SNs as a function of dose was analyzed using inverse-variance weighted linear regression, and the ERR/Gy was estimated. Excess absolute risks were also calculated.

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Research data used in this work were from previously published studies. When applicable, links to data are provided in the text.

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Results: The ERR/Gy for subsequent meningiomas was estimated at 0.44 (95% CI, 0.19-0.68); for malignant CNS neoplasms, 0.15 (95% CI, 0.11-0.18); for sarcomas, 0.045 (95% CI, 0.023-0.067); and for lung cancer, 0.068 (95% CI, 0.03-0.11). Younger age at time of primary diagnosis was associated with higher risk of subsequent meningioma and sarcoma, whereas no significant effect was observed for age at exposure for risk of malignant CNS neoplasm, and insufficient data were available regarding age for lung cancer. Females had a higher risk of subsequent meningioma (odds ratio, 1.46; 95% CI, 1.22-1.76; $P < .0001$) relative to males, whereas no statistically significant sex difference was seen in risk of malignant CNS neoplasms, sarcoma SNs, or lung SNs. There was an association between chemotherapy receipt (specifically alkylating agents and anthracyclines) and subsequent sarcoma risk, whereas there was no clear association between specific chemotherapeutic agents and risk of CNS SNs and lung SNs.

Conclusions: This PENTEC systematic review shows a significant radiation dose-response relationship for CNS SNs, sarcomas, and lung SNs. Given the linear dose response, improved conformality around the target volume that limits the high dose volume might be a promising strategy for reducing the risk of SNs after RT. Other host- and treatment-related factors such as age and chemotherapy play a significant contributory role in the development of SNs and should be considered when estimating the risk of SNs after RT among childhood cancer survivors.

Introduction

Radiation therapy (RT) is critical in the management of pediatric malignancies. However, RT can be toxic and can predispose survivors to complications that may affect duration and quality of life, with one serious complication being that of a treatment-induced subsequent neoplasm. This comprehensive review from Pediatric Normal Tissue Effects in the Clinic (PENTEC) aims to estimate the excess and absolute risk of central nervous system (CNS) subsequent neoplasms (SNs), sarcomas, and lung malignancies in cancer survivors who were treated with RT as children as well as the modification of this risk by factors related to the host and to other treatments.

Clinical Significance

Radiation therapy is commonly used as part of the definitive or adjuvant treatment for many primary pediatric CNS malignancies (eg, medulloblastoma, ependymoma, glioma, and germ cell tumors) and non-CNS malignancies (eg, Hodgkin lymphoma, rhabdomyosarcoma, Ewing sarcoma, Wilms tumor, and neuroblastoma). RT doses to and irradiated volumes of the brain and other organs in each of these indications vary depending on tumor histology and primary site. For example, CNS-directed RT can vary from low-dose whole-brain RT (eg, for hematologic malignancies) to focal RT alone (eg, for ependymomas and gliomas) to craniospinal RT with focal boosts (eg, in medulloblastoma and other CNS embryonal tumors). For non-CNS−directed RT, doses and volumes can vary from low-dose, large-flank field RT used in Wilms tumor with favorable histology to high-dose, focal RT used in pediatric sarcomas.

With advances in multimodality therapy, survival after childhood cancer is improving, with more than 80% of children treated for pediatric cancers now 5-year survivors.[1,2] Childhood cancer survivors are at risk of late effects from treatment of their primary cancer, making it imperative to fully evaluate the therapeutic ratio of RT (ie, optimally balancing the desire to reduce late morbidity and increase oncologic control).

Although the risk of SNs after RT in childhood cancer survivors is well established, further characterization of the contributing factors, including the specific contribution of RT dose, is needed. The incidence of SNs in childhood cancer survivors is approximately 9% at 30 years from primary cancer diagnosis,[3] and SNs represent the most common etiology of excess mortality in long-term childhood cancer survivors, with reported standardized mortality ratios around 15. In fact, beyond 20 years from initial diagnosis, the cumulative risk of death associated with development of SNs exceeds that associated with primary tumor recurrence in childhood cancer survivors.[4] Given the significant morbidity and mortality that results from SNs, as well as the increase in risk of SNs with increased longevity of childhood cancer survivors, it is critical to gain a better understanding of the contribution and risk of SNs after RT.

Endpoint Characterization

Characterization of SNs can be made via an actuarial risk, a relative risk compared with the standard population of nonexposed patients with cancer, or as an attributable risk as a result of a specific predisposing factor or exposure. SNs are often distinguished from relapses of the primary childhood cancer (eg, locoregional recurrence, distant metastases) by histologic differentiation as well as latency period, with subsequent malignancies often developing at a later time from initial diagnosis than primary tumor recurrence.[5] Differences in definitions have further challenged the characterization of SNs, because some reports solely include subsequent malignant neoplasms, whereas others include both benign and malignant neoplasms and occasionally nonmelanoma skin cancers as well. Detection of SNs also varies, from those that present as clinically overt or symptomatic tumors to those that are coincidentally found as part of medical care at survivorship clinics, from imaging for other health problems, or as part of systematic surveillance for primary tumor

recurrences or SNs among asymptomatic high-risk survivors. Additionally, the time course to the various SNs differs, with subsequent hematologic malignancies (ie, myelodysplastic syndrome and acute leukemia) most often occurring within 5 years of treatment of the primary tumor versus subsequent solid malignancies that often present more than 5 to 10 years (and even many decades) from initial treatment.[6,7]

For this review, the endpoints of primary interest included the following SNs observed in childhood cancer survivors who received RT: (1) subsequent CNS SNs (distinguishing high-grade gliomas from meningiomas); (2) subsequent sarcomas; and (3) subsequent lung cancers. Although other SNs outside of these 3 categories were observed, for the purpose of this study, only the aforementioned SN types were included and analyzed. Other sites of SNs may be considered by PENTEC in the future.

Anatomy and Developmental Dynamics

From a radiation biology standpoint, radiation's carcinogenic potential stems from its promotion of cell proliferation and re-entering of the cell cycle with escape from senescence and apoptosis.[8] Although radiation's production of irreparable DNA damage is essential for its efficacy, developing organs and tissues in children can be particularly sensitive to off-target mutational events, increasing the risk of developing an RT-related SN in children compared with adults with already developed tissues. Confirming the vulnerability of developing organs to radiation-induced damage, disproportionate rates of secondary leukemias and thyroid cancers have been observed in children <10 years old versus adult atomic bomb survivors,[9,10] and higher rates of SNs have also been observed among children exposed to therapeutic doses of radiation compared with adults exposed to those same doses,[11,12] even after accounting for known genetic predispositions.

The etiology of SNs in childhood cancer survivors is complex and often multifactorial, including a combination of underlying genetic predisposition (with or without a known germline genetic driver), environmental factors, sex, age at the time of primary diagnosis, attained age, organ-specific factors, hormonal factors, immunosuppression, and treatment-related factors (eg, RT doses and techniques, chemotherapy, and other antineoplastic agents). Especially in pediatric cancers, where the prevalence of having an underlying germline mutation in a predisposition gene is approximately 9%,[13] the role of genetic predisposition to SN risk cannot be understated. There is likely an additional interaction of underlying genomics with treatment-related exposures, as evidenced by the very high SN rate (approximately 40%-50%) among those with hereditary retinoblastoma who receive RT.[14,15] With regard to RT and the risk of SNs, there is a clear dose-response relationship observed after low-dose total body exposure among atomic bomb survivors in the Life Span Study cohort,[6] and a linear dose response has also been observed after high-dose fractionated RT. The 1 known exception of the linear dose-response relationship after therapeutic doses of RT is for thyroid cancer, in which there is a plateau bell−shaped dose-effect relationship with a decrease in radiation-induced risk after exposure of 20 Gy or more, which is consistent with findings in radiobiology and thought to be due to cell killing with higher doses.[16,17]

Defining Volumes: Irradiated Volume and Dose Distribution

Although most of the included studies provided the prescribed dose (and range) of RT exposure, few studies provided dosimetric information regarding dose at the site of SN development. In this study, the prescription dose was generally used in the dose-SN risk analysis. Determining whether the SN was in the high-dose region of the irradiated volume (defined as within the target volume) or within the lower dose volume (often referred to as the low-dose bath with intensity modulated radiation therapy [IMRT] plans), was not possible for CNS SNs and subsequent lung cancers, but information regarding this detail was sufficiently available for the subsequent sarcoma analysis. A major limitation of this or any such study relying on prescribed dose is that the actual dose giving rise to the SN may be different than what is used in the modeling effort. Additionally, even when the dose at the site of the SN is reconstructed, the uncertainty in that dose is estimated to be at least 10% owing to limitations in the retrospective reconstruction of dose,[18] and if the SN arose near the edge of the target volume, then an even higher dose uncertainty should be assigned.

Review of Dose-Volume Response Data and Risk Factors

Search methodology and data extraction

A comprehensive literature search was performed using the Covidence platform in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method.[19] Search terms used are in Appendix E1. Eligible studies included those that assessed risk of CNS SNs after cranial RT as a child, subsequent sarcomas after RT to any site as a child, and subsequent lung cancers after chest RT as a child. Only studies with sufficient (>7-year) median follow-up were included to balance latency time with inclusivity. For the specified SN endpoints, any information about RT exposure and SN was deemed valuable, including data from studies that found no SNs when reporting on late effects with appropriate follow-up. As shown in Appendix E1 and Appendix E2, 2156 studies were screened for potential inclusion for CNS SNs, 1790 studies for subsequent sarcomas, and 1003 studies for subsequent lung cancer. Three authors (J.M., A.O., and K.B.R.) reviewed all

abstracts and excluded articles that were not relevant, leaving 235 articles for full review for CNS SNs, 469 for subsequent sarcomas, and 49 for subsequent lung cancer. After these studies were read in full and assessed for eligibility, 83 studies were identified for CNS SNs, 118 for subsequent sarcomas, and 10 for subsequent lung cancer. Of these, 61 had adequate data (and thus were used) for quantitative analysis for CNS SNs, 47 for sarcomas, and 10 for lung cancer, with adequate data defined as those studies that provided information about dose response (either studies that reported odds ratios (ORs) or relative risk (RR) or studies that allowed for calculations by providing the incidence of SNs at different dose levels), latency period, and/or contribution of sex, age, or chemotherapy to risk of SNs. Four additional studies (3 for CNS SNs and 1 for lung cancer) known to the authors were later added that were not identified in the initial search but met eligibility criteria (Tables E1-E4 in Appendix E2 show the lists of included studies).

In addition to available RT data, when available, data regarding age, sex, primary diagnosis, latency from primary cancer to SNs, and chemotherapy exposure were also collected for analysis. Information regarding smoking history was only sparsely available for those with subsequent lung neoplasms, limiting analysis of the contribution of smoking on subsequent lung cancer risk to qualitative only. For the purpose of this review and its focus on RT contribution to risk, data focusing on risk of SNs in patients with known genetic predispositions (ie, hereditary retinoblastoma) were excluded. For CNS SNs, analyses were performed separately for subsequent meningiomas and subsequent CNS malignancies, given the different phenotypes of these. In addition, for the dose-response analysis for CNS SNs, analyses were performed separately for patients with a primary diagnosis of acute lymphocytic leukemia (ALL) versus primary CNS malignancy.

Mathematical Models

Dose-response meta-analyses

Odds ratio or RR estimates with corresponding 95% confidence intervals (CIs) comparing the risk of developing an SN at different dose levels were extracted from each study where these were given. Alternatively, ORs were calculated if sufficient data for cases and controls were reported at different dose levels. Generally, when the incidence of an event is low, such as for SNs, then the OR and RR estimates will be approximately the same numerically. The excess risks ratio (ERR) per Gy was derived for a given type of SN using each of the individual OR or RR estimates at a given dose point extracted from the included studies. If dose levels were given as ranges without indication of the mean or median, then the midpoint in the range interval was used for the modeling. The pooled ERRs/Gy with 95% CIs were estimated using inverse variance weighted linear regression. Sensitivity analyses were performed using a leave-one-out strategy for CNS SNs, where ERR/Gy estimates were derived by sequentially excluding 1 study at a time to assess how much each study's exclusion would affect the slope estimate. In the sarcoma and lung SN analyses, the Levenberg-Marquardt algorithm was used for determining the best-fitting function and its confidence intervals.[20]

The ERR can be converted to absolute risk under the assumption of a given background incidence using the formulae discussed in the "PENTEC-State of the Science" article from this issue. A reference absolute risk (AR) is needed for a nonexposed individual. This AR will vary substantially with the attained age of the reference patient. The excess AR represents an average patient according to study cohorts, and the effect will be modified by, for example, age according to the previously provided effect estimates. We provide estimates using cumulative incidences of the given neoplasm in the general population at an attained age of 50 and 75 years and representative assumptions of RT dose and chemotherapy. Personalized calculations using a given exposure can be estimated using the same approach. Cumulative incidence data are extracted from available resources as detailed and referenced in individual sections that follow.

Latency time distribution for various types of SNs

The median latent time to the development of a given type of SN was extracted from each study where reported. This was compared with the median follow-up time in the corresponding study to assess whether there was an association between reported latency time and length of follow-up. We further examined this association in relation to the number of SNs reported in each study and estimated a weighted average of the median latent time for the different types of SNs.

Effect of age at exposure meta-analysis

The ORs, RRs, or hazard ratios for SNs were extracted individually for each studied SN type and assessed in a univariate model. Data were transformed to the common scale of ERR assuming a background incidence of 0.1% for all 3 endpoints. A sensitivity analysis against this assumption was performed. In addition, we recalculated reported data to have the lowest reported age group as the reference (ERR = 0). After reconciling the effect measures on the common scale of ERR, all studies of ERR versus age were plotted together, and linear regression of the type *ERR∼age at exposure* weighted by inverse variance was performed. Here, the reference group was excluded in the fit, and the fit was performed with zero intercept on the ERR axis at age 0. To account for varying width of the lowest age bin, the data were renormalized by shifting along the x-axis to a common "age 0." This is consistent with the mathematical form of a linear regression but adjusts for the shift of the intercept arising from a different reference group in different studies. Details of the fit are provided from the generating R scripts

available online and referenced in each section. If a study could not be included in the linear regression, it is discussed separately in the results section.

Effect of sex meta-analysis

The ORs were calculated using event (occurrence of an SN) and nonevent data for males and females in a univariate model. Studies that were included in this analysis consisted of those with at least 100 patients with childhood cancer and sufficient data to calculate ORs. Excluded from this analysis were studies that reported matched case-control data on sex, as matching in case-control studies will distort the association between the matching variables and outcome. Although some studies with adult populations were included, most patients in these studies were <21 years of age at primary cancer diagnosis. For each of the studied malignancies, a fixed-effects meta-analysis using the Mantel-Haenszel method was performed in Review Manager, version 5.4.1 (software that can carry out meta-analyses).[21]

Chemotherapy exposure meta-analysis

For CNS SNs and lung SNs, given a lack of sufficient data for quantitative analysis, a qualitative analysis was performed. For secondary sarcoma, the same approach as for sex was used, with ORs calculated in univariate analysis for alkylating agents and anthracyclines (yes vs no for each agent). In addition, we sought after studies reporting multivariable analysis of the same agents and reported a synthesized multivariate estimate using inverse variance weighting of the reported multivariate ORs.

Review of Data

CNS SNs: Overall CNS SN cohort

Dose response

Tables E1 and E2 in Appendix E3 summarize the individual studies included in the dose-response analysis. Combining all individual data points of RRs or ORs at given dose levels for subsequent CNS malignancies using inverse variance weighting resulted in a significant dose-response relationship with an estimated pooled ERR/Gy of 0.146 (95% CI, 0.112-0.181). Similarly, the estimated pooled ERR/Gy for subsequent meningiomas was 0.436 (95% CI, 0.192-0.680).

The leave-one-out analyses showed that no single study had a major effect on the resulting dose-response curve when removed from the fit for subsequent CNS malignancies, whereas for subsequent meningiomas, removing the study by Kok et al[22] resulted in a higher estimated ERR/Gy of 0.69. The dose-response data along with leave-one-out analyses are shown for subsequent CNS malignancies in Fig. 1 and for subsequent meningiomas in Fig. 2.

The cumulative incidence of brain and CNS tumors excluding endocrine tumors in the normal population in the NORDCAN countries at 50 and 75 years, respectively, is 0.54% and 1.55%.[23,24] With these numbers, a dose of 20 Gy would lead to an excess absolute risk of CNS malignancy of 1.6% at age 50 (95% CI, 1.1%-2%) and 4.5% at age 75 (95% CI, 3.4%-5.6%), and a dose of 50 Gy would lead to an excess absolute risk of CNS malignancy of 3.9% at age 50 (95% CI, 3.0%-4.9%) and 11% at age 75 (95% CI, 8.7%-14%).

Dose response: ALL survivors receiving cranial radiation therapy

There were 9 publications that provided event rates and/or relative risk estimates of subsequent malignant CNS

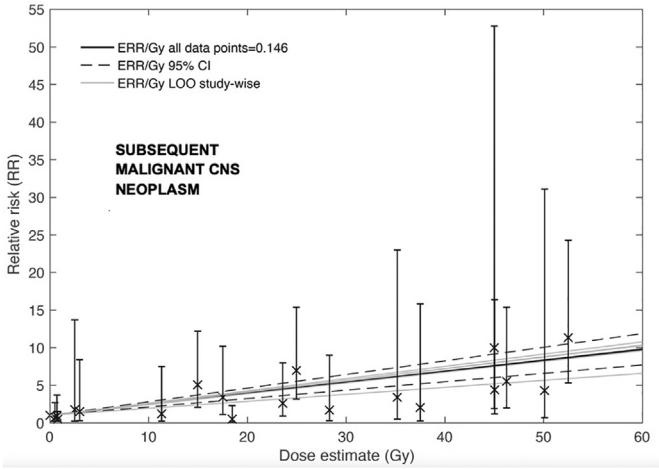

Fig. 1. Individual data points used to estimate the pooled excess relative ratio (ERR)/Gy for subsequent malignant neoplasms are shown along with the resulting dose-response curve and 95% confidence intervals. The shaded lines show the resulting dose-response curves from the leave-one-out (LOO) analysis. Vertical bars show the odds ratio (OR)/relative risk (RR) and 95% confidence interval of the individual data points.

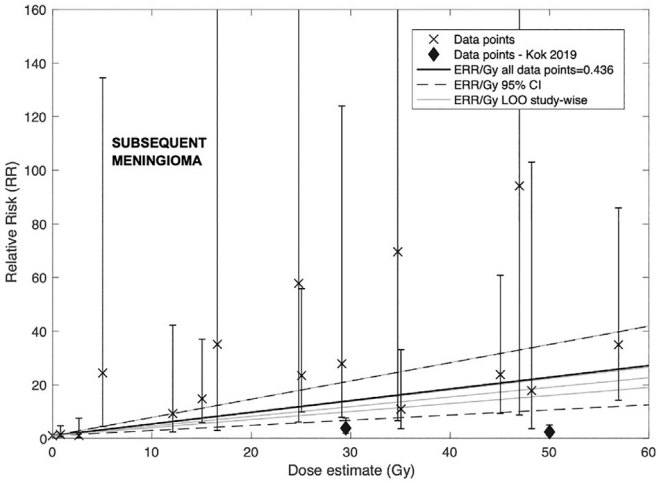

Fig. 2. Individual data points used to estimate the pooled excess relative ratio (ERR)/Gy for subsequent meningiomas are shown along with the resulting dose-response curve and 95% confidence intervals. The shaded lines show the resulting dose-response curves from the leave-one-out (LOO) analysis. Vertical bars show the odds ratio (OR)/relative risk (RR) 95% confidence interval of the individual data points.

neoplasms and meningiomas after whole-brain RT for ALL (Tables E1 and E2 in Appendix E3). Doses used were generally less than 30 Gy, most commonly 18 or 24 Gy. We analyzed the dose response of CNS SNs in this specific population because patients receive a relatively low radiation dose to their whole brain and may represent a unique biological cohort. Figure 3 shows rates of CNS SNs among this population by whole-brain dose. In the 2 studies with rates of subsequent meningioma ≥25%, surveillance imaging was performed, resulting in the detection of asymptomatic cases.

Latency

For the latent time analysis, 40 studies of 736 subsequent CNS malignant neoplasms were available and revealed a weighted average median latency time of 10.3 years (range, 1.0-20.3 years) (Table E1 in Appendix E3) after a median follow-up of 12 years. There were 32 studies of 1035 subsequent meningiomas available, resulting in a considerably longer weighted average median latency time of 20.5 years (range, 5.0-30.2 years) (Table E2 in Appendix E3) after a median follow-up of 16 years. Figure 4 shows the median latency times from each study as a function of the median follow-up time. This figure highlights that the reported latent times are longer in studies with longer follow-up time, suggesting that the latency estimated in studies with shorter follow-up is downward biased. However, comparing cohorts with a given median follow-up time shows that the latent period in meningioma tends to be longer than that of malignant CNS neoplasms.

Age

The analysis of age at exposure versus risk of subsequent malignant CNS neoplasms did not reveal a significant association (95% CI of regression b, −0.056 to 0.2 ERR per year; $P = .23$), in agreement with the reports with the largest number of patients. See https://osf.io/739hn for details on this analysis. However, Neglia et al[25] (14,361 5-year survivors) suggest an interaction of age with radiation dose, where children younger than 5 years have a higher sensitivity to radiation dose (vs those 5 years of age or older), although the interaction was not statistically significant ($P = .15$). Nevertheless, given the much steeper point estimates for the excess odds ratio (EOR) per Gy in young children (0.64 per Gy for children aged <5 years compared with 0.15 per Gy for children aged 10-20 years), additional caution may be warranted when estimating the risk in younger patients.

Five studies reported data amenable for analysis for the effect of age at exposure for meningioma (Table E2 in Appendix E3). Four of these[22,26-28] allowed quantitative synthesis. The linear regression $ERR = b \times Age$ yields $b = -0.070$ (95% CI, −0.065 to −0.076; $P < .0001$), corresponding to a 70% decrease in excess risk for a 10-year-old child relative to a newborn. This result remained highly significant with any of the 3 studies left out of the sensitivity analysis. See https://osf.io/qx2t3 for details. One important study from Journy et al,[29] not included in this analysis, suggests an interaction where younger children have a higher sensitivity to radiation dose, reporting excess ORs for subsequent meningioma per Gy of radiation decreasing from EOR = 4.8 per Gy at ages <5 years to EOR/Gy = 0.22 at ages ≥10 years. Because the Journy et al report is matched with 4 cases per controls in each age interval, it could not be included in the univariable analysis of the current study, and other reports did not allow verification of the interaction between age and dose-risk relationship.

Sex

The risk of subsequent meningiomas was higher in females than males (OR, 1.46; 95% CI, 1.22-1.76; 7 studies; 52,507 patients; 456 events; $P < .0001$) (Fig. 5), whereas no difference between sexes was seen in risk of malignant CNS neoplasms (OR, 0.94; 95% CI, 0.68-1.31; 4 studies; 32,952 patients; 142 events; $P = .71$) (Appendix E4).

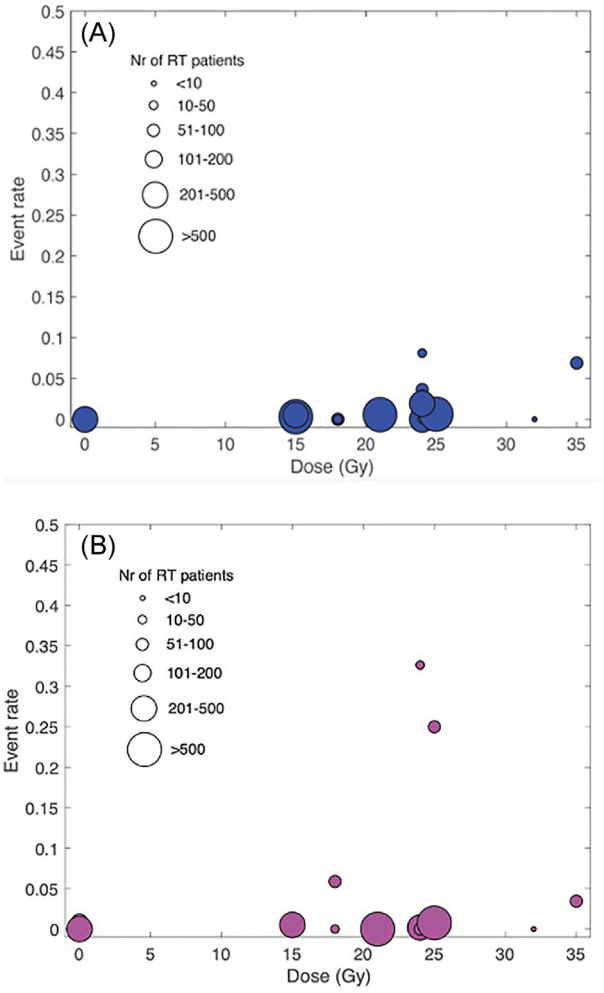

Fig. 3. Rate of central nervous system (CNS) subsequent neoplasms (SNs) including (A) malignant CNS neoplasms and (B) meningiomas by dose in childhood cancer survivors of acute lymphocytic leukemia treated with whole-brain radiation therapy. As noted, the 2 studies with rates of subsequent meningioma ≥25% used surveillance imaging (and thus detected asymptomatic cases), whereas this was not routinely done in the other studies.

Interestingly, the OR for females versus males in Fig. 5 is smaller than what is reported in the NORDCAN database[23] (ERR = 2.5 at 50 years and 1.46 at 75 years, compared with the ERR of 0.46 [95% CI, 0.22-0.76] observed in the current study—OR is essentially equal to ERR + 1 at these background incidences). This challenges the assumption of a pure multiplicative effect of treatment-induced risk to the background spontaneous risk. In light of these systematic uncertainties, we refrain from providing an absolute risk estimate for meningioma.

Chemotherapy

Overall, there is weak evidence supporting that specific chemotherapeutic agents affect the risk of CNS SNs. With regard to subsequent malignant CNS neoplasm, among the

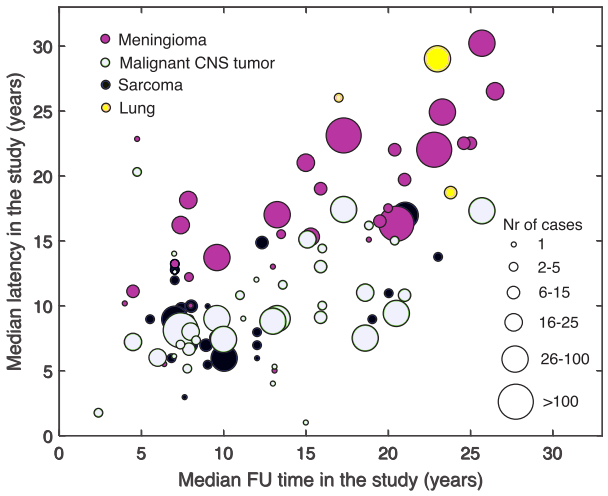

Fig. 4. Median latency times from each study are shown as a function of the median follow-up time for subsequent malignant central nervous system (CNS) neoplasms (green circles), meningiomas (purple circles), sarcoma (blue circles), and lung cancer (red circles), with data points sized according to the number of study participants.

Childhood Cancer Survivor Study (CCSS) cohort, Neglia et al[25] showed that chemotherapy exposure (categorized as yes or no as well as by specific agents including alkylating agents, anthracyclines, epipodophyllotoxins, platinum agents, and antimetabolites) did not increase the risk of subsequent glioma after accounting for radiation dose. A similar lack of association between alkylating agents that penetrate the brain and subsequent risk of SNs was observed among a cohort of childhood cancer survivors in France and the United Kingdom.[30] In the French Childhood Cancer Survivor study, Journy et al[29] also found no increase in risk of glioma after various chemotherapeutic exposures with the exception of epipodophyllotoxin exposure (although no dose-response relationship was observed). Similarly, there was no association between chemotherapy exposure on risk of subsequent glioma in the British Childhood Cancer Survivor Study (BCCSS).[31] Walter et al[28] also showed that among a cohort of children treated for ALL, there was no effect of intrathecal chemotherapy on risk of subsequent glioma.

In the CCSS cohort, Friedman et al[32] found no effect of various chemotherapeutic agents (alkylators, anthracyclines, epipodophyllotoxin, and platinum) on risk of meningioma, although an updated report from the CCSS from Turcotte et al[26] suggests a weak association between both alkylators and platinums and subsequent meningioma risk (albeit without a dose-response relationship). In the BCCSS, the dose of intrathecal methotrexate was associated in a linear fashion with risk of subsequent meningioma, with a 36-fold increased risk among those exposed to 70 mg/m^2 or more compared with those unexposed.[31] However, this finding of increased risk of meningioma after intrathecal therapy has not been confirmed in other series from the CCSS[33] nor the

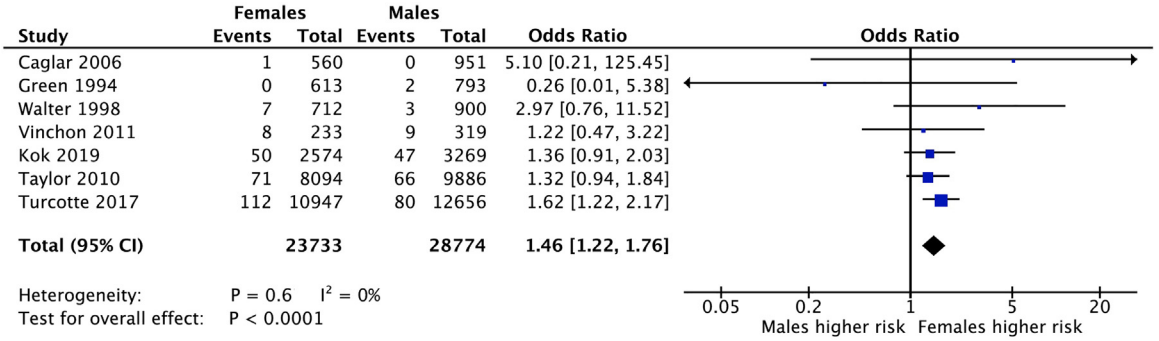

Fig. 5. Risk of meningioma versus sex. Studies are ordered by inverse variance. The risk of subsequent meningiomas was higher in females than males; this result was statistically significant ($P < .0001$).

Dutch LATER cohort.[22] Additionally, in the BCCSS cohort, there was no effect of other cytotoxic agents on risk of subsequent meningioma.[31] In the French Childhood Cancer Survivor study, Journy et al found a modest association between cumulative dose of alkylating agent and risk of subsequent meningioma but no association with other chemotherapeutic agents.[29] In the Dutch LATER cohort, only carboplatin exposure was associated with increased risk of subsequent meningioma, although without a dose-response relationship; the authors postulate that this effect could have been seen in part owing to the fact that the main subgroup of patients who received carboplatin were those with medulloblastoma.[22] Last, Cardous-Ubbink et al found that among childhood cancer survivors treated at the Emma Children's Hospital in Amsterdam, chemotherapy (yes or no) was not associated with the risk of subsequent meningioma on multivariate analysis, although specific chemotherapy agents and doses were not specified.[34] Altogether, there is not enough evidence to definitively conclude a consistent relationship between specific chemotherapeutic agents and the risk of subsequent meningioma.

Subsequent sarcoma

Dose response

Table E3 in Appendix E3 lists studies included in the sarcoma dose-response meta-analysis. Combining all individual data points of RRs at given dose levels for sarcoma using inverse variance weighting resulted in a significant dose-response relationship with an estimated pooled ERR/Gy of 0.045. More specifically, the linear regression $ERR = b \times Dose$ yields $b = 0.045$ (95% CI, 0.023-0.067; $P = .002$). However, there is a suggestion of a biphasic dose response (see Fig. 6A), with much higher RRs and rates of subsequent sarcoma above 55 Gy, similar to findings from Henderson et al,[35] who reported an OR of 116 for ≥50 Gy (mean dose, 53 Gy) compared with an OR of 16 for 30 to 50 Gy (mean dose, 37 Gy). However, the significance of this apparent bimodal response must be tempered by considering the small number of patients in the higher dose bins (reflected in the large confidence intervals shown) and the lack of a known mechanism for this potential threshold effect for an increase in the steepness of the dose response.

Of note, among 14 studies with information regarding the location of the subsequent sarcoma after RT exposure, 113 of 128 subsequent sarcomas (88%) occurred in field and 12% occurred out of field, of which approximately one-third (or 4% of the total) were labeled as being at or near the field edge. When analyzing dose response from matched case-control studies reporting dose to the site of subsequent sarcoma, the ERR could be described using ERR/Gy = 0.131 (95% CI, 0.0821-0.180; $P < .0001$) (Fig. 6B).

Excess absolute risk of a subsequent soft-tissue sarcoma for a 20-Gy exposure and anthracyclines (univariate value, so representing an "average" combination) lead to an EAR = Dose × 0.05 Gy^{-1} + 2.42 = 3.42. Assuming a background cumulative incidence of 0.07% and 0.25% for soft-tissue sarcoma at 50 and 75 years, respectively,[23] then the excess absolute risk becomes 0.24% (95% CI, 0.2%-0.28%) and 0.86% (95% CI, 0.7%-1%) at 50 and 75 years after 20-Gy exposure, respectively, and 0.3% (95% CI, 0.3%-0.4%) and 1.2% (95% CI, 0.95%-1.5%) at 50 and 75 years after 50-Gy exposure, respectively.

Latency

For the latent time analysis, 29 studies with 312 subsequent sarcomas were available and revealed a weighted average median latency time of 11 years (range, 4-23 years) (Fig. 4) after a median follow-up of 9 years. As with CNS SNs, longer latencies were observed with longer reported follow-up.

Age

A tendency toward decreased risk of subsequent sarcoma with increasing age at exposure was seen ($b = -0.032$; 95% CI, −0.06 to −0.003 ERR per year; $P = .035$), meaning that a 10-year-old is at approximately 30% lower relative risk than an infant. This result was, however, sensitive to leaving out a study, which would often lead to insignificant slope of the regression. See https://osf.io/q5hk4 for details.

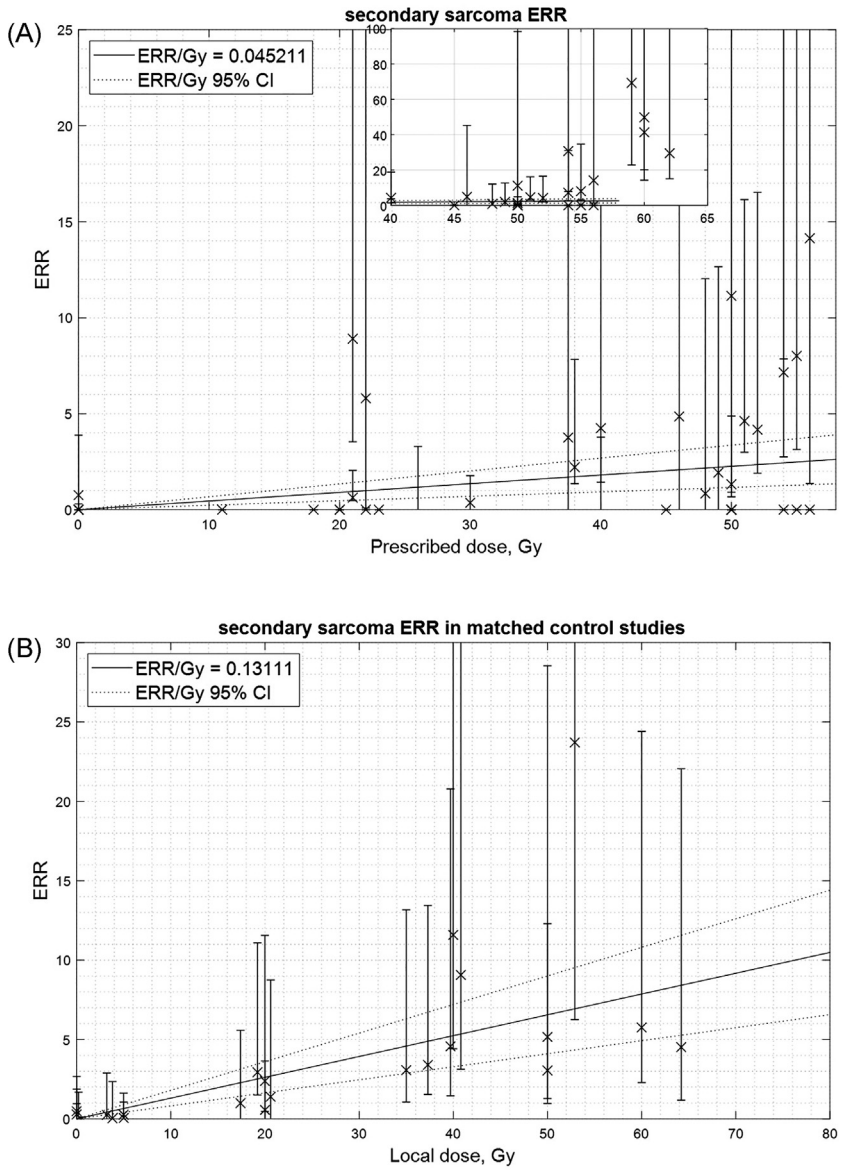

Fig. 6. Individual data points used to estimate the pooled excess relative ratio (ERR)/Gy for subsequent sarcomas among (A) cohort studies and (B) matched case-control studies are shown along with the resulting dose-response curve and 95% confidence intervals. Vertical bars show the ERR 95% confidence interval of the individual data points. (A) Insert represents dose response from 40 to 65 Gy, with the ERR/Gy higher than the linear fit for doses >60 Gy.

Sex

The risk of subsequent sarcomas showed a numerical higher value in females compared with males (OR, 1.56; 95% CI, 0.84-2.90; 9 studies; 18,701 patients; 38 events; P = .16, Fig. 7), which was not statistically significant.

Chemotherapy exposure

Figure 8 depicts univariate and multivariate analyses of the effect of alkylating agents and anthracyclines on the risk of subsequent sarcoma. There is good evidence that anthracyclines or alkylating agents both will increase the risk of subsequent sarcoma. Correlations by indication and study heterogeneity make it difficult to draw conclusions of the relative contributions of the 2 classes of drugs. Univariate analyses suggest that alkylating agents are the main driver, but the large CCSS study by Henderson et al[35] points to anthracyclines as the dominant risk factor. Because there is a high correlation between patients receiving both agents and confounding by indication, we suspect that the multivariate analyses can be unstable in this situation. It can be concluded, however, that evidence points to an increased risk of subsequent sarcoma when common pediatric chemotherapy regimens including alkylators and/or anthracyclines are received.

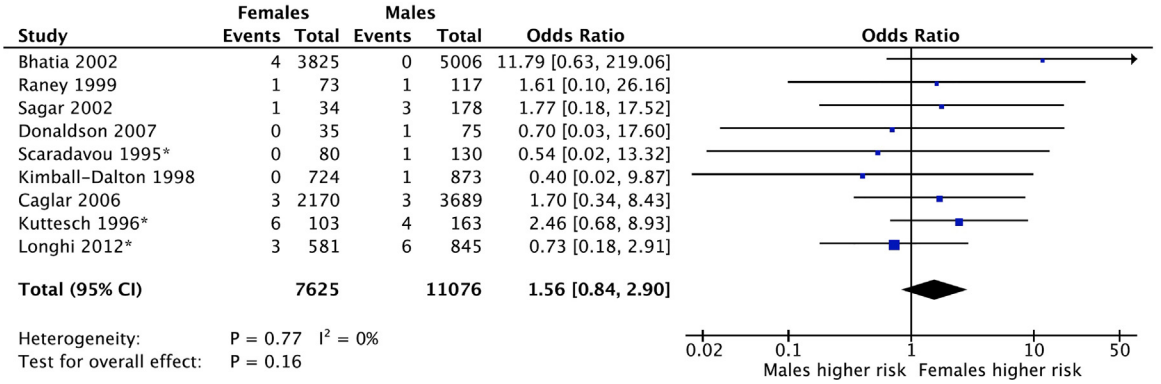

Fig. 7. Risk of secondary sarcomas versus patient sex. The studies are ordered by inverse variance. *Studies that included adults in the cohort; the majority of patients in these cohorts were older than 21 years at primary cancer diagnosis.

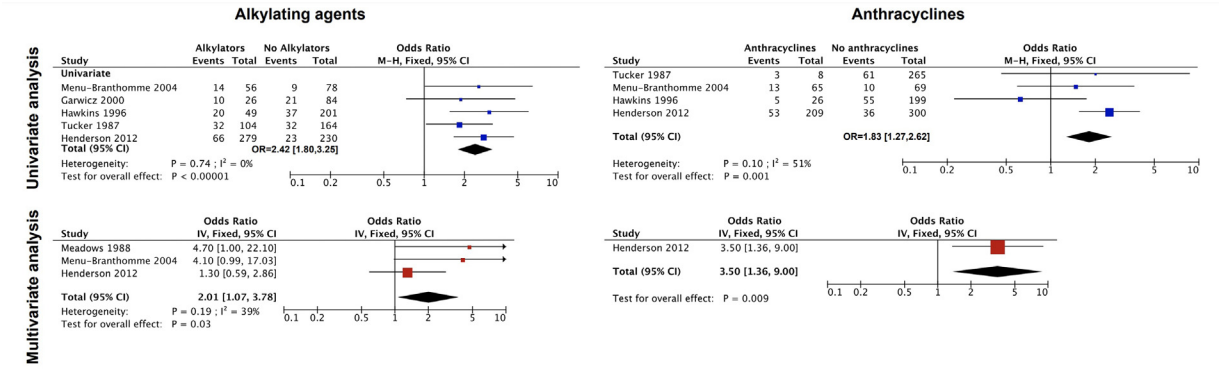

Fig. 8. Association between chemotherapy agents and risk of subsequent sarcoma. Top row: univariate analyses; bottom row: multivariate analyses. The left column shows data for alkylating agents and the right, data for anthracyclines.

Subsequent lung cancer

Dose response

Combining all individual data points of RRs at given dose levels for lung cancer using inverse variance weighting resulted in a significant dose-response relationship with an estimated ERR/Gy of 0.068; linear model ERR = 0.068 × Dose (95% CI, 0.03-0.11; P = .003) (Fig. 9). See Table E4 in Appendix E3 for studies used in the dose-response analysis.

Using a background cumulative incidence of lung cancer at attained age of 50 and 75 years of 0.20% and 4.4%, respectively,[23] we estimated excess absolute risks after 20-Gy exposure of 0.27% at 50 years of age (95% CI, 0.12%-0.4%) and 6% at 75 years of age (95% CI, 2.6%-9.7%), and after 50-Gy exposure, we estimate excess absolute risks of 0.7% at 50 years (95% CI, 0.3%-1.1%) and 15% at 75 years of age (95% CI, 6.6%-24%).

Latency

For the latent time analysis, 3 studies of 143 subsequent lung cancer were available and revealed a weighted average median latency time of 25 years (range, 19-29 years) (Fig. 4) after a median follow-up of 23 years.

Age

There was insufficient data to perform an analysis on the effect of age at exposure versus risk of subsequent lung cancer. However, among the CCSS cohort, Ghosh et al[36] found that older age at diagnosis was associated with an increased risk of subsequent lung cancer on multivariate analysis (with a reference group of age 0-4 years at diagnosis; hazard ratios for age 5-9 years, 10-14 years, and 15-21 years were 7.0, 11.4, and 27.0, respectively). This is a unique finding and opposite of what most others report regarding the age-dependency of RT-associated SNs at other sites.

Sex

No statistically significant sex difference was seen in the risk of subsequent lung cancer (OR, 1.04; 95% CI, 0.60-1.80; 3 studies; 32,956 patients; 52 events; P = .88) (Fig. 10).

Chemotherapy exposure

Ghosh et al evaluated the risk of subsequent lung cancer among the CCSS cohort and observed a significant effect of anthracycline cumulative dose, bleomycin exposure, and

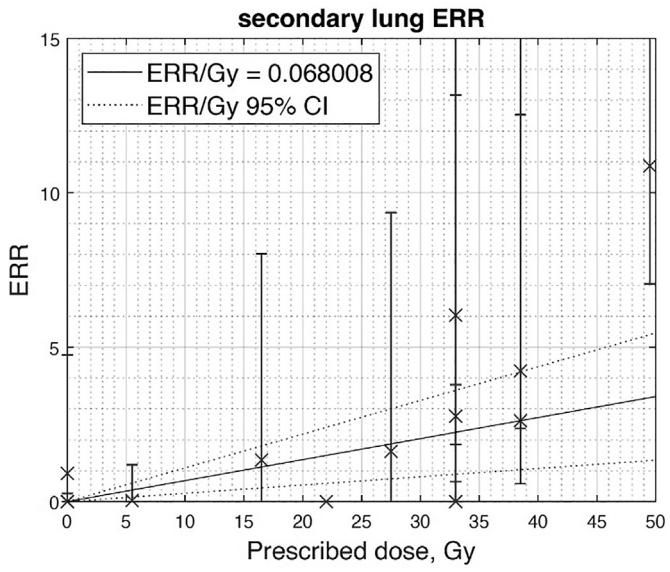

Fig. 9. Individual data points used to estimate the pooled excess relative ratio (ERR)/Gy for subsequent lung cancer are shown, along with the resulting dose-response curve and 95% confidence intervals. Vertical bars show the ERR 95% confidence intervals of the individual data points.

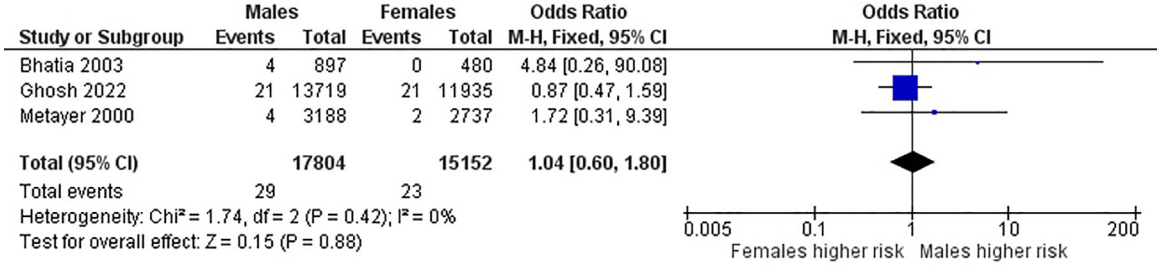

Fig. 10. Risk of secondary lung cancer by patient sex. The studies are ordered by inverse variance.

epipodophyllotoxin cumulative dose on risk of subsequent lung cancer; however, after adjusting for chest RT and age, there was only a trend toward a significant association for bleomycin.[36] Travis et al found an association with treatment with alkylating agents and increased subsequent lung cancer risk (RR, 4.2) among patients treated for Hodgkin lymphoma.[37] Behringer et al also observed the highest incidence of subsequent lung cancer among survivors who received combined modality therapy rather than chemotherapy or RT alone.[38] In a meta-analysis of subsequent lung cancer in Hodgkin lymphoma survivors by Ibrahim et al, the RRs of subsequent lung cancer after RT alone versus combined modality therapy versus chemotherapy alone were 4.88, 5.15, and 2.39, respectively.[39] Taken together, the risk of subsequent lung cancer, at least among Hodgkin survivors, does appear to depend in part on chemotherapy exposure, but there are limited data comparing specific agents.

Smoking

Travis et al found that among a cohort of Hodgkin lymphoma survivors, current smoking increased lung cancer risk by more than 20-fold.[37] Additionally, the risk from smoking appeared to further increase the risks from primary treatment, with an additive relationship observed and the largest risk seen among moderate to heavy smokers who also received RT and alkylating agents (RR, 49.1). Ghosh et al did not find smoking history to be an independent risk factor for subsequent lung cancer among the CCSS cohort after adjusting for other diagnostic and treatment factors.[36] However, patients who developed lung cancer were more likely to have a smoking history (50% vs 30%). In the meta-analysis by Ibrahim et al, although data regarding smoking history were limited, 80% of patients with a lung SN were smokers.[39] Thus, although overall data are limited regarding the effect of smoking in childhood cancer survivors, there does appear to be some contribution toward the risk of

Table 1 Summary of data

	Malignant CNS neoplasm	Meningioma	Sarcoma	Lung
Dose response	Linear, ERR/Gy = 0.15	Linear, ERR/Gy = 0.44	Linear, ERR/Gy = 0.05	Linear, ERR/Gy = 0.07
Excess absolute risk				
After 20 Gy exposure	1.6% at age 50 4.5% at age 75	N/A*	0.2% at age 50 0.9% at age 75	0.3% at age 50 6% at age 75
After 50 Gy exposure	3.9% at age 50 11% at age 75	N/A*	0.3% at age 50 1.2% at age 75	0.7% at age 50 15% at age 75
Latency, weighted average median, y	10	21	11	25
Follow-up time, median, y	12	16	9	23
Age	No effect	Risk decreases with age at time of RT	Risk decreases with age at time of RT	Insufficient data
Sex	No effect	Female > male (odds ratio, 1.5)	No effect	No effect
Chemotherapy	N/A†	N/A†	Anthracyclines, alkylators	N/A†

Abbreviations: CNS = central nervous system; ERR = excess relative ratio; N/A = not applicable; RT = radiation therapy.
* Inconsistent results from assuming independent multiplicative risks for sex, dose, and attained age.
† Not enough data to determine a consistent relationship.

subsequent lung cancer, as to be expected based on data from the adult literature.

Data Summary

Table 1 displays the summary of the variables evaluated and their effect on SN development.

Dose-Volume Recommendations

The available data are consistent with a linear dose response for all SNs (CNS SNs, sarcomas, and lung SNs), without a bell-shaped curve and without a threshold, supporting an approach of ALARA (as low as reasonably achievable) to nontarget tissue as the most appropriate approach for minimizing the risk of SNs. For sarcomas, although there is the suggestion of a nonlinear increase in SN risk after 55 Gy, establishing a threshold effect is difficult based on available data. Nevertheless, these data do give pause to dose escalating beyond 55 to 60 Gy for pediatric tumors without a known benefit in oncologic control.

Additionally, the majority of SNs appear to occur in the high-dose region, at least for the sarcoma SNs (even more if those at the field edge are included), rather than in the low-dose bath. As such, making the target volume dose coverage as conformal as possible, which can reduce the high-dose volume where SNs are most likely to occur, may be the more promising strategy for reducing SNs rather than reducing low-dose spill. Other strategies to reduce high-dose volume include a reduction in clinical target volume and planning target volume margins, which is feasible with daily image guided RT as well as improvements in diagnostic imaging and planning. However, because the low-dose volume is much larger than the high-dose volume, the integrated risk theoretically could be meaningful in both regions. The current analysis supports the use of decreased clinical target volume and planning target volume margins and a volume reduction approach when clinically feasible (ie, lower radiation dose to the initially involved site that has responded to systemic therapy) to limit the high-dose volume (as is done for rhabdomyosarcoma and Ewing sarcoma to account for prechemotherapy and postchemotherapy extent of tumor, for example) as a potential method to decrease risk of SNs.

Early reports based on SN risk calculations indicated that the volume receiving low doses was especially concerning.[11] These calculations were largely based on atomic bomb survivor data, which have been more recently shown to greatly overestimate the risk/Gy compared with therapeutic RT.[30] Because IMRT has now been used for >20 years, recent and ongoing studies will continue to shed light on the risk of SN in the low-dose bath after IMRT compared with 3-dimensional (3D) conformal RT (which was the predominant technique of the studies included in our analysis). Existing data at this time, although somewhat less mature than ideal, show that the risk for SNs is not greater for IMRT than 3D conformal therapy.[40–42] Similar studies comparing protons to photons have also not shown a significant benefit to protons at this time, but these are even less mature.[43]

Special Situations

The data herein analyzed describe the risk of SNs after delivery of RT with conventional fractionation, and for most included studies, older techniques (ie, predating proton

therapy and even IMRT). Although none of the included studies used IMRT, many studies used multibeam 3D conformal techniques that can result in a similar low-dose bath. The presented data and models may not apply to the following situations:

- Hypofractionation
- Proton therapy
- Suspected or confirmed cancer predisposition syndromes known to be associated with increased sensitivity to radiation-related carcinogenesis

Caveats

Despite the risk of SNs after RT, RT remains a critical modality of treatment in pediatric cancers and contributes to the long-term survival of many patients. With this in mind, for many pediatric cancers, it is not possible to omit radiation or reduce the volume or dose to the tumor with the goal of reducing the risk of SNs. However, the data from this study can help to inform optimal treatment decision making and appropriate counseling about potential late effects. Additionally, opportunities to reduce dose (especially high dose) to surrounding normal tissue without a compromise in cure are critical for treatment of pediatric malignancies and reduction in risk of SNs.

Limitations

The central limitation of our analyses is that the radiation doses used in our analysis and modeling are uncertain. We estimate this level of uncertainty to be at least 10%. This estimate is based on a number of factors, including the fact that the dose at the location of the SNs was rarely known and the prescribed doses were the only dosimetric data stated in most publications. Even if we assume the SNs were always in the high-dose volume, to the extent that there is an inhomogeneous dose, there is still uncertainty in the dose at the location of the SNs. In addition, the delivered dose can be different than the stated prescribed dose owing to inaccuracies of manual dose calculations where computerized treatment planning was not available, or if a treatment planning system was used, there are potential uncertainties in those calculations depending on the sophistication of the system. For the lung SNs, there is an additional uncertainty owing to the likely presence of lung blocks, because nearly all the studies were of patients with Hodgkin lymphoma who got mantle irradiation for at least part of their treatment. If we assume the lung SNs were in the open field, then there is a 10% to 15% systematically higher dose to the site of the SN than the prescribed dose owing to increased lung transmission. We conservatively chose to scale up the prescribed doses stated in the publications by 10% for modeling purposes to account for this effect.

Another source of dosimetric uncertainty is that the stated doses were generally given as a range of doses, that is, dose bins. These bins were often 20 Gy wide or more. We systematically used the mean dose for the bin as the dose to assign to events. To the extent that the actual patient doses were not uniformly distributed in the bin (which is to be expected, in particular for observational studies spanning multiple childhood cancer types, calendar periods of diagnosis, and, accordingly, varying treatment scenarios), the true mean dose could be different, potentially skewing the dose-response curve.

Moreover, the quantitative volume of irradiated normal tissue was not known. Older studies often included patients treated with parallel opposed fields, whereas newer studies include more sophisticated conformal techniques that can reduce high-dose normal-tissue exposures to varying degrees. Conversely, the latter tend to have shorter follow-up intervals within which to observe SNs. All other things being equal, the risk of an SN would be expected to increase with increasing volumes of irradiated normal tissue, even though, to date, there is no large body of empirical evidence supporting this hypothesis for SNs. Thus, differences in risk that we are associating with dose could be confounded by changes in target volume and treatment technique. For whole-brain RT, this concern about volume effects is not germane, but for other body sites, the volume of irradiated normal tissue depends on the standard of care at the time of treatment as well as individual tumor and target variations.

In addition, in older studies in which survival rates are lower than in more recent analyses, death secondary to disease may mask the true rate of SNs without a competing risk analysis. Also, it is likely that virtually all the reported rates of SNs are low because SN events continue to occur for many decades after therapy, yet follow-up duration rarely extended past about 20 years.

Excess absolute risks were calculated at example attained ages of 50 and 75 years, and a substantial difference was seen between those estimates. It is relatively robust to conclude that modeled lifetime risks will be dominated by excess absolute risks occurring relatively late in life. However, it should be noted that as the attained age increases, the results become increasingly dependent on the modeling assumptions that the treatment-related ERR is multiplied on an increasing background cumulative risk. Lifetime follow-up of existing historic cohorts, as childhood cancer survivors mature into older ages, will allow for future validation of these projected risk estimates. To our knowledge, to date, no empirical data are available for SN risks beyond an attained age of 60 years. For further discussion of these modeling challenges, see the PENTEC state of science introductory article by Bentzen et al and the vision paper by Stokkevåg et al in this issue.

It is possible that the pooling of risk estimates from multiple sources may mask real effects that are seen in individual studies. Throughout this review, we were cognizant of this risk and depicted the associated findings in individual studies where possible.

Last, our analysis was limited to only CNS SNs, sarcomas, and lung SNs, and thus, our findings are not applicable to other types of SNs.

Data Reporting Standards

For combining the results in a meaningful way and further evaluation of SN risk with modern techniques, it is vital that published data sets and ongoing and/or future central registries evaluating risk of SNs after RT conform to consistent reporting standards. These should include the following:

- Patient sex
- Clinical diagnosis
- Genetic predisposition (if any)
- Age at time of RT
- Prescribed RT dose and fractionation
- RT technique (ie, photon-based 2D, 3D, IMRT, volumetric modulated arc therapy; proton therapy—passive scatter, spot scanning, intensity modulated proton therapy)
- Number of patients in the study and number of those with or without SNs
- Dose-volume histogram data for the tissues at risk for an SN so that the effect of irradiated volume can be better defined
- Time from RT to SN development, with sufficient follow-up when determining the risk of SNs given the importance of follow-up on latency
- RT dose at the site of SN development and/or information regarding proximity to target volume (or at least an estimate)
- Use of chemotherapy (agent, timing, and dose)
- Frequency of clinical follow-up for late complications of RT
- Lifestyle behavior (ie, smoking and drinking) during and after completion of therapy
- Frequency of imaging follow-up in the RT field

Future Investigations

The overarching goal of this study and future investigations regarding SN risk is to (1) inform optimal treatment decision making to increase cure rates while reducing late morbidity and mortality and (2) guide surveillance strategies. With modification of treatment regimens to optimize the therapeutic ratio and with improvement of surveillance strategies, the morbidity of late effects including SNs can, in fact, be decreased.[44] With this in mind, additional studies and centralized registries are needed to better elucidate the following:

1. Effect on SN risk of more sophisticated RT techniques that reduce integral dose, such as proton therapy, and whether this effect influences the therapeutic ratio in disease sites with multiple local control treatment options (eg, Ewing sarcoma) and disease sites where chemotherapy may be delivered in lieu of RT (eg, Hodgkin lymphoma)
2. Comprehensive lifetime follow-up of long-term survivors to fully determine the risk of SNs given the importance of follow-up length on latency results
3. Methods to define and mitigate the RT-induced injury that leads to SN development
4. Genomic variants that may predispose to increased risk of subsequent malignancies, specifically after RT exposure (eg, chromosome 6q21 in children with Hodgkin lymphoma)[45]
5. Effect of irradiated volume on the risk of SNs and the role of the low- versus high-dose volumes in the risk of SNs
6. Genomic changes of subsequent malignancies after RT to better understand methods to mitigate or intervene upon these changes and reduce the potential for development of SNs
7. Influence of subsequent lifestyle behavior (eg, smoking and drinking) on risk of SNs after RT
8. Influence of chemotherapy agents and novel immunotherapy agents on SN risk and their potential joint effects with RT
9. Organ-specific risk of SNs and potential implications for RT planning
10. Potential harms and benefits of surveillance with imaging and follow-up, or other methods to screen for SNs after RT exposure among asymptomatic high-risk childhood cancer survivors (eg, CNS imaging after CNS RT exposure)

Conclusion

Subsequent neoplasms, particularly those that are malignant, have been termed "the agony of victory" owing to their lethality and the significant morbidities attendant to eradicating them. The association of RT dose with their induction, and the latency to their occurrence, have been subjects of study and debate for decades. This PENTEC report serves to fill several gaps and suggests future investigations to explore those left unfilled.

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