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Published in:
Neuro-Oncology

DOI:
10.1093/neuonc/noy124

Publication date:
2019

Risk of benign meningioma after childhood cancer in the DCOG-LATER cohort: contributions of radiation dose, exposed cranial volume, and age

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Running title

Meningioma risk after childhood cancer

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Funding

This work was supported by the Dutch Cancer Society (grant numbers DCOG2011-5027 and UVA2012-5517). Judith Kok is appointed on a Flexible Onderzoeker in Opleiding (OiO) grant awarded by the Academic Medical Center (AMC) Executive Board to C.M. Ronckers/L.C. Kremer in 2012.

Conflict of interest

The authors declare no potential conflicts of interest.

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Abstract

Background

Pediatric cranial radiotherapy (CrRT) markedly increases risk of meningiomas. We studied meningioma risk factors with emphasis on independent and joint effects of CrRT dose, exposed cranial volume, exposure age, and chemotherapy.

Methods

The DCOG-LATER cohort includes five-year childhood cancer survivors (CCSs) diagnosed 1963-2001. Histologically confirmed benign meningiomas were identified from the population-based Dutch Pathology Registry (PALGA; 1990-2015). We calculated cumulative meningioma incidence and used multivariable Cox regression and linear excess relative risk (ERR) modelling.

Results

Among 5,843 CCSs (median follow-up: 23.3 years, range: 5.0-52.2 years), 97 developed a benign meningioma, including 80 after full- and 14 after partial-volume CrRT. Compared to CrRT doses of 1-19 Gy, no CrRT was associated with a low meningioma risk (HR=0.04,95%CI:0.01-0.15), while increased risks were observed for CrRT doses 20-39 Gy (HR=1.66,95%CI:0.83-3.33) and 40+ Gy (HR=2.81,95%CI: 1.30-6.08). CCSs diagnosed before age 5 vs 10-17 years showed significantly increased risks (HR=2.38,95% CI:1.39-4.07). In this dose-adjusted model, volume was not significantly associated with increased risk (HR full vs. partial=1.66,95%CI:0.86-3.22). Overall, the ERR/Gy was 0.30 (95%CI:0.03-unknown). Dose effects did not vary significantly according to exposure age nor CrRT volume. Cumulative incidence after any CrRT was 12.4% (95%CI:9.8%-15.2%) 40 years after primary cancer diagnosis. Among chemotherapy agents (including methotrexate and cisplatin), only carboplatin (HR=3.55,95%CI:1.62-7.78) appeared associated with meningioma risk. However, we saw no carboplatin dose-response and all nine exposed cases had high-dose CrRT.

Conclusion

After cranial radiotherapy one in eight survivors developed late meningioma by age 40 years, associated with radiation dose- and exposure age, relevant for future treatment protocols and awareness among survivors and physicians.

Keywords

Meningioma; cranial radiotherapy; childhood cancer survivors; radiation dose; radiation volume

Key Points

1 in 8 childhood cancer survivors treated with cranial radiotherapy develops a late meningioma

Meningioma risk is dose dependent with no modification of the dose-response by age or exposed volume

Our study contributes new evidence that can be useful for meningioma surveillance recommendations

Importance of the study

There is considerable debate on the justification for or against active screening for meningioma among asymptomatic childhood cancer survivors. Cranial radiotherapy markedly increases the risk of meningioma, however, the roles of exposed cranial volume and age at radiotherapy are unclear. We studied a large, well-characterized cohort of childhood cancer survivors with near-complete and unbiased assessment of late meningioma via national pathology registration. We found that one in eight survivors developed a late meningioma by age 40 years after cranial radiotherapy. We showed evidence for increased risk by radiation dose and among patients treated at the youngest ages, however, no significant modification of the radiation dose-response by age nor by radiation-exposed cranial volume. Our study contributes new evidence to the key element of adequate risk stratification for surveillance recommendations by evaluating the modifying effects of exposed cranial volume and exposure-age on the radiation dose-response association.

Introduction

Among childhood cancer survivors (CCSs) who had cranial radiotherapy (CrRT), a markedly elevated incidence of subsequent central nervous system (CNS) neoplasms has been established.[1] Meningiomas represent the most common type and, although mostly benign, meningiomas can cause serious neurologic morbidity.[2] Meningiomas typically occur beyond 10 years after treatment; median/mean interval from primary cancer diagnosis to meningioma diagnosis of more than 20 years have been reported in large cohort studies among CCSs.[2,3] Furthermore, the excess risk does not seem to plateau over time.[2,4] Meningioma risk appears to increase with increasing radiation dose,[2-5] while the role of exposed cranial volume has not been studied. Some studies reported that a lower age at childhood cancer diagnosis was associated with an increased risk of meningioma[4,6,7] which may reflect a higher sensitivity to radiation, as observed for other tissues (e.g. the thyroid gland).[8] However, studies that evaluated this hypothesis directly, by evaluating meningioma risk among CCSs[3,5] and among children treated for tinea capitis,[9] found no clear variation in the strength of the radiation dose-response by exposure age.

Of all chemotherapy drugs evaluated in two large cohorts of CCSs, platinum agents and intrathecal methotrexate were the only ones for which some evidence of excess meningioma risk was reported.[3,6,7] However, these initial findings have not been replicated.

Finding the right balance between benefits and drawbacks of active surveillance for CNS tumors, in particular meningioma, among asymptomatic individuals who had CrRT, is challenging.[2,10] Adequate risk stratification is one of several key elements to enable balanced decision making on surveillance recommendations, as currently ongoing by the International Guideline Harmonization Group (IGHG).[11]

We examined the independent and joint effects of CrRT dose, exposed cranial volume, and age at childhood cancer treatment to determine excess risk of meningiomas in the Dutch Cancer Oncology Group – Long-Term Effects after Childhood Cancer (DCOG-LATER) cohort of five-year CCSs.

Methods

The full DCOG-LATER cohort includes 6,165 individuals who were treated for childhood cancer between 1/1/1963 and 12/31/2001 in one of the seven Dutch pediatric oncology and stem cell transplant centers before age 18 years and who survived at least five years after diagnosis. The study protocol was exempted from review by institutional review boards of all participating centers. More details were reported elsewhere.[12]

Cancer diagnosis, treatment information

Information on prior cancer diagnosis, treatments for primary tumor and all recurrences, and cancer predisposition syndromes was collected by dedicated data managers.[12] The 1440 survivors who received radiotherapy directed to the head – including those who received total body irradiation (TBI) – were assigned to one of three subgroups: full-cranial volume (full-CrRT; defined as 100% of the cranium in field), partial-cranial volume (partial-CrRT; defined as any CrRT with less than 100% of the cranium in field), and radiotherapy to the head without cranial involvement (no brain tissue in the field; not considered CrRT). For leukemia, CNS tumors, and retinoblastoma survivors (77.4% of 1440), two experienced radiation technologists (JLK and AvE) reviewed treatment protocols; for other childhood cancer types (19.1%) simulation films or anatomical diagrams in radiotherapy charts were used when available. When the radiotherapy record was missing or uninformative, volume was assigned by childhood cancer type and protocol (3.5%). The total dose for primary tumor and recurrences, including boost dose, was determined. We calculated the total maximum prescribed CrRT dose (in case of multiple CrRT treatments for primary tumor or recurrences) as follows: Dose was summed when the same location was irradiated (maximum dose to smallest CrRT field was assessed). In case of two or more non-overlapping CrRT fields, the dose to the field with the highest dose was assigned.

Definition and ascertainment of subsequent meningiomas

Histologically confirmed subsequent benign meningiomas diagnosed between 1/1/1990-5/1/2015 were identified by linkage based on family name, gender, and date of birth with the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA), which reached nationwide coverage in 1990.[13] All pathology reports are summarized into short digital excerpts which contain one or more codes to classify the result of the pathologist review. These were manually reviewed by one author (JLK) to identify eligible cases (morphology codes M9530-9539 and brain topography codes (Supplementary Table 1)). In case of doubt, excerpts were discussed with two experts, including a late effects outpatient clinic doctor (CMR, HvdP). Cohort members were traced for vital status and emigration status as reported previously.[12]

Sibling comparison group

Because no reference rates on histologically confirmed benign meningiomas are available in the general population for this predominantly young population, we included a sibling comparison group to parallel the meningioma incidence in CCSs to the incidence in the general population. CCSs who participated in a 2013-2014 questionnaire survey (N=3,172) were asked to invite their siblings. These siblings (N=1663) were approached and after consent 883 (53%) siblings were linked with PALGA as described above.

Statistical analyses

Survivors who declined -usage of health care data (N=152; 2.5%) and those who died, emigrated, or were lost-to-follow-up prior to 1990 (N=170; 2.8%) were excluded. Follow-up started five years after childhood cancer diagnosis or 1/1/1990, whichever came last, and ended on the date of diagnosis of the first histologically confirmed meningioma, death, last known vital status (emigration/lost-to-follow-up), or end-of-study (5/1/2015), whichever came first.

Cumulative incidence of benign meningiomas was estimated, considering death as a competing risk.[14] Multivariable Cox regression models were used to estimate meningioma risks associated with

prescribed CrRT dose (no CrRT, 1-19 Gy, 20-39 Gy, 40+ Gy). To construct a multivariable model, we first tested binary indicators for hematopoietic cell transplantation (HCT) and single chemotherapeutic agents with at least 5 exposed meningioma cases (n=15) in univariable models. Those with a univariable *P*-value <0.1 were separately tested in models with CrRT dose, exposed cranial volume, and basic demographic factors. The final model included, in addition to CrRT dose, exposed cranial volume, and basic demographic factors, those binary indicators for HCT and single chemotherapeutic agents that remained significantly associated with meningioma risk ($P<0.05$) or that considerably changed the effect of the CrRT dose risk estimate if removed. In addition, we calculated the overall linear excess relative risk per Gy (ERR/Gy) among exposed individuals (Supplementary Methods). Joint effect of CrRT and other characteristics were assessed in two ways. First, we estimated the joint effects of CrRT dose (≤25, >25 Gy) with exposed cranial volume (full-CrRT, partial-CrRT), and with age at childhood cancer diagnosis as surrogate for CrRT age (<5, ≥5 years). Since the prescribed CrRT doses show scattered peaks at standard-protocol doses (e.g. 18-25 Gy, 50-54 Gy, etc.) we classified CCSs simultaneously according to CrRT dose (≤25 Gy vs. >25 Gy) and age at childhood cancer diagnosis (<5 vs. 5+ yrs), and CrRT dose and exposed cranial volume. Second, we evaluated whether the effects of continuous CrRT dose is modified by age at diagnosis, volume, and sex by estimating separate ERRs/Gy for strata of the hypothesized effect modifiers; heterogeneity of ERRs/Gy was evaluated with likelihood ratio tests. Non-linearity of the dose-response relationship was evaluated by testing whether a loglinear modification term for linear dose was significantly different from zero. We evaluated proportionality of hazards for each variable in the multivariable Cox regression model by adding interaction terms with attained age (the time scale) and found no evidence of non-proportionality. *P*-values < .05 were considered statistically significant and all statistical tests were two-sided. STATA (*StataCorp. 2013. Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP) and Epicure software (Risk Sciences International, Ottawa) were used.

Results

This analysis includes 5,843 five-year CCSs contributing 102,937 person-years at risk during 1/1/1990-5/1/2015. Median time since childhood cancer diagnosis was 23.3 years (range: 5.0-52.2 years) and median attained age at end of follow-up was 30.6 years (range: 5.8-67.5 years). Nearly half of the cohort was treated for either leukemia (33.2%) or CNS tumors (13.0%) (Table 1). In total, 1277 survivors received CrRT, including 956 full-CrRT and 321 partial-CrRT, and another 163 survivors received radiotherapy to the head without cranial involvement (Supplementary Figures 1a,1b,1c). The proportion of cohort members treated with CrRT strongly decreased over time, i.e. 36.2%, 18.7%, and 12.5% for those diagnosed in 1963-1984, 1985-1994, and 1995-2001, respectively, largely attributed to a strong decline in proportion of patients, mainly leukemia survivors, treated with 20-39 Gy CrRT; 20.9% in 1963-1984, 2.4% in 1985-1994, 1.2% in 1995-2001 (data not shown).

Characteristics of survivors with subsequent meningioma

In total, 97 survivors (1.7%) developed at least one histologically confirmed benign meningioma. Among meningioma cases, median time since childhood cancer diagnosis was 24.9 years (range: 8.5-44.5 years, interquartile range (IQR): 20.6-30.6) and median age at first meningioma diagnosis was 31.7 years (range: 15.5-49.9 years, IQR: 27.3-36.6). All but three patients with a subsequent benign meningioma had a history of CrRT, including 80/94 with full-CrRT for either acute lymphoblastic leukemia (ALL; n=48), medulloblastoma (n=19), non-Hodgkin lymphoma (NHL; n=7), acute myeloid leukemia (AML; n=3), or a germ cell tumor (n=3) (Table 1). Another 14/94 CrRT patients with meningioma had received partial-CrRT for other types of CNS tumors (n=13), or soft tissue sarcoma (STS; n=1). Among meningioma patients who received any CrRT, 45.4% received a dose of 40 Gy or more compared to 10.6% of CrRT-treated patients in the total cohort. The dose distribution varied between the full-CrRT and partial-CrRT group; the majority of partial-CrRT (90.0%) received a dose of 40 Gy or more, while full-CrRT individuals were more equally distributed over the dose categories (Supplementary Figure 2). Two survivors who developed a meningioma after partial-CrRT had a

confirmed neurofibromatosis diagnosis: one diagnosed with meningioma 13 years after a nerve sheath tumor and one diagnosed 25 years after a glioma. Three patients developed an intervening subsequent malignant neoplasm (SMN) before the meningioma was detected; only one received CrRT for the SMN and that patient had already received full-CrRT for the childhood cancer. Our record linkages with the pathology registry (this paper) and the national cancer registry[12], revealed five malignant meningioma, including four survivors with a preceding benign meningioma and included in the analyses presented here.

Comparison with sibling cohort

In our sibling cohort (N=883), 1 female developed a meningioma at the age of 45, whereas her sibling Hodgkin lymphoma survivor did not. After adjustment for attained age and sex, the incidence of meningiomas in the survivor cohort was significantly higher than among siblings (HR=17.79; 95%CI: 2.48-127.76, *P*<0.00001).

Independent effects of demographic and treatment-related risk factors

In multivariable models, having had any CrRT was a strongly influential factor for meningioma risk. Next, of the three related characteristics (dose, volume, age), CrRT dose appeared to be the most influential risk factor. Compared to survivors who received 1-19 Gy CrRT dose (10 cases/324 cohort members), survivors treated without CrRT had a strongly and significantly lower meningioma risk (HR=0.04, 95% CI: 0.01-0.15; 3 cases/4,525 cohort members), while CrRT doses 20-39 Gy (HR=1.66, 95% CI: 0.83-3.33; 48 cases/445 cohort members) and 40+ Gy (HR=2.81, 95% CI: 1.30-6.08; 35 cases/493 cohort members) inferred higher risk (Table 2). In other words, the reference group in this analysis (1-19 Gy CrRT) had a strongly increased risk compared to the group without CrRT. In the same dose-adjusted model , full-CrRT was not significantly associated with increased risk compared to partial-CrRT (HR=1.66, 95% CI: 0.86-3.22). In addition to CrRT risk, survivors who had received carboplatin (9 cases /409 cohort members) vs. no carboplatin had a statistically significantly increased risk (HR=3.55, 95% CI: 1.62-7.78), without evidence for a carboplatin dose-response

relationship. Individual chemotherapy agents other than carboplatin (including methotrexate (57 exposed cases) and cisplatin (2 exposed cases)) were not associated with risk of meningioma. Of note, of nine patients with a meningioma after carboplatin-containing regimens, one had a prior ependymoma while all eight others received high-dose full-CrRT (primary 30 Gy, boost of >20 Gy to the fossa posterior) for medulloblastoma. Median CrRT doses were 55 Gy and 25 Gy for meningeoma cases with and without carboplatin, respectively, and this distribution was similar to the difference in CrRT dose by carboplatin status in the entire cohort. Without adjustment for CrRT dose, the effect of carboplatin was stronger (HR=5.79, 95% CI: 2.80-11.98; data not shown). The demographic factors sex (HR=1.36, 95% CI: 0.91-2.04 for females vs. males) and age at childhood cancer diagnosis, (HRs of 2.38, 95% CI: 1.39-4.07 and 1.09, 95% CI: 0.62-1.91 for ages 0-4 and 5-9 years, respectively, vs. ages 10-17) were not statistically significantly associated with meningioma risk. Parallel analyses with time since rather than age at childhood cancer diagnosis in the model showed HRs of 2.18 (95% CI: 1.13-4.23) and 3.98 (95% CI: 1.57-10.11) for 20-29 years and >30 years since diagnosis vs. 5-19 years, respectively, while risk estimates for other covariates (Table 2, model 1) were not materially altered (not shown).

Combined effects of age/dose and volume/dose categories

Compared to young patients (<5 year) with a low CrRT dose (≤25 Gy), meningioma risk was nonsignificantly increased among young patients with a high CrRT dose (>25 Gy) (HR=1.84, 95%CI: 0.95-3.56); those treated at older ages (5+ years), regardless of CrRT dose, had significantly lower meningioma risk (HR=0.47, 95% CI: 0.27-0.81 for age 5+, ≤25 Gy and HR=0.61, 95%CI: 0.33-1.13 for age 5+, >25 Gy) (Table 2, model 2). In contrast, there was no clear effect of exposed cranial volume with HRs for survivors treated with full-CrRT at doses ≤25 Gy (HR=1.03, 95% CI: 0.56-1.89) and full CrRT at doses >25 Gy (HR =1.45, 95% CI: 0.75-2.83) in comparison with any partial-CrRT (Table 2, model 3).

Effect modification of continuous CrRT dose with age, volume, and sex

When CrRT dose was analyzed as a continuous variable, adjusted for sex, age at diagnosis, and CrRT volume (no/partial/full) we observed a statistically significant linear dose-response among CrRT-exposed individuals (ERR/Gy of 0.30, 95% CI: 0.03-unknown; Table 3, model 1). We found no evidence for nonlinearity of the dose-response relationship (p=.62). We did not observe significant modifications of the dose-response by age at diagnosis, exposed cranial volume, or sex (Table 3, models 2-5).

Cumulative incidence of subsequent meningioma

The cumulative incidence of benign meningiomas varied according to CrRT characteristics. For survivors treated with CrRT the cumulative incidence was 12.4% (95% CI: 9.8%-15.2%) 40 years after diagnosis (Figure 1, panel A) and 7.3% (95% CI: 4.5%-10.8%) by age 45 (Figure 1, Panel B). For survivors without CrRT the cumulative incidence was much lower (0.3%, 95% CI: 0.1%-1.2% 40 years after diagnosis (Figure 1, panel A) and 0.3%, 95% CI: 0.1-1.2 by age 45 (Figure 1, panel B)). By CrRT doses, the cumulative incidence 40 years after diagnosis were 5.6% (95% CI: 2.3%-11.0%), 13.1% (95% CI: 9.6%-17.1%) , and 9.4% (95% CI: 6.3%-13.3%) for 1-19 Gy, 20-39 Gy, and 40+ Gy, respectively (Figure 1, panel C). Similar patterns were observed by attained age (Figure 1, panel D).

When evaluated separately by age at childhood cancer diagnosis, the cumulative incidences of meningioma for survivors diagnosed at age 0-4 years, age 5-9 years, and age 10-17 years were 5.2% (95% CI: 3.7%-7.1%), 4.3% (95% CI: 2.6%-6.4%), and 3.7% (95% CI: 2.1%-5.9%) 40 years after diagnosis (Figure 2, panel A) and 5.3% (95% CI: 3.7%-7.3%), 4.3% (95% CI: 2.6%-6.6%), and 2.4% (95% CI: 1.5%-3.5%) by age 45 (Figure 2, panel B), respectively. Fifteen-year cumulative incidences was similar across periods of diagnosis (0.2%, 95% CI: 0.1%-0.7% for 1963-1984, 0.1%, 95% CI: 0.0%-0.4% for 1985-1994, and 0.1%, 95% CI: 0.0%-0.4% for 1995-2001, Figure 2, panel C).

Discussion

Our nationwide study with complete information on histologically confirmed benign meningiomas after childhood cancer shows that, after cranial radiotherapy, one in eight survivors developed a late meningioma 40 years after primary cancer diagnosis. We found evidence for increased risk by radiation dose and among patients treated at the youngest ages, however, no significant modification of the radiation dose-response by age nor by radiation-exposed cranial volume.

CrRT is the most important risk factor for meningioma risk among CCSs; nearly all cases (97%) occurred among survivors who were treated with CrRT. Consistent with our findings of a dose-related excess risk, CrRT has frequently been reported to linearly increase risk of meningioma in a dose-related fashion among young CCSs,[3-5] atomic bomb survivors,[15] and children treated for tinea capitis,[9] as summarized in Supplementary Table 2. While a main effect of age at childhood cancer diagnosis has been reported by others,[4,6,7] data are inconsistent as to whether age modifies the radiation dose-response curve. We hypothesized that younger exposure age, as crude indicator of vulnerability during brain development, is related to higher radiation sensitivity, in other words, that the effect of radiation dose on meningioma risk varies by age at radiotherapy. Our results did not firmly support this hypothesis, consistent with earlier reports by Neglia et al. (66 meningioma cases) and Taylor et al. (137 meningioma cases) for the US/Canadian and UK childhood cancer survivor studies.[3,5] Our analyses are based on prescribed CrRT dose, whereas the latter two studies[3,5] used absorbed CrRT dose in a case-control setting. Although it can be assumed that the prescribed CrRT dose is almost similar to the absorbed dose at the organ at risk, the meninges, for meningioma cases treated with full-CrRT (n=80 cases), the prescribed CrRT dose may represent an overestimation of the true absorbed dose at the meningioma location for partial-CrRT treated patients (n=14 cases). A new aspect of our study is that we analyzed the potential modifying effect of exposed cranial volume on the relation between radiation dose and meningioma risk. Our second hypothesis was that a higher volume of brain tissue exposed, will increase the radiation dose-related risk of meningioma. We did,

however, not find evidence of a stronger dose-response among patients treated with full-CrRT compared to those treated with partial-CrRT; there was a suggestive, but nonsignificant main effect of full-CrRT (HR=1.66 for full vs partial). Of note, these results need to be interpreted with caution owing to a combination of factors: (1) the lack of statistical significance; (2) the probability that CrRT-volume may be a surrogate of other patient characteristics that influence meningioma risk (e.g. other risk factors such as NF1 status) or early detection (e.g. head MRIs or CTs for other side effects of CNS tumors or their treatment) not covered in our study variables. Also, there is a strong correlation between CrRT dose and exposed cranial volume (higher doses with partial volumes) as such that no meningioma cases were observed among the few patients treated with less than 40 Gy partial CrRT, as illustrated in Supplementary Figure 2.

Owing to clinical reality the radiation exposure metrics we applied tend to overestimate the volume of the brain exposed to the summed doses of main field and boost, since the sum of doses is assigned to the entire cranium. This is particularly true for medulloblastoma patients. Therefore, the true risk may be slightly overestimated in this study. Sensitivity analyses based on the full CrRT dose of approximately 30 Gy (i.e. disregarding the additional boost dose of around 24 Gy used in medulloblastoma protocols) provide a lower boundary for the estimated dose-related risk. Of note, CCS cohorts include individuals with several characteristics (e.g. radiotherapy, volume, and age, and demographic characteristics) that are quite correlated. For example, the proportion of survivors who were treated with CrRT declined over time, (from 36% prior to 1985 to 13% during 1995-2001); since 1985 prophylactic CrRT was eliminated from the DCOG-ALL protocols.[16] Moreover, although CrRT remained indicated for ALL patients with CNS involvement up to 2004,[17] the dose was reduced from 24 to 18 Gy in 1988.[18]

We did not find an effect of sex on meningioma risk, nor was there significant variation in the radiation dose-response according to sex, unlike some other studies reporting higher risks among women, after adjustment for CrRT dose.[2,4,6]

Only three previous studies showed some effects of chemotherapy: Two CCSS reports indicated increased meningioma risk after treatment with platinum agents without a clear dose-response.[6,7] At face value, these findings seem consistent with our finding of elevated risks associated with carboplatin (but not for cisplatin). However, the multivariable models from the cited studies[6,7] included only a radiotherapy yes/no indicator, which is likely insufficient to fully adjust for the radiotherapy dose effects. Importantly, carboplatin can be part of medulloblastoma protocols, a patient group considered at highest risk for meningioma because they all received full-CrRT and boosts up to total doses exceeding 50 Gy. We question the causality of the carboplatin-meningioma association, due to lack of dose-response relation, collinearity with high-risk radiotherapy characteristics, no observed meningioma cases among survivors with carboplatin exposure without CrRT, no relation of cisplatin with meningioma risk, and no clear evidence on carboplatin carcinogenicity from in vitro and in vivo studies. Nonetheless, we cannot entirely discard a true, albeit small, effect of carboplatin either.

In the British Childhood Cancer Survivor Study cohort meningioma risk among individuals receiving 1-39, 40-69, and 70 or more mg/m² of intrathecal methotrexate was increased by 15-fold, 11-fold, and 36-fold, respectively, compared to unexposed survivors.[3] The authors added a strong cautionary note to their findings: few survivors were treated with intrathecal methotrexate without CrRT and no effects were observed for non-intrathecal methotrexate. These findings have not been confirmed by other studies, including our results reported here.

Strengths of our study are the large cohort size with detailed individual treatment information and objective and near complete data on histologically confirmed benign meningiomas from linkage to the nationwide registry of histo- and cytopathology (PALGA)[13] for more than 95% of the total cohort. Other studies relied on initial self-report and/or linkage with tumor registries.[2,3] In addition, a comparison with a sibling group was performed, to obtain more insight into the incidence of meningiomas, which enabled us to parallel the meningioma incidence in CCSs to the general

population. PALGA is an internationally unique resource to ascertain benign meningiomas, because benign CNS tumors are not typically recorded completely in cancer registries, although this is changing in more recent years.

Several weaknesses of our approach deserve attention as well. PALGA has complete national coverage from 1990 onwards; tumors occurring during 1968-1989 were not recorded reliably. By including only follow-up time since 1990 and the fact that most meningiomas occur >20 years after childhood cancer, a follow-up interval which nearly all surviving cohort members completed after 1990, we are confident that the underestimation of the true cumulative incidence caused by left truncation is minimal. Secondly, as in most studies on meningioma, true incidence is likely not captured; we report on *histologically confirmed benign meningiomas* while a certain proportion of such tumors can remain asymptomatic/indolent for some time. Other factors may have increased the meningioma detection rate: medical care has changed, including access to and indications for brain imaging as well as indications for surgery of cranial masses suspect for meningioma. Also, between 1996 and 2006, Dutch late effects outpatient clinics were implemented in which CCSs are followed-up according to evidence-based Dutch guidelines. These guidelines do not recommend active screening for CNS tumors among asymptomatic individuals. Nevertheless, all survivors received guideline-based follow-up at fixed intervals, which is more frequent for those with high-intensity treatment (including those who received radiotherapy). It is quite possible that more intensive medical attention in the outpatient clinics slightly increased the detection rates of asymptomatic meningioma, for example among patients with a history of seizures, headaches, or other neurologic problems owing to a brain tumor or CNS metastases, but also brain surgery, hydrocephalus, or high-dose radiotherapy. Longer follow-up of available cohorts with complete treatment information and adequate follow-up methods to detect these benign tumors, as well as pooled analyses of these studies are needed to shed light on the influence of these issues on meningioma incidence rates.

The results of this study can be used to inform surveillance recommendations for long-term CCSs who had CrRT, such as those currently being formulated by the International Guideline Harmonization Group.[19] Although risk estimation in terms of prescribed CrRT dose is necessary in light of surveillance guideline development, further studies are forthcoming to express excess risk in terms of cranial-volume-based absorbed dose distributions. These will be useful to inform future pediatric radiotherapy treatment guidelines. To fully disentangle effects of dose, volume, age, and the potential role of chemotherapy agents, an international pooling effort is warranted to achieve sufficient statistical power.

In conclusion, one in eight CCSs exposed to cranial radiotherapy develop a late meningioma 40 years after childhood cancer diagnosis and this risk is dose- and exposure age-related. We did not find significant modifications of the radiation dose-response by age or by exposed cranial volume. While the proportion of patients in need of (full) CrRT with curative intent has decreased over time, this treatment cannot be abolished without compromising cancer survival for children with intracranial tumors or other indications for CrRT. These findings are important to raise awareness among survivors, their parents, and care-providers about these long-term sequelae, and to support ongoing efforts to reduce the radiation exposure to healthy tissues, where feasible, without compromising treatment efficacy.

Acknowledgement

We thank all data managers in the seven participating centers and Aslihan Mantici and Anja van Eggermond for obtaining the data for this study. Furthermore, we thank the following other members of the DCOG-LATER group for their contributions: Lilian Batenburg, Margreet Veening, Marloes Louwerens, Gea Huizinga, Lideke van der Steeg, Hanneke de Ridder-Sluiter, and Andrica de

Vries. We thank the staff of the PALGA Foundation for providing record linkage data on meningiomas from their registry.

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Figure Legends

Figure 1. Cumulative incidence of meningiomas for survivors with and without cranial radiotherapy by time since childhood cancer diagnosis (panel A) and attained age (panel B) and according to cranial radiotherapy dose by time since childhood cancer diagnosis (panel C) and attained age (panel D), accounting for death as competing risk.

Figure 2. Cumulative incidence of meningiomas for 5-year survivors according to age at diagnosis categories by time since childhood cancer diagnosis (panel A) and attained age (panel B) and according to period of childhood cancer diagnosis by time since childhood cancer diagnosis (panel C) and attained age (panel D), accounting for death as competing risk.

Table 1. Patient characteristics of the DCOG LATER cohort eligible for analyses (N=5,843) for survivors without meningioma (N=5,746) and survivors with meningioma (N=97)

	Survivors without meningioma		Survivors with meningioma	
	N	%	N	%
Childhood cancer type				
Leukemia	1,910	33.2	52	53.6
Non Hodgkin lymphoma	548	9.5	7	7.2
Hodgkin lymphoma	395	6.9	0	0
Central nervous system non medulloblastoma	615	10.7	13	13.4
Medulloblastoma	134	2.3	19	19.6
Neuroblastoma	313	5.5	0	0
Retinoblastoma	31	0.5	0	0
Renal tumors	578	10.1	0	0
Hepatic tumors	52	0.9	0	0
Bone tumors	343	6.0	0	0
Soft tissue tumors	423	7.4	3	3.1
Germ cell tumors	221	3.9	3	3.1
Other and unspecified	183	3.2	0	0
Sex				
Male	3,222	56.1	47	48.5
Female	2,524	43.9	50	51.5
Age at childhood cancer diagnosis				
0-4 y	2,595	45.2	46	47.4
5-9 y	1,557	27.1	26	26.8
10-17 y	1,594	27.7	25	25.8
Calendar year of childhood cancer diagnosis				
1963-1984	1,721	30.0	70	72.2
1985-1994	2,091	36.4	22	22.7
1995-2001	1,934	33.7	5	5.1
Attained age at end of follow-up				
<20	763	13.3	4	4.1
20-29	1,975	34.4	36	37.1
30-39	1,826	31.8	45	46.4
40+	1,182	20.6	12	12.4
Time since childhood cancer diagnosis				
<20	2,106	36.7	24	24.7
20-29	2,062	35.9	47	48.5
30-39	1,257	21.9	25	25.8
40+	321	5.6	1	1.0
Childhood cancer treatment[a]				
Surgery only	573	10.0	0	0
Chemotherapy, no radiotherapy	2,897	50.4	1	1.0
Radiotherapy, no chemotherapy	428	7.5	17	17.5
Radiotherapy and chemotherapy	1,775	30.9	79	81.4
No treatment / treatment unknown	73	1.3	0	0
CrRT (including TBI)[a]				
No[b]	4,522	78.7	3	3.1
Partial cranial volume	307	5.3	14	14.4
Full cranial volume[c]	876	15.3	80	82.5

(Continued on the following page)

Table 1. Patient characteristics of the DCOG LATER cohort eligible for analyses (N=5,843) and meningioma patients (N=97) (Cont'd)

	Total cohort		Meningioma patients	
	N	%	N	%
CrRT dose (including TBI)[a]				
No Head/Cranium or TBI dose	4,522	78.7	3	3.1
1-19 Gy	314	5.5	10	10.3
20-39 Gy	397	6.9	48	49.5
40+ Gy	458	8.0	35	36.1
Carboplatin[a]				
No	5,308	92.4	88	90.1
Yes	400	7.0	9	9.3
Hematopoietic cell transplantation[a]				
No	5,314	92.5	90	92.8
Yes	365	6.4	6	6.2
WHO grade of first benign meningioma[d]				
1	NA	NA	45	80.4
2	NA	NA	11	19.6
Unknown	NA	NA	41	
Calender period of first benign meningioma diagnosis				
1990-1999	NA	NA	12	12.4
2000-2009	NA	NA	47	48.4
2010-2015[e]	NA	NA	38	39.2

Abbreviations: NA=not applicable; CrRT=cranial radiotherapy; TBI=total body irradiation
Numbers do not always add up to 100% because of missing values or rounding.
[a]Treatment data includes primary treatment and all recurrences; chemotherapy (yes/no), radiotherapy (yes/no), and hematopoietic cell transplantation (yes/no) was missing for 32, 32, and 68 survivors, respectively.
[b]Includes n=163 (2.8%) patients irradiated to facial and other parts of head without cranial involvement, no meningioma cases. Of the three patients without a history of CrRT were diagnosed with a meningeoma 14,37, and 26 years post-STS (n=2) or post-ALL (n=1), respectively.
[c]Includes n=210 patients treated with TBI, among which 4 developed a meningioma.
[d]Percentages were based on cases with a known WHO grade as reported by the pathologist, according to the WHO classification in use at the time of diagnosis.
[e]Includes January till April 2015.

Table 2. Multivariable Cox regression models for risk of meningioma by demographic and treatment-related risk factors (model 1) and additionally by age at diagnosis/cranial radiotherapy dose (model 2), and cranial radiotherapy volume/dose (model 3) combinations[a]

			Model 1		Model 2		Model 3	
	N total	N cases	HR	95% CI	HR	95% CI	HR	95% CI
Sex								
Male	3,269	47	REF		REF		REF	
Female	2,574	50	1.36	0.91-2.04	1.36	0.91-2.04	1.37	0.92-2.06
Age at diagnosis								
0-4 y	2,641	46	2.38	1.39-4.07			2.35	1.40-3.96
5-9 y	1,583	26	1.09	0.62-1.91			1.10	0.63-1.94
10-17 y	1,619	25	REF				REF	
CrRT exposure								
No CrRT	4,525	3	0.04	0.01-0.15				
1-19 Gy	324	10	REF					
20-39 Gy	445	48	1.66	0.83-3.33				
40+ Gy	493	35	2.81	1.30-6.08				
Exposed cranial volume								
Partial CrRT			REF					
Full CrRT			1.66	0.86-3.22	1.40	0.73-2.66		
Carboplatin								
No	5,396	88	REF		REF		REF	
Yes	409	9	3.55	1.62-7.78	4.26	1.95-9.31	4.31	1.97-9.45
CrRT exposure (age/dose)								
No CrRT	4,525	3			0.01	0.00-0.05		
0-4 y / ≤25 Gy	313	31			REF			
0-4 y / >25 Gy	153	15			1.84	0.95-3.56		
5+ y / ≤25 Gy	382	23			0.47	0.27-0.81		
5+ y / >25 Gy	414	24			0.61	0.33-1.13		
CrRT exposure (volume/dose)								
No CrRT	4,525	3					0.01	0.00-0.05
Partial CrRT[b] / ≤25 Gy	13	0					REF	
Partial CrRT[b] / >25 Gy	300	14						
Full CrRT / ≤25 Gy	682	54					1.03	0.56-1.89
Full CrRT / >25 Gy	267	25					1.45	0.75-2.83

Abbreviations: CI=confidence interval; CrRT=cranial radiotherapy; Gy=Gray; HR=Hazard Ratio; N=number; REF=reference category

[a]Models include only 96 meningioma cases due to missing values.

[b]Dose groups were collapsed.

Table 3. Effect modification of cranial radiotherapy dose-response for risk of meningioma[a]

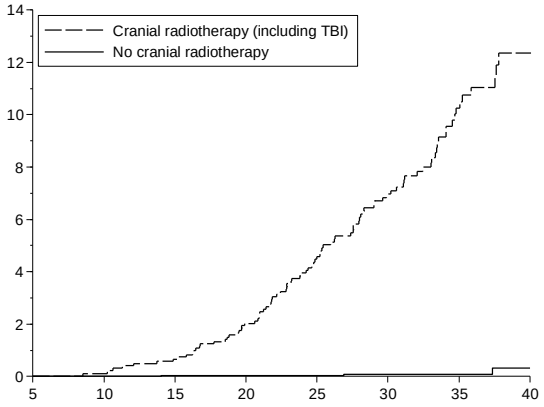
	N total	N cases	ERR/Gy	95% CI	P interaction
Model 1: All patients	1,262	93	0.30	0.03-UNK[b]	
Model 2: Age at diagnosis					0.86
0-4 y	2,641	46	0.31	0.10-1.36	
5-9 y	1,583	26	0.31	0.10-1.35	
10-17 y	1,619	25	0.27	0.08-1.19	
Model 3: Volume					0.98
Partial	313	14	0.30	0.09-1.32	
Full	979	79	0.30	0.09-1.29	
Model 4: Age at diagnosis and volume					0.55
0-4 y / partial	86	6	0.52	0.13-2.49	
5-17 y / partial	227	8	0.22	0.05-1.06	
0-4 y / full	380	40	0.29	0.09-1.28	
5-17 y / full	569	39	0.30	0.09-1.32	
Model 5: Sex					0.96
Male	3,269	47	0.30	0.10-1.29	
Female	2,574	50	0.30	0.09-1.28	

Abbreviations: ERR=excess relative risk; Gy=Gray; N=number; UNK=unknown

[a]All models adjusted for sex, age at diagnosis (<5, 5-9, 10+ years), cranial radiotherapy (no, partial, full). Coefficients for those variables were fixed at the values estimated in model 1 to improve stability of the model fitting. For likelihood ratio tests (P interaction), fixed parameters were counted as free, resulting in conservative p-values.

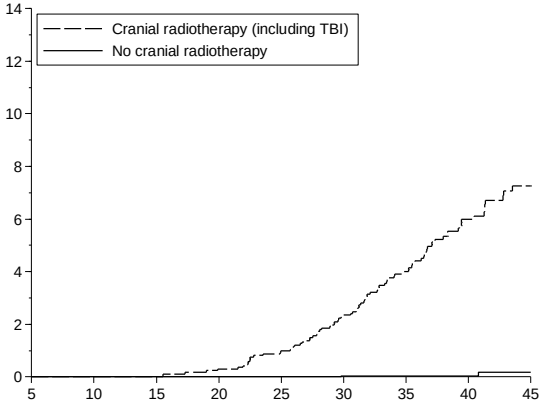
[b]Due to a very flat likelihood to the right of the maximum likelihood estimate, even much larger values are consistent with the data.

Panel A



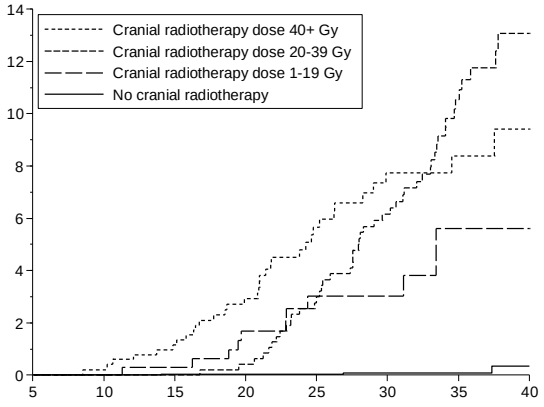
No at risk								
Cranial radiotherapy (including TBI)	632	856	998	903	702	542	278	79
No cranial radiotherapy	3388	3826	3677	2698	1833	1055	557	241

Panel B



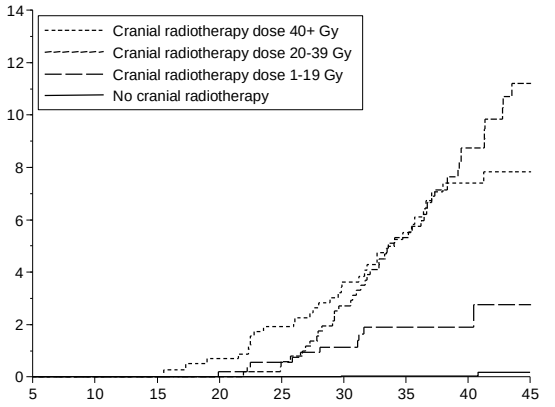
0	199	583	929	964	816	615	378	146
9	1746	2813	3256	2903	2142	1347	783	414

Panel C



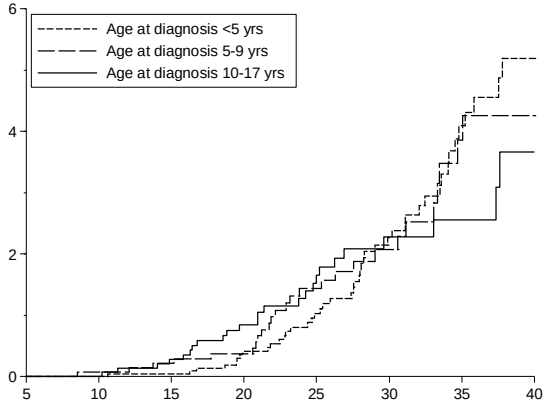
No at risk								
No cranial radiotherapy	3294	3712	3547	2579	1737	979	510	223
Cranial radiotherapy dose 1-19 Gy	215	270	275	219	157	110	28	6
Cranial radiotherapy dose 20-39 Gy	93	239	402	428	395	341	208	54
Cranial radiotherapy dose 40+ Gy	403	444	438	365	242	165	89	37

Panel D

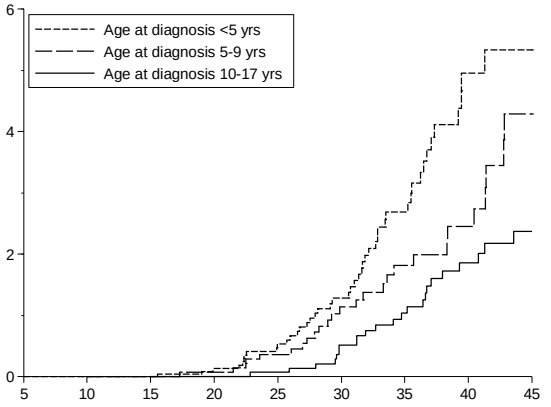


0	1704	2741	3154	2785	2039	1265	721	370
9	81	182	262	255	200	126	57	15
0	44	184	367	419	402	350	238	90
0	113	280	391	396	308	217	144	85

Panel A



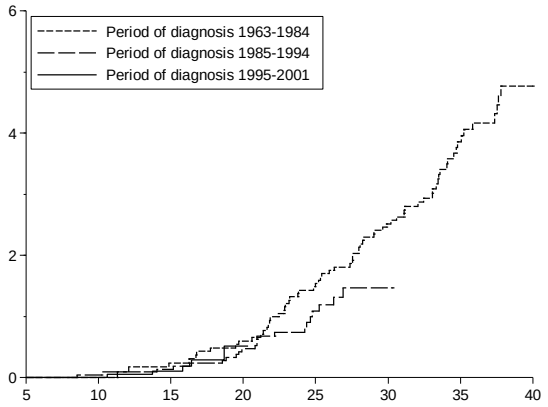
Panel B



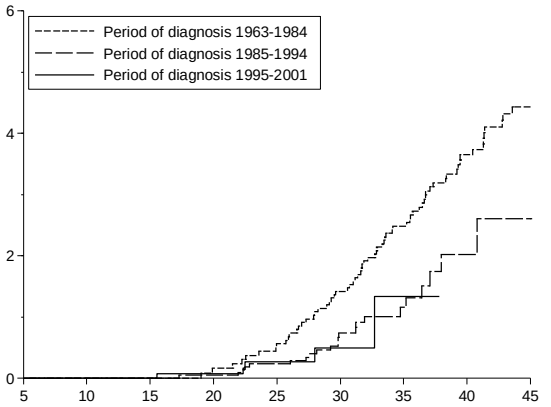
No at risk								
Age at diagnosis <5 years	1787	2114	2113	1651	1188	762	397	178
Age at diagnosis 5-9 years	1120	1288	1304	996	691	422	214	62
Age at diagnosis 10-17 years	1145	1309	1285	967	667	420	227	82

	10	1947	2205	1895	1433	987	581	272	98
	0	7	1203	1354	1115	814	539	310	111
	0	0	2	957	1340	1174	852	586	355

Panel C



Panel D



No at risk								
Period of diagnosis 1963-1984	0	837	1371	1594	1607	1562	838	322
Period of diagnosis 1985-1994	2113	2020	1976	1924	939	42	0	0
Period of diagnosis 1995-2001	1939	1854	1355	96	0	0	0	0

	0	199	647	1140	1460	1557	1401	996	550
	6	894	1457	1870	1773	1157	552	172	14
	4	861	1306	1196	655	261	19	0	0