Included studies CNS neoplasm surveillance

Year	Bibliography
2019	Co et al. Meningioma Screening With MRI in Childhood Leukemia Survivors Treated With Cranial Radiation. J Rad Oncol Biol Phys 2019;104:640-643.
2019	Remes et al. Radiation-Induced Meningiomas After Childhood Brain Tumor: A Magnetic Resonance Imaging Screening Study. JOAYA Oncol 2019; 1-9.
2019	Salloum et al. Late morbidity and mortality among medulloblastoma survivors diagnosed across three decades: A report from the Childhood Cancer Survivor Study. J Clin Oncol 2019;731-740.
2019	Swerdlow et al. Risk of Meningioma in European Patients Treated With Growth Hormone in Childhood: Results From the SAGhE Cohort. J Clin Edocrinol Metab 2019;10:658-664.
2019	Ueda et al. Therapy related secondary malignancies after treatment for secondary malignancy: Cases from a single institution. Journal of Nippon Medical School 2019;86:207-214.
2018	Kok et al. Risk of benign meningioma after childhood cancer in the DCOG-LATER cohort: contributions of radiation, exposed cranial volume, and age. Neuro-oncology 2018; 20:1-12.
2018	Lee et al. Irradiation-induced secondary tumors following pediatric central nervous system tumors: experiences of a single institute in Taiwan (1975-2013). Int J Radiat Oncol Biol Phys 2018;101:1243-1252.
2017	Bowers et al. Morbidity and mortality associated with meningioma after cranial radiotherapy: A report from the Childhood Cancer Survivor Study. J Clin Oncol 2017;35:1570-1576.
2017	Felice et al. Second Neoplasms in Children Following a Treatment for Acute Leukemia and/or Lymphoma: 29 Years of Experience in a Single Institution in Argentina. Journal of pediatric hematology oncology 2017; 39: 406-4012.
2017	Turcotte et al. Temporal Trends in Treatment and Subsequent Neoplasm Risk Among 5-Year Survivors of Childhood Cancer, 1970-2015. JAMA. 2017;317(8):814-824.
2015	Bilginer et al. De novo formation of brain tumors in pediatric population following therapeutic cranial irradiation. Childs Nerv Syst 2015;31:893-899.
2015	Brignardello et al. GH replacement therapy and second neoplasms in adult survivors of childhood cancer: a retrospective study from a single institution. J Endocrinol Invest 2015;38:171-176.
2015	Ning et al. Evidence of high mortality in long term survivors of childhood medulloblastoma. J Neurooncol 2015;122:321-327.
2015	Tsui et al. Subsequent neoplasms in survivors of childhood central nervous system tumors: risk after modern multimodal therapy. Neuro Oncol 2015;17:448-456.
2015	Felicetti et al. Meningiomas after cranial radiotherapy for childhood cancer: a single institution experience. J Cancer Res Clin Oncol 2015; 141:1277-1282.
2014	Patterson et al. Growth hormone exposure as a risk factor for the development of subsequent neoplasms of the central nervous system: A report from the Childhood Cancer Survivors Study. J Clin Endocrinol Metab 2014;99:2030-2037.
2014	Sabin et al. Incidental detection of late subsequent intracranial neoplasms with magnetic resonance imaging among adult survivors of childhood cancer. J Cancer Surviv 2014;8:329-335.
2013	Bowers et al. Subsequent neoplasms of the CNS among survivors of childhood cancer: a systematic review. Lancet Oncol 2013;14:e321-28.
2013	Hudson et al. Clinical ascertainment of health outcomes among adults treated for childhood cancer. JAMA 2013;22:2371-2381.
2013	Schmiegelow et al. Second malignant neoplasms after treatment of childhood

	acute lymphoblastic leukemia. J Clin Oncol 2013;31:2469-2476.
2013	Strodbeck et al. Risk of subsequent cancer following primary CNS tumor. J Neurooncol 2013;112:285-295.
2012	Galloway et al. Analysis of dose at the site of second tumor formation after radiotherapy to the central nervous system. Int J Radiation Oncology Biol Phys 2012;82:90-94.
2012	Galloway et al. Second tumors in pediatric patients treated with radiotherapy to the central nervous system. Am J Clin Oncol 2012;35:279-283.
2011	Reulen et al. Long-term risks of subsequent primary neoplasms among survivors of childhood cancer. JAMA 2011;22:2311-2319.
2011	Vinchon et al. Radiation-induced tumors in children irradiated for brain tumor: a longitudinal study. Childs Nerv Syst 2011;27:445-453.
2010	Friedman et al. Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. J Natl Cancer Inst 2010;102:1083-95.
2010	Taylor et al. Population-based risks of CNS tumors in survivors of childhood cancer: The British Childhood Cancer Survivor Study. J Clin Oncol 2010;28:5287-93.
2009	Armstrong et al. Long-term outcomes among adult survivors of childhood central nervous system malignancies in the Childhood Cancer Survivor Study. J Natl Cancer Inst 2009;101:946-58.
2009	Banerjee et al. Radiation-induced meningiomas: A shadow in the success story of childhood leukemia. Neuro-Oncology 2009;11:534-549.
2009	Taylor et al. Survival after second primary neoplasms of the brain or spinal cord in survivors of childhood cancer: results from the British Childhood Cancer Survivor Study. J Clin Oncol 2009;27:5781-5787.
2007	Cardous-Ubbink et al. Risk of second malignancies in long-term survivors of childhood cancer. Eur J Cancer 2007;43:351-362.
2007	Goshen et al. High incidence of meningioma in cranial irradiated survivors of childhood acute lymphoblastic leukemia. Pediatr Blood Cancer 2007;49:294-297.
2007	Hijiya et al. Cumulative incidence of secondary neoplasms as a first event after acute lymphoblastic leukemia. JAMA 2007;297:1207-15.
2007	Inskip et al. New malignancies following childhood cancer in the United States, 1973-2002. Int J Cancer 2007;121:2233-40.
2006	Neglia et al. New primary neoplasms of the central nervous system in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Natl Cancer Inst 2006;98:1528-37.
2002	Bhatia et al. Low incidence of second neoplasms among children diagnosed with acute lymphoblastic leukemia after 1983. Blood 2002;99:4257-4264.
2000	Löning et al. Secondary neoplasms subsequent to Berlin-Frankfurt-Munster therapy of acute lymphoblastic leukemia in childhood: significantly lower risk without cranial radiotherapy. Blood 2000;95:2770-5.
1998	Little et al. Risks of brain tumour following treatment for cancer in childhood: modification by genetic factors, radiotherapy and chemotherapy. Int J Cancer 1998;78:269-275.
1998	Walter et al. Secondary brain tumors in children treated for acute lymphoblastic leukemia in St Jude Children's Research Hospital. J Clin Oncol 1998;16:3761-3767.
1994	Rosso et al. Second malignant tumors after elective end of therapy for a first cancer in childhood: a multicenter study in Italy. Int J Cancer 1994;59:451-6.

Evidence tables CNS neoplasm surveillance

What is the prognosis of subsequent CNS neoplasms?				
Banerjee et al. Radiation-induced meningiomas: A shadow in the success story of childhood leukemia. Neuro-Oncology 2009;11:534-549.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Retrospective cohort study Treatment era: Not reported Follow-up: >10 yr	60 ALL survivors treated with CRT who are >10 yr post-treatment and aged >18 yr at follow-up Primary cancer diagnosis: ALL (100%) Age at primary cancer diagnosis: Meningioma cases: Range 1-8 yr Age at follow-up: Not reported Genetic predisposition: Not reported	No treatment data available of cohort of survivors CRT: 60 (100%) CRT dose meningioma cases: Range 21-46 Gy	Survivors with subsequent meningioma: 11 (22.4%) Prognosis: - 11 (100%) alive at end of follow-up - 8 (72.7%) minimal postoperative morbidity - Meningiomas were significantly larger in diameter if diagnosed at time of symptomatology: mean 51 mm vs. 23 mm, *p*=0.001	As a part of different research projects, the patients have been followed with brain MRI since 1991, although the follow-up has not been systematic. Four patients presented with neurological symptoms: one with generalized seizures, and the others with headache and visual disturbances. Three patients had multiple meningiomas. **Risk of bias:** - Selection bias: unclear how many patients were included in the original cohort of survivors. - Attrition bias: low risk, for 49 (81.7%) patients follow-up was complete. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome.

Abbreviations: ALL, acute lymphoblastic leukemia, CRT, cranial radiotherapy.

What is the prognosis of subsequent CNS neoplasms?				
Bhatia et al. Low incidence of second neoplasms among children diagnosed with acute lymphoblastic leukemia after 1983. Blood 2002;99:4257-4264.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective cohort study Treatment era: 1983-1995 Follow-up: Median 5.5 (range 0-16.1) years; 54,883 person-years of follow-up	8,831 ALL patients aged <21 years at primary cancer diagnosis Primary cancer diagnosis: ALL (100%) Age at primary cancer diagnosis: Median 4.7 (range 0-20.8) years Age at follow-up: Not reported Genetic predisposition: Not reported	Radiotherapy: 38% Radiotherapy dose: Ranged from 0 to 18 Gy to cranium (for CNS prophylaxis) and 24 Gy to cranium and 6-12 Gy to spine (for treatment of CNS disease) Cyclophosphamide: 79% Anthracyclines: 79%	ALL survivors with subsequent CNS neoplasms: - Glioblastoma multiforme: n=9 - Anaplastic astrocytoma: n=4 - PNET: n=3 - Meningioma: n=2 - Medulloblastoma: n=1 Cumulative incidence subsequent CNS neoplasms: - 10-year: 0.47% (95% CI 0.2-0.6) - 15-year: 0.90% (95% CI 0.4-1.4) Prognosis: - 11 (57.9%) out of 19 survivors with a subsequent CNS neoplasms have died	Unclear how CNS neoplasms were detected. Very limited follow-up time (5.5 years) does not inform about meningioma risk. Early risk (i.e. first 10-15 years) is very small but specific cumulative incidence for the radiotherapy exposed population is not provided. No direct screening so true incidence might be underestimated. **Risk of bias:** - Selection bias: unclear how many patients were included in the original cohort of survivors. - Attrition bias: low risk, during the study, there was documented contact with 90% of patients within the previous 5 years and 78% within the previous 2 years. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome.

Abbreviations: ALL, acute lymphoblastic leukemia; CNS, central nervous system; PNET, primitive neuroectodermal tumor.

What is the prognosis of subsequent CNS neoplasms?				
Bowers et al. Morbidity and mortality associated with meningioma after cranial radiotherapy: A report from the Childhood Cancer Survivor Study. J Clin Oncol 2017;35:1570-1576.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective cohort study Treatment era: 1970-1986 Follow-up: - Meningioma: Median 22.8 (range 5.5-38) years - No meningioma: Median 25.7 (range 8.4-39) years	4,221 childhood cancer survivors diagnosed <21 years, treated with CRT <5 years of primary cancer diagnosis, who survived ≥5 years after diagnosis Primary cancer diagnosis: - Meningioma: Leukemia (58.0%), CNS tumor (36.1%), other (5.9%) - No meningioma: Leukemia (62.6%), CNS tumor (25.1%), other (12.3%) Age at primary cancer diagnosis: - Meningioma: Median 4.0 (range 0-18) years - No meningioma: Median 5.0 (range 0-20) years Age at follow-up: - Meningioma: Median 35 (range 15-56) years - No meningioma: Median 32 (range 9-55) years Genetic predisposition: Not reported	CRT: 4,221 (100%) CRT dose: - Meningioma: 1.5-19.9 Gy: 23 (13.6%) 20-29.9 Gy: 71 (42.0%) ≥30 Gy: 75 (44.4%) - No meningioma: 1.5-19.9 Gy: 1,214 (30.0%) 20-29.9 Gy: 1,409 (34.8%) ≥30 Gy: 1,416 (34.9%) Missing: 13 (0.3%) Chemotherapy: Not reported	Survivors with subsequent meningioma: - All meningioma: n=199 in n=169 survivors - Benign meningioma: n=164 - Malignant meningioma: n=5 Cumulative incidence subsequent meningioma: - 30-year: 5.8% (95% CI 4.8-6.8) - By age 40 years: 5.6% (95% CI 4.7-6.7) Prognosis subsequent meningioma: - Median follow-up of survivors with a meningioma was 72 (range 3.8-395) months - 22 (13%) out of 169 had died - 3-year overall survival: 95% (95% CI, 90% to 97%) - 5-year overall survival: 91% (95% CI, 85% to 95%) - 6 (27.3%) out of 22 deaths were attributed to a meningioma Neurological outcomes: - 149 (88.2%) out of 169 survivors with meningioma reported at least one neurological sequela at some point 5 years from primary cancer diagnosis - 66 (39%) reported seizures, 91 (53.8%) auditory-vestibularvisual deficits, 96 (56.8%) focal neurologic dysfunction and 91 (53.8%) severe headaches after the diagnosis of meningioma	Unclear how CNS neoplasms were detected. **Risk of bias:** - Selection bias: unclear how many patients were included in the original cohort of survivors. - Attrition bias: unclear for how many survivors follow-up data was complete. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome.

			- Adjusting for sex and CRT dose, survivors had an increased risk of neurologic sequelae within ± 6 months of meningioma diagnosis, including seizures (HR 10.0 (95% CI 7.0-15.3), auditory-vestibular-visual sensory deficits (HR 2.3 (95% CI 1.3-4.0), focal neurologic dysfunction (HR 4.9 (95% CI 3.2-7.5) and severe headaches (HR 3.2 (95% CI 1.9-5.4)	

Abbreviations: CNS, central nervous system; CRT, cranial radiotherapy.

What is the prognosis of subsequent CNS neoplasms?				
Brignardello et al. GH replacement therapy and second neoplasms in adult survivors of childhood cancer: a retrospective study from a single institution. J Endocrinol Invest 2015;38:171-176.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective cohort study <u>Treatment era:</u> <1990->2000 <u>Follow-up:</u> Not reported, at least ≥5 years after primary cancer diagnosis	49 childhood cancer survivors <18 years at primary cancer diagnosis who survived ≥5 years after primary cancer diagnosis, who visited the long-term follow-up clinic at age ≥18 years at least once, with GHD <u>Primary cancer diagnosis:</u> Hematological malignancies (30.6%), ALL (20.4%), AML (10.2%), brain tumors (69.4%) <u>Age at primary cancer diagnosis:</u> Range 0-18 years <u>Age at follow-up:</u> Not reported	<u>GH treatment:</u> 26 (53.1%) for at least 12 months during childhood <u>CRT (non-TBI):</u> - Total: 45 (91.8%) - GH treated patients: 24 (92.3%) - GH untreated patients: 21 (91.3%) <u>CRT dose (non-TBI):</u> 18-64 Gy <u>TBI:</u> 10 (20.4%) <u>TBI dose:</u> 12-14 Gy	<u>Subsequent meningioma:</u> - Overall: n=10 in 9 patients - GH treated patients: n=5 in 5/26 patients (19.2%) - GH untreated patients: n=5 in 4/23 patients (17.4%) <u>Prognosis:</u> - 4 patients diagnosed with meningioma underwent neurosurgery, due to the onset of neurological symptoms or to the progressive enlargement of the lesion - At the time of the study, 2 operated meningiomas showed a complete recovery - Non-operated meningiomas were followed-up with regular MRI scans, one of which recently showed tumor progression requiring neurosurgery	In three cases the presence of meningioma was suspected on the basis of neurological symptoms (i.e. headache or seizures). The other cases were detected by MRI in asymptomatic patients. At least one MRI / CT performed ten years or more after cancer diagnosis. **Risk of bias:** - <u>Selection bias:</u> unclear how many patients were included in the original cohort of survivors. - <u>Attrition bias:</u> low risk, medical follow-up data available for 49 out of 49 (100%) survivors. - <u>Detection bias:</u> unclear if the outcome assessors were blinded for important

	Genetic predisposition: 0 (0%)			determinants related to the outcome.

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CRT, cranial radiotherapy; GH, growth hormone; GHD, growth hormone deficiency; TBI, total body irradiation.

What is the prognosis of subsequent CNS neoplasms?				
Felice et al. Second Neoplasms in Children Following a Treatment for Acute Leukemia and/or Lymphoma: 29 Years of Experience in a Single Institution in Argentina. Journal of pediatric hematology oncology 2017; 39: 406-4012.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Retrospective cohort study Treatment era: 1987 -2016 Follow-up: Not reported; From 17 patients who achieved complete remission of secondary neoplasm and stayed alive: Median 110 (range 4-276) months	3,321 patients with childhood acute leukemia or lymphoma Primary cancer diagnosis: Acute leukemia (85%), lymphoma (15%) Age at primary cancer diagnosis: Median 6 (range 1-16) yr Age at follow-up: Not reported Genetic predisposition: No genetic/molecular studies for ruling-out genetic predisposition to develop cancer were performed to any patient. However, no phenotypic stigmata were detected in any case.	No treatment data available of cohort of survivors Treatment among survivors with a subsequent CNS neoplasm: - Chemotherapy: 5 - Radiotherapy: 4 - HSCT: 1 patient with glioblastoma multiforme with relapsed NHL	Survivors with subsequent CNS neoplasms:: - 3 glioblastoma multiforme - 1 meningioma - 1 PNET Prognosis: - 1/1 (100%) with meningioma alive and in complete remission for 178 months - 4/4 (100%) with glioblastoma multiforme and PNET died	Unclear how CNS neoplasms were detected. **Risk of bias:** - Selection bias: unclear how many patients were included in the original cohort of survivors. - Attrition bias: unclear for how many patients follow-up was complete. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome.

Abbreviations: CNS, central nervous system; CRT, cranial radiotherapy.

What is the prognosis of subsequent CNS neoplasms?				
Felicetti et al. Meningiomas after cranial radiotherapy for childhood cancer: a single institution experience. J Cancer Res Clin Oncol 2015; 141:1277-1282				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective cohort study Treatment era: 1974-1993 (for meningioma cases) Follow-up: Median 24.6 (range 13.2-36.8) yr	90 childhood cancer survivors <18 years at primary cancer diagnosis aged ≥18 years, treated with CRT Primary cancer diagnosis: ALL/non-Hodgkin lymphoma (48.9%), medulloblastoma (21.1%), ependymoma (7.8%), astrocytoma (6.7%), germinoma (4.4%), other (11.1%) Age at primary cancer diagnosis: <18 yr (58.9% <10 yr; 41.1% >10 yr) Age at follow-up: Range 18- >40 yr Genetic predisposition: Not reported	Whole brain radiotherapy: 90 (100%) Spinal radiotherapy: 30 (33.3%) CRT dose: 18-54 Gy Spinal radiotherapy dose: 18-47 Gy	Survivors with subsequent CNS meningioma: 15 (16.7%) Prognosis: - 10 (66.6%) diagnosed with "suspected meningioma" on CT/MRI underwent surgery due to the large volume with mass effect or progressive enlargement of the lesion, or due to the onset of neurological symptoms - 1 (6.7%) died during anesthesia induction, due to cardiac arrhythmia	In four patients, meningioma was suspected on the basis of neurological symptoms (i.e., headache or seizures), whereas all other cases were discovered by MRI in asymptomatic patients. Multiple meningeal tumors were discovered in four CCS. **Risk of bias:** - Selection bias: unclear how many patient from the original cohort were included in the study. - Attrition bias: low risk, medical follow-up data available for all survivors. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome.

Abbreviations: ALL, acute lymphoblastic leukemia; CRT, cranial radiotherapy.

What is the prognosis of subsequent CNS neoplasms?
Galloway et al. Analysis of dose at the site of second tumor formation after radiotherapy to the central nervous system. Int J Radiation Oncology Biol Phys 2012;82:90-94. ***Galloway et al.*** Second tumors in pediatric patients treated with radiotherapy to the central nervous system. Am J Clin Oncol 2012;35:279-283.

Study design Treatment era Years of follow-up	Participants	Treatment	Main outcomes	Additional remarks
Retrospective cohort study Treatment era: 1963-2006 Follow-up: Median 4.7 (range 0.1-45.4) years	370 patients ≤19 years at CRT Primary cancer diagnosis: Glioma (31.5%), ALL/AML (26.3%), medulloblastoma (17.0%), ependymoma (11.2%), germinoma (3.8%), nongerminomatous germ cell tumor (10.1%) Age at radiotherapy: Median 8.1 (range 0.2-19.0) years Age at follow-up: Median 21.2 (range 2.4-59.9) years Genetic predisposition: 6 (1.6%) with a known diagnosis of neurofibromatosis	CRT: 370 (100%) Radiation volumes: - Part of the brain: 172 (47%) - Whole brain: 79 (21%) - Craniospinal axis: 119 (32%) Radiation dose (28% Cobalt): - Tumor bed: median 53.1 (range 6-75.6) Gy - Craniospinal axis: median 30 (range 12-45.6 Gy) Chemotherapy: 210 (56.6%)	Survivors with secondary neoplasms: - Meningioma: n=10 - Glioma: n=4 - Sarcoma: n=1 - Thyroid tumor: n=1 Cumulative incidence secondary neoplasms: - 10-year: 3% - 15-year: 4% - 20-year: 8% - 25-year: 19% - 30-year: 24% Prognosis: - Deaths from tumor recurrence was greater than from second tumor until 20 years when the rate of death between late recurrences of the primary second tumor was essentially equal (although small numbers (n=8)). - 63% of secondary primary neoplasms were meningiomas and for these there was an 89% 5-year survival.	The total number of patients surviving their primary cancer is unknown. 81% of presumed living patients contacted within last 5 years of analysis Two patients developed a third tumor at 3.6 and 9.5 years after treatment for their secondary tumor and 22.0 and 32.7 years after treatment for their primary tumor, respectively. Six patients with a known diagnosis of neurofibromatosis did not develop a secondary tumor. Unclear how CNS neoplasms were detected. **Risk of bias:** - Selection bias: unclear how many patients were included in the original cohort of survivors. - Attrition bias: low risk, 81% of presumed living patients have been contacted within last 5 years before the analysis, but numbers not reported. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome.

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CNS, central nervous system; CRT, craniospinal radiotherapy.

What is the prognosis of subsequent CNS neoplasms?				
Hijiya et al. Cumulative incidence of secondary neoplasms as a first event after acute lymphoblastic leukemia. JAMA 2007;297:1207-15.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective cohort study Treatment era: 1962-1998 Follow-up: Median 18.7 (range 2.4-41.3) years after ALL diagnosis; 29,179 person-years of follow-up	1,290 ALL survivors aged <21 years at primary cancer diagnosis of whom remained in complete remission ≥10 years after diagnosis Primary cancer diagnosis: ALL (100%) Age at primary cancer diagnosis: Not reported (0-21 years) Age at follow-up: Median 24.8 (range 6.1-52.5) years Genetic predisposition: Not reported	Not reported	CAYA cancer survivors with subsequent CNS neoplasms in first complete remission or after relapse: - Meningioma: n=24, 16 among patients in first complete remission - Glioblastoma multiforme: n=10 - Astrocytoma: n=9 - Oligodendroglioma: n=2 - Other: n=3 Prognosis: 15/16 (93.8%) of patients in first complete recommission with meningioma alive at last follow-up	CNS neoplasms detected by no direct imaging assessment; passive reporting or detection. 1 patient with meningioma died after developing hepatocellular carcinoma as a third neoplasm. **Risk of bias:** - Selection bias: low risk, 1,290 out of 1,290 (100%) eligible survivors were included in the study. - Attrition bias: low risk, medical follow-up data available (i.e. follow-up contact in the last 2 years) for 1,022 out of 1,290 (79.2%) survivors. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome.

Abbreviations: ALL, acute lymphoblastic leukemia; CNS, central nervous system.

What is the prognosis of subsequent CNS neoplasms?				
Lee et al. Irradiation-induced secondary tumors following pediatric central nervous system tumors: experiences of a single institute in Taiwan (1975-2013). Int J Radiat Oncol Biol Phys 2018;101:1243-1252.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**

Retrospective cohort study Treatment era: 1975-2013 Follow-up: Mean 21 years for survivors since primary cancer diagnosis	681 CNS tumor survivors ≤18 years at primary cancer diagnosis treated with CRT who survived ≥5 years since primary cancer diagnosis Primary cancer diagnosis: CNS tumor (100%) of whom 128 (19%) medulloblastoma Age at primary cancer diagnosis: Mean 8.8 (range 3-16.5) years Age at follow-up: Not reported Genetic predisposition: Neurofibromatosis-related disease was excluded	CRT: 681 (100%) CRT dose: Median 52.5 Gy Chemotherapy: Not reported	Survivors with subsequent CNS neoplasms: - Meningioma: n=13 - High-grade glioma: n=6 Prognosis: - 3 out of 13 (23.1%) patients with meningioma died during follow-up; 10-yr survival: 76.9%. - All 6 patients with high-grade glioma died after aggressive multimodality treatment after a mean period of 9.5 (range 4-15) months.	Unclear how CNS neoplasms were detected. **Risk of bias:** - Selection bias: unclear how many survivors from the original cohort were included in the study group. - Attrition bias: unclear for how many survivors of the total study group follow-up data was complete (for 99 out of 128 (77.3%) medulloblastoma patients follow-up was complete). - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome.

Abbreviations: CNS, central nervous system; CRT, cranial radiotherapy.

What is the prognosis of subsequent CNS neoplasms?				
Löning et al. Secondary neoplasms subsequent to Berlin-Frankfurt-Munster therapy of acute lymphoblastic leukemia in childhood: significantly lower risk without cranial radiotherapy. Blood 2000;95:2770-5.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Prospective cohort study Treatment era: 1979-1995 Follow-up: Median 5.7 (range	5006 ALL patients aged <21 years at primary cancer diagnosis Primary cancer diagnosis: ALL (100%) Age at primary cancer	CRT: 77.2% CRT dose: Median 12 (range 12-30) Gy via risk stratified protocols Cyclophosphamide:	ALL survivors with secondary CNS neoplasms: - Gioblastoma: n=4 - Astrocytoma: n=4 - PNET: n=3 - Meningioma: n=2 SIR secondary CNS neoplasms: - 18.6 (95% CI 9.8-29.4)	The total number of patients surviving their primary cancer is unknown. Unclear how CNS neoplasms were detected. **Risk of bias:**

1.5-18) years since primary cancer diagnosis; 28,605 person-years of follow-up	<u>diagnosis:</u> Median 4.8 (range 0-20) years <u>Age at follow-up:</u> Not reported <u>Genetic predisposition:</u> Not reported	100% Mean dose 3000 (range 2000-5000) mg/m^2 <u>Anthracyclines:</u> 100% Mean dose 240 (range 120-280) mg/m^2	<u>Cumulative incidence secondary CNS neoplasms in survivors in first complete remission:</u> - 5-year: 0.1% - 10-year: 0.4% - 15-year: 1.0% (95% CI 0.4-1.8) <u>Prognosis:</u> - 7 out of 13 (53.8%) survivors with subsequent CNS neoplasms have died. The median survival time for patients with CNS neoplasms was 14 months	- <u>Selection bias:</u> unclear how many patients were included in the original cohort of survivors. - <u>Attrition bias:</u> unclear for how many survivors follow-up data was complete, probably all patients? - <u>Detection bias:</u> unclear if the outcome assessors were blinded for important determinants related to the outcome.

Abbreviations: ALL, acute lymphoblastic leukemia; CNS, central nervous system; CRT, cranial radiotherapy; PNET, primitive neuroectodermal tumor; SIR, standardized incidence ratio.

What is the prognosis of subsequent CNS neoplasms?

Patterson et al. Growth hormone exposure as a risk factor for the development of subsequent neoplasms of the central nervous system: A report from the Childhood Cancer Survivors Study. J Clin Endocrinol Metab 2014;99:2030-2037.

Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective cohort study <u>Treatment era:</u> 1970-1986 <u>Follow-up:</u> <10 - ≥20 years	12,098 childhood cancer survivors ≤21 years at primary cancer diagnosis; 338 patients with GH treatment and 11,760 patients without GH treatment <u>Primary cancer diagnosis:</u> Leukemia (29.9% GH, 33.8% non-GH), CNS tumor (48.8% GH, 11.5% non-GH), Hodgkin lymphoma (0.3% GH, 13.9% non-GH), non-Hodgkin lymphoma (3.0% GH, 7.5% non-GH), Wilms tumor (0.3% GH, 9.0% non-GH), neuroblastoma (4.7% GH,	<u>CRT:</u> GH treated patients: 303 (89.6%) GH untreated patients: 3974 (33.8%) <u>CRT dose:</u> GH treated patients: - <10 Gy: 13 (3.8%) - 10-19.9 Gy: 32 (9.5%) - 20-29.9 Gy: 50 (14.8%) - 30-45 Gy: 36 (10.7%) - >45 Gy: 172 (50.9%) GH untreated patients: - <10 Gy: 370 (3.1%) - 10-19.9 Gy: 1168	<u>Survivors with subsequent CNS neoplasms:</u> GH treated patients: - Meningioma: 10 (3.0%) - Glioma: 6 (1.8%) - Other: 0 (0.0%) GH untreated patients: - Meningioma: 138 (1.2%) - Glioma: 49 (0.4%) - Other: 16 (0.1%) <u>Prognosis:</u> - 66 (30.1%) survivors died after the diagnosis of a subsequent CNS neoplasm; 7 had been treated with GH and 59 had not - 4 of the GH treated subjects (all glioma) died due to complications of the CNS neoplasm - None of the GH-treated survivors died of complications of a meningioma as a	Patients treated with GH may have experienced more intensive surveillance for secondary neoplasms due to the CRT than patients not on GH treatment. However, the frequency of CNS imaging is not known. Unclear how CNS neoplasms were detected. GH treatment was self-reported and verified by medical records if doubt and when it remained doubtful this was excluded from analysis. **Risk of bias:**

	6.8% non-GH), soft tissue sarcoma (12.4% GH, 8.6% non-GH), bone malignancies (0.6% GH, 8.8% non-GH) Age at primary cancer diagnosis: Range 0-21 years Age at follow-up: Range 0->40 years Genetic predisposition: Not reported	(9.9%) - 20-29.9 Gy: 1303 (11.1%) - 30-45 Gy: 295 (2.5%) - >45 Gy: 838 (7.1%) Alkylating agents: GH treated patients: 218 (64.5%) GH untreated patients: 6060 (51.5%)	subsequent neoplasm - 39 of the survivors without GH treatment died due to complication of a CNS subsequent neoplasm, of which 6 had meningioma, 26 had glioma, and 7 had another CNS neoplasm - After adjustment for attained age at follow-up, sex, age at primary diagnosis, CRT dose, time since CRT, intrathecal methotrexate, estrogen and/or progesterone treatment, and alkylating agent exposure, the adjusted rate ratio for death due to any CNS subsequent neoplasm associated with GH exposure was 1.6 (95% CI 0.5- 4.9)	- Selection bias: high risk, 12,098 out of 20,276 (59.7%) eligible survivors were included in the study. - Attrition bias: unclear for how many survivors follow-up data was complete, probably all patients? - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome.

Abbreviations: CNS, central nervous system; CRT, cranial radiotherapy; GH, growth hormone.

What is the prognosis of subsequent CNS neoplasms?				
Schmiegelow et al. Second malignant neoplasms after treatment of childhood acute lymphoblastic leukemia. J Clin Oncol 2013;31:2469-2476.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective cohort study Treatment era: 1980-2007 Follow-up: Not reported	642 ALL survivors ≤21 years at primary cancer diagnosis with a secondary malignant neoplasm Primary cancer diagnosis: ALL (100%) Age at primary cancer diagnosis: Median 5.2 (50% range 3.2-10.3) years (total group); Median 4.2 (50% range 2.6-8.7) years (patients with secondary CNS neoplasms)	CNS radiation: At least 230 (35.8%) Epipodophyllotoxin: At least 185 (28.7%) Cyclophosphamide: At least 312 (48.6%)	ALL patients with secondary CNS neoplasms: - Meningioma: n=22 - Other CNS tumor: n=116 Prognosis: Overall survival after non-meningioma brain tumor did not improve over time, with 5-year estimates of 19.6% ± 5.5% before 2000 and 16.6% ± 5.3% afterward (*P*=0.76)	The original cohort of childhood cancer survivors (including those patients without a secondary malignant neoplasm) is unclear. Unclear how CNS neoplasms were detected. **Risk of bias:** - Selection bias: unclear how many patients were included in the original cohort of survivors. - Attrition bias: unclear for how many survivors follow-up data was complete. - Detection bias: unclear if the

	Age at follow-up: Median 14.7 (50% range 11.0-19.2) years at secondary CNS neoplasm diagnosis Genetic predisposition: Not reported			outcome assessors were blinded for important determinants related to the outcome.

Abbreviations: ALL, acute lymphoblastic leukemia; CNS, central nervous system; HSCT, hematopoietic stem cell transplantation.

What is the prognosis of subsequent CNS neoplasms?				
Taylor et al. Survival after second primary neoplasms of the brain or spinal cord in survivors of childhood cancer: results from the British Childhood Cancer Survivor Study. J Clin Oncol 2009;27:5781-5787.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment[a]**	**Main outcomes**	**Additional remarks**
Retrospective cohort study Treatment era: 1940-1991 Follow-up: 310,816 person-years of follow-up from 5-year survival	17,980 childhood cancer survivors <15 years at primary cancer diagnosis who survived ≥5 years after diagnosis Primary cancer diagnosis: Leukemia (27.0%), CNS tumor (22.9%), genetic retinoblastoma (3.1%), nongenetic retinoblastoma (3.6%), lymphoma (12.3%), other (31.2%) Age at primary cancer diagnosis: Range 0-14 years Age at follow-up: Not mentioned Mean time interval from	Radiotherapy: 9223 (51.3%) No radiotherapy: 3835 (21.3%) Chemotherapy: 6633 (36.9%) No chemotherapy: 6038 (33.6%)	Childhood cancer survivors with subsequent CNS neoplasms: - Glioma: n=73 - Low-grade glioma: n=27 - High-grade glioma: n=41 - Meningioma: n=137 - Low-grade meningioma: n=129 - High-grade meningioma: n=8 - Schwannoma: n=16 - PNET: n=9 - Other: n=12 Prognosis subsequent glioma (5-year relative survival): - High-grade (n=41) vs. low grade (n=31): 4.9% (95% CI 0.8-14.6) vs. 38.9% (95% CI 22.1-55.4), p<0.001 - Genetic risk yes (n=12) vs. no (n=60): 18.4% (95% CI 9.83-29.1) vs. 25.1% (95% CI 6.0-50.7), p=0.37 - Age at subsequent glioma diagnosis ≥30 years (n=20) vs. 20-29 years (n=19) vs. ≤19 years	Genetic risk included neurofibromatosis type 1 and 2, Gorlin's syndrome, tuberous sclerosis, Von Hippel-Lindau syndrome, and any syndrome known to increase risk of brain or spinal cord tumors. Relative survival is the ratio of observed survival in the childhood cancer survivor cohort to the expected survival in a comparable group of individuals from the general population. Perhaps those with a genetic risk are under more close surveillance so that tumors are detected earlier vs. general population and thus have lower mortality rates. **Risk of bias:**

	primary cancer diagnosis to subsequent CNS neoplasm: - Glioma (n=73): 17.4 years - Low-grade glioma (n=31): 15.5 years - High-grade glioma (n=42): 18.7 years - Meningioma (n=137): 23.1 years - Low-grade meningioma (n=129): 23.5 years - High-grade meningioma (n=8): 15.9 years - Schwannoma (n=16): 20.0 years - PNET (n=9): 9.2 years		(n=33): 25.2% (95% CI 9.2-45.2) vs. 15.8% (95% CI 3.9-35.1) vs. 25.2% (95% CI 9.2-45.2), p=0.93 - Year of subsequent glioma diagnosis 1996-2002 (n=34) vs. 1986-1995 (n=22) vs. 1959-1985 (n=34): 20.7% (95% CI 9.0-35.5) vs. 18.2% (95% CI 5.7-36.4) vs. 18.8% (95% CI 4.0-40.3), p=0.91 - Sex female (n=36) vs. male (n=36): 19.5% (95% CI 8.6-33.7) vs. 19.5% (95% CI 8.6-33.7), p=0.74 - Age at primary cancer diagnosis 10-14 years (n=18) vs. 5-9 years (n=21) vs. 0-4 years (n=33): 11.1% (95% CI 1.9-29.9) vs. 14.3% (95% CI 3.6-32.2) vs. 27.4% (95% CI 13.7-43.1), p=0.19 - Primary cancer diagnosis ALL (n=18) vs. CNS tumor (n=32) vs. other (n=22): 5.6% (95% CI 0.4-22.5) vs. 15.7% (95% CI 5.7-30.1) vs. 36.5% (95% CI 17.5-55.9), p=0.09 - Year of primary cancer diagnosis 1980-1991 (n=24) vs. 1970-1979 (n=31) vs. <1970 (n=17): 20.9% (95% CI 7.6-38.6) vs. 12.9% (95% CI 4.1-27.1) vs. 29.6% (95% CI 10.8-51.5), p=0.73 Factors associated with mortality from all causes in childhood cancer survivors with subsequent glioma in multivariate Cox regression analysis: - High-grade (n=41) vs. low grade (n=31): HR 3.15 (95% CI 1.58-6.28) - Genetic risk yes (n=12) vs. no (n=60): HR 0.51 (95% CI 0.21-1.21) - Age at subsequent glioma diagnosis ≥30 years (n=20) vs. 20-29 years (n=19) vs. ≤19 years (n=33): HR 0.53 (95% CI 0.15-1.89) vs. HR 0.51 (95% CI 0.20-1.32) vs. reference, p for trend=0.39 - Year of subsequent glioma diagnosis 1996-2002 (n=34) vs. 1986-1995 (n=22) vs. 1959-1985 (n=34): HR 1.34 (95% CI 0.40-4.49) vs. HR 1.42 (95% CI 0.49-4.08) vs. reference, p for trend=0.76	- Selection bias: low risk, 17,980 out of 17,981 (99.99%) eligible survivors were included in the study. - Attrition bias: low risk, medical follow-up data available for 17,980 out of 17,980 (100%) survivors. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome.

			- Sex female (n=36) vs. male (n=36): HR 0.82 (95% CI 0.45-1.47) - Age at primary cancer diagnosis 10-14 years (n=18) vs. 5-9 years (n=21) vs. 0-4 years (n=33): HR 1.75 (95% CI 0.77-3.99) vs. HR 0.85 (95% CI 0.44-1.65) vs. reference, p for trend=0.34 - Primary cancer diagnosis ALL (n=18) vs. CNS tumor (n=32) vs. other (n=22): reference vs. HR 1.45 (95% CI 0.66-3.20) vs. HR 0.59 (95% CI 0.27-1.32) - Year of primary cancer diagnosis 1980-1991 (n=24) vs. 1970-1979 (n=31) vs. <1970 (n=17): HR 0.76 (95% CI 0.22-2.59) vs. HR 1.08 (95% CI 0.49-2.41) vs. reference, p for trend=0.74 <u>Prognosis subsequent meningioma (5-year relative survival):</u> - High-grade (n=7) vs. low grade (n=125): 57.3% (95% CI 17.2-84.0) vs. 84.3% (95% CI 76.5-90.0), p=0.09 - Genetic risk yes (n=5) vs. no (n=127): 40.1% (95% CI 5.2-75.4) vs. 84.6% (95% CI 76.9-89.9), p=0.03 - Age at subsequent meningioma diagnosis ≥30 years (n=58) vs. 20-29 years (n=55) vs. ≤19 years (n=19): 83.4% (95% CI 70.8-91.0) vs. 85.6% (95% CI 73.0-92.7) vs. 73.9% (95% CI 48.0-88.4), p=0.51 - Year of subsequent meningioma diagnosis 1996-2002 (n=74) vs. 1986-1995 (n=43) vs. 1959-1985 (n=15): 83.9% (95% CI 73.1-90.7) vs. 84.1% (95% CI 69.2-92.3) vs. 73.6% (95% CI 43.8-89.4), p=0.64 - Sex female (n=65) vs. male (n=67): 81.7% (95% CI 69.9-89.3) vs. 84.0% (95% CI 72.6-91.1), p=0.81 - Age at primary cancer diagnosis 10-14 years (n=25) vs. 5-9 years (n=46) vs. 0-4 years (n=61): 80.5% (95% CI 58.8-91.7) vs. 85.1% (95% CI	

			70.8-92.8) vs. 82.2% (95% CI 69.9-89.9), p=0.89 - Primary cancer diagnosis ALL (n=40) vs. CNS tumor (n=70) vs. other (n=22): 5.6% (95% CI 0.4-22.5) vs. 15.7% (95% CI 5.7-30.1) vs. 36.5% (95% CI 17.5-55.9), p=0.09 - Year of primary cancer diagnosis 1980-1991 (n=19) vs. 1970-1979 (n=64) vs. <1970 (n=40): 78.6% (95% CI 52.2-91.6) vs. 89.3% (95% CI 78.5-94.9) vs. 76.1% (95% CI 61.4-86.0), p=0.16 <u>Factors associated with mortality from all causes in childhood cancer survivors with subsequent meningioma in multivariate Cox regression analysis:</u> - High-grade (n=7) vs. low grade (n=125): HR 4.95 (95% CI 1.37-17.92) - Genetic risk yes (n=5) vs. no (n=127): HR 7.38 (95% CI 1.30-41.97) - Age at subsequent meningioma diagnosis ≥30 years (n=58) vs. 20-29 years (n=55) vs. ≤19 years (n=19): HR 0.95 (95% CI 0.23-4.01) vs. HR 0.91 (95% CI 0.31-2.73) vs. reference, p for trend=0.96 - Year of subsequent meningioma diagnosis 1996-2002 (n=74) vs. 1986-1995 (n=43) vs. 1959-1985 (n=15): HR 1.34 (95% CI 0.35-5.16) vs. HR 1.58 (95% CI 0.51-4.91) vs. reference, p for trend=0.80 - Sex female (n=65) vs. male (n=67): HR 1.23 (95% CI 0.61-2.52) - Age at primary cancer diagnosis 10-14 years (n=25) vs. 5-9 years (n=46) vs. 0-4 years (n=61): HR 1.56 (95% CI 0.58-4.20) vs. HR 1.21 (95% CI 0.51-2.88) vs. reference, p for trend=0.39 - Primary cancer diagnosis ALL (n=40) vs. CNS tumor (n=70) vs. other (n=22): reference vs. HR 1.11 (95% CI 0.32-3.88) vs. HR 0.88 (95% CI 0.21-3.69) - Year of primary cancer diagnosis 1980-1991	

			(n=19) vs. 1970-1979 (n=64) vs. <1970 (n=40): HR 0.34 (95% CI 0.06-1.79) vs. HR 0.25 (95% CI 0.08-0.76) vs. reference, p for trend=0.06	

Abbreviations: ALL, acute lymphoblastic leukemia; CNS, central nervous system; HR, hazard ratio.

[a] Data from ***Taylor et al.*** Population-based risks of CNS tumors in survivors of childhood cancer: The British Childhood Cancer Survivor Study. J Clin Oncol 2010;28:5287-93.

What is the prognosis of subsequent CNS neoplasms?				
Ueda et al. Therapy related secondary malignancies after treatment for secondary malignancy: Cases from a single institution. Journal of Nippon Medical School 2019; epub ahead of print.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort study Treatment era: 1980-2014 Follow-up: Median 7 yr, mean 10 yr, maximum 33 yr from primary cancer diagnosis	275 childhood cancer survivors <15 years at primary cancer diagnosis who survived >1 yr Primary cancer diagnosis: All types of childhood cancer Meningioma cases: ALL: n=4 Age at primary cancer diagnosis: Not reported Age at follow-up: Not reported; Median 29 yr at meningioma diagnosis Genetic predisposition: Not reported	*Treatment of study group not reported* CRT dose for primary malignancy Meningioma cases: 18Gy: n=2 24Gy: n=2 Second malignancy infield or out of field: Meningioma cases: In field: n=4 Chemotherapy: Meningioma cases: Cyclophosfamide n=2 Daunorubicin n=2	Survivors with secondary meningioma: 4 (1.5%) Prognosis: 4/4 (100%) alive at end of follow-up	**Risk of bias:** - Selection bias: low risk, 275 of 328 (84%) eligible survivors were included in the study. - Attrition bias: low risk, 53 of 328 (16.2%) were excluded because there was a lack of follow-up data or follow-up <1 yr. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome.

Abbreviations: ALL, acute lymphoblastic leukemia; CRT, cranial radiotherapy.

What is the prognosis of subsequent CNS neoplasms?				
Walter et al. Secondary brain tumors in children treated for acute lymphoblastic leukemia in St Jude Children's Research Hospital. J Clin Oncol 1998;16:3761-3767.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective cohort study Treatment era: 1967-1988 Follow-up: Median 15.9 (range 5.5-29.9) years	1,612 ALL patients ≤18 years at primary cancer diagnosis Primary cancer diagnosis: ALL (100%) Age at primary cancer diagnosis: 0-5 years: n=946 >5 years: n=666 Age at follow-up: Not reported Genetic predisposition: Not reported	Based on St Jude ALL research program studies V-XI (1967-1988) CRT: - None: n=361 - 10-21 Gy: n=386 - >21-30 Gy: n=793 - >30 Gy*: n=62 Chemotherapy: methotrexate, epipodophyllotoxins, cytarabine, hydrocortisone Intrathecal chemotherapy administrations**: - None: n=119 - 1-10: n=839 - >10: n=654 Treatment by era: - 1967-1979 (n=826): Majority 24 Gy CRT and intrathecal methotrexate - 1979-1983 (n=428): 24 Gy CRT for high-risk patients and 18	ALL survivors with subsequent CNS neoplasms: - Overall: n=22 in 21 patients - Glioblastoma multiforme: n=4 - Anaplastic astrocytoma: n=2 - Other high-grade glioma: n=4 - Low-grade oligodendroglioma: n=1 - Meningioma: n=11 in 10 patients 20-yr cumulative incidence subsequent CNS neoplasms in ALL patients: - Overall: 1.39% (95% CI 0.63-2.15) Prognosis: - 11 out of 11 (100%) patients with low-grade neoplasms (n=10 with meningioma and n=1 with low-grade oligodendroglioma) are alive with a median survival of 2.5 (range 0.5-10) years after subsequent CNS tumor diagnosis - 8 out of 10 (80.0%) patients with high-grade neoplasms have died with a median survival of 7 (range 0.1-25) months after subsequent CNS tumor diagnosis - 2 out of 10 (20.0%) patients with high-grade neoplasms are alive with survival 5 months and 7.8 years after subsequent CNS tumor diagnosis, respectively	97.1% ALL patients survived and were contacted in 2 years before this analysis. Unclear how CNS neoplasms were detected. * patients who had CRT at doses >30 Gy most likely represent the group who had both initial CRT (18 or 24 Gy) and later craniospinal axis radiation for an isolated cranial relapse. These patients have a worse prognosis/life expectancy owing to the relapse, and thus less patient-years at risk to develop a CNS tumor years/decades later. **Intrathecal chemotherapy administrations: methotrexate only for cohort treated 1967-1983 and triple-agent (methotrexate, hydrocortisone, cytarabine) for patients treated 1984-1988 (Protocol XI) **Risk of bias:** - Selection bias: unclear how many patients were included in the original cohort of survivors. - Attrition bias: low risk, 97.1%

		Gy or no CRT for low-risk patients, and intrathecal methotrexate and epipodophyllotoxins - 1984-1988 (n=358): 18 Gy CRT for higher risk patients and 24 Gy for CNS leukemia, and triple intrathecal chemotherapy (methotrexate, hydrocortisone, cytarabine) replaced single-agent methotrexate - Patients with isolated CNS relapse craniospinal radiotherapy and systemic chemotherapy with or without intrathecal chemotherapy		of surviving ALL patients have been contacted in 2 years before the analysis, but numbers not reported. - <u>Detection bias:</u> unclear if the outcome assessors were blinded for important determinants related to the outcome.

Abbreviations: ALL, acute lymphoblastic leukemia; CNS, central nervous system; CRT, cranial radiotherapy.

Does early diagnosis result in better outcome?				
Co et al. Meningioma Screening With MRI in Childhood Leukemia Survivors Treated With Cranial Radiation. J Rad Oncol Biol Phys 2019;104:640-643.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Prospective cohort compared with a historical control group	<u>Screening group:</u> 70 childhood ALL survivors treated with CRT before age 18 and survived ≥10 years, without neurologic	<u>CRT:</u> 176 (100%) <u>CRT dose:</u> - Screened group: 12 Gy: 1 (1%)	<u>Survivors with subsequent meningioma:</u> - Screened group: 15 (21.4%) - Unscreened group: 9 (8.5%) *P*=0.014	Seventeen unscreened patients underwent MRI to investigate symptoms at a median interval of 24 years after CRT (16 had headaches, 2 vomiting, 2

Treatment era: Not reported Follow-up: - Screened group: Mean 27 (range 19-33) yr since last CRT - Unscreened group: Mean 29 (range 23-37) yr since last CRT	symptoms Control group: 106 unscreened childhood cancer survivors treated with CRT before age 18 and survived ≥10 years, who underwent cranial MRI presenting with symptoms Primary cancer diagnosis: - Screened group: ALL - Unscreened group: Not reported Age at CRT: - Screened group: Median 7 (range 2-16) yr - Unscreened group: Median 6 (range 1-17) yr Age at diagnosis of meningioma: - Screened group: Mean 33 (range 25-46) yr - Unscreened: Mean 34 (range 27-41) yr Genetic predisposition: Not reported	18 Gy: 63 (90%) 24 Gy: 6 (9%) - Unscreened group: 12 Gy: 1 (1%) 18 Gy: 93 (88%) 24 Gy: 11 (11%) 25 Gy: 1 (1%) Chemotherapy: Not reported	Cumulative incidence subsequent meningioma: - Screened group: At 25 years: 7.4% At 30 years: 26.7% - Unscreened group: At 25 years: 4.0% At 30 years: 20.7 Size: - Screened group: Mean 1.6 (range 0.6-3.8) - Unscreened group: Mean 2.6 (range 1.0-7.2) *P*=0.13 Extent of resection: - Screened group: 4 gross total resection; 1 subtotal resection - Unscreened group: 2 gross total resection; 2 subtotal resection *P*=0.52 Post-operative complications: - Screened group: 0 major; 2 minor (oral infection; wound hematoma not requiring evacuation) - Unscreened group: 1 major (cerebrospinal fluid leak); 0 minor *P*=0.20 Persistent neurologic deficits: - Screened group: 0 - Unscreened group: 3 (2.8% (95% CI 0.6-8.0) *P*=0.25	dizziness, 1 papilledema, and 1 visual disturbance; some had more than 1 sign or symptom). Of the 15 meningiomas detected in the screened group, 10 had no surgery, 4 had upfront surgery and 1 had surgery in progression; none were treated with postoperative radiotherapy. Of the 9 meningiomas detected in the unscreened group, 5 had no surgery and 4 had upfront surgery;3 were treated with postoperative radiotherapy. Comparison of the observed rate of diagnosed meningioma in the screened versus the unscreened patients is subject to both lead-time and length-time biases. **Risk of bias:** - Selection bias: unclear how many patients from the original cohort of survivors were included in the study. - Attrition bias: low risk, all survivors in the study group underwent MRI screening.. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: low risk, the patients did not significantly

				differ on age at CRT, CRT dose, and time to first MRI, although more males than females were included in the screened group.

Abbreviations: ALL, acute lymphoblastic leukemia; CRT, cranial radiotherapy.

Who needs surveillance? At what age or time from exposure should surveillance be initiated? At what frequency should surveillance be performed?				
Armstrong et al. Long-term outcomes among adult survivors of childhood central nervous system malignancies in the Childhood Cancer Survivor Study. J Natl Cancer Inst 2009;101:946-58.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective cohort study Treatment era: 1970-1986 Follow-up: Median 19.6 (range 5.1-34.6) years from primary CNS cancer diagnosis; 27,500 person-years from time of entry into cohort	1,877 childhood cancer survivors diagnosed with a primary CNS malignancy <21 years of age who survived ≥5 years after diagnosis Primary cancer diagnosis: Astrocytoma/glial tumor (65.7%), medulloblastoma/PNET (21.0%), ependymoma (7.9%), other CNS tumor (5.4%) Age at primary cancer diagnosis: Median 7.5 (range 0-20) years Age at follow-up: Range 0 - ≥35 years Genetic predisposition: Not reported	Surgery only: 431 (29.0%) Surgery and radiotherapy: 689 (41.6%) Surgery and radiotherapy and chemotherapy: 447 (27.0%) Other: 88 (5.3%) CRT and spinal radiotherapy: 410 (26.2%) CRT, no spinal radiotherapy: 674 (43.0%) No CRT or spinal radiotherapy: 483 (30.8%) CRT dose: 272 (17.3%) >0 - <50 Gy	Cumulative incidence benign meningioma: - 25-year: 3.3% (95% CI 2.2-4.5) SIRs subsequent CNS neoplasms: - All CNS neoplasms (n=20): 25.3 (95% CI 15.5-39.1) - Astrocytoma/glial tumor (n=15): 24.3 (95% CI 13.6-40.1) - Malignant meningioma (n=4): 714.7 (95% CI 192.3-1829.7) - Medulloblastoma/PNET (n=1): 13.1 (95% CI 0.2-72.8) 25-year cumulative incidence subsequent CNS neoplasms after CRT: - 25-year cumulative incidence after 0 Gy: 1.0% (95% CI 0-2.3) - 25-year cumulative incidence after <50 Gy: 5.2% (95% CI 2.1-8.3) - 25-year cumulative incidence after ≥50 Gy: 7.1% (95% CI 4.5-9.6) Median time interval from primary cancer diagnosis to subsequent CNS tumor: - All CNS neoplasms (n=20): 14.0 years - Astrocytoma/glial tumor (n=15): 14.0 years - Malignant meningioma (n=4): 23.7 years	To assess the occurrence of subsequent neoplasms among survivors, cumulative incidence was estimated using death as a competing risk. Subsequent neoplasms may be underreported despite a thorough validation process. CNS neoplasm cases came to diagnosis either by clinical symptomatic presentation or possibly screening but study cannot quantify these rates. Does not inform us about risk after RT for ALL or other non-CNS neoplasms. No SIR for benign meningioma. Updated data pending, Bowers updated analysis under review. **Risk of bias:** - Selection bias: high risk, 1,877 out of 2,888 (65.0%) eligible survivors were included in the study. However,

		813 (51.8%) ≥50 Gy	- Medulloblastoma/PNET (n=1): 14.0 years Cumulative incidence meningioma over time: - Incidence increased sharply with continued follow-up (no data reported)	participants and nonparticipants were similar in terms of sex, cancer diagnosis, and age at diagnosis. - Attrition bias: low risk, subsequent neoplasms and chronic medical conditions were assessed in 1,877 (100%) survivors included in the study. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: low risk, CRT analyses were adjusted for follow-up.

Abbreviations: CNS, central nervous system; CRT, cranial radiotherapy; PNET, primitive neuroectodermal tumor; SIR, standardized incidence ratio.

Who needs surveillance? At what age or time from exposure should surveillance be initiated? At what frequency should surveillance be performed?				
Bhatia et al. Low incidence of second neoplasms among children diagnosed with acute lymphoblastic leukemia after 1983. Blood 2002;99:4257-4264.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective cohort study Treatment era: 1983-1995 Follow-up: Median 5.5 (range 0-16.1) years; 54,883 person-years of follow-up	8,831 ALL patients aged <21 years at primary cancer diagnosis Primary cancer diagnosis: ALL (100%) Age at primary cancer diagnosis: Median 4.7 (range 0-20.8) years Age at follow-up: Not reported Genetic predisposition: Not reported	Radiotherapy: 38% Radiotherapy dose: Ranged from 0 to 18 Gy to cranium (for CNS prophylaxis) and 24 Gy to cranium and 6-12 Gy to spine (for treatment of CNS disease) Cyclophosphamide: 79% Anthracyclines: 79%	ALL survivors with subsequent CNS neoplasms: - Glioblastoma multiforme: n=9 - Anaplastic astrocytoma: n=4 - PNET: n=3 - Meningioma: n=2 - Medulloblastoma: n=1 Cumulative incidence subsequent CNS neoplasms: - 10-year: 0.47% (95% CI 0.2-0.6) - 15-year: 0.90% (95% CI 0.4-1.4) Relative risk of subsequent CNS neoplasms in multivariable Cox regression analysis: - Craniospinal radiotherapy yes vs. no: 2.4 (95% CI 1.1-5.2) - Craniospinal radiotherapy dose 18 Gy vs. 0 Gy: 2.1 (95% CI 0.7-3.6) - Craniospinal radiotherapy dose 24 Gy vs. 0 Gy: 4.2	Unclear how CNS neoplasms were detected. Very limited follow-up time (5.5 years) does not inform about meningioma risk. Early risk (i.e. first 10-15 years) is very small but specific cumulative incidence for the radiotherapy exposed population is not provided. No direct screening so true incidence might be underestimated. Issue with ALL patient over time – in the last decade hardly any CNS radiation in this population, for sure not spinal and not in this dose (max. 12 Gy).

			(95% CI 0.5-37.7) - Age at ALL diagnosis >5 years vs. 0-5 years: 0.6 (95% CI 0.2-1.5) - Sex female vs. male: 2.54 (95% CI 0.9-6.4) - Cyclophosphamide dose 1-2000 mg/m^2 vs. none: 0.7 (95% CI 0.2-2.6) - Cyclophosphamide dose >2000 mg/m^2 vs. none: 0.9 (95% CI 0.3-2.9) - Anthracycline dose 1-200 mg/m^2 vs. none: 0.6 (95% CI 0.2-1.9) - Anthracycline dose >200 mg/m^2 vs. none: 1.8 (95% CI 0.5-6.5) - Relapse of primary disease yes vs. no: 2.5 (95% CI 0.9-7.6) <u>Median time interval from primary cancer diagnosis to subsequent CNS neoplasms:</u> - All CNS neoplasms (n=19): 7.1 (range 3.9-13.0) years <u>SIRs subsequent CNS neoplasms over time:</u> - 0-5 years follow-up: 10.8 (95% CI 2.8-24.0) - 6-10 years follow-up: 17.5 (95% CI 8.7-29.3) - 11-15 years follow-up: 3.2 (95% CI 0.3-9.1)	<u>Prognosis:</u> 11 (57.9%) out of 19 survivors with a subsequent CNS neoplasms have died. **Risk of bias:** - <u>Selection bias:</u> unclear how many patients were included in the original cohort of survivors. - <u>Attrition bias:</u> low risk, during the study, there was documented contact with 90% of patients within the previous 5 years and 78% within the previous 2 years. - <u>Detection bias:</u> unclear if the outcome assessors were blinded for important determinants related to the outcome. - <u>Confounding:</u> low risk, analyses were adjusted for CRT and follow-up.

Abbreviations: ALL, acute lymphoblastic leukemia; CNS, central nervous system; PNET, primitive neuroectodermal tumor; SIR, standardized incidence ratio.

Who needs surveillance? At what age or time from exposure should surveillance be initiated? At what frequency should surveillance be performed?				
Bowers et al. Subsequent neoplasms of the CNS among survivors of childhood cancer: a systematic review. Lancet Oncol 2013;14:e321-28.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Systematic review including 14 retrospective cohort studies examining the risk of subsequent CNS neoplasms in	164,334 childhood cancer survivors (ranging from 2,169-47,697 per study) aged <21 years at primary cancer diagnosis <u>Primary cancer diagnosis:</u>	<u>CRT:</u> Ranging from 38-78%	<u>Risk of CNS neoplasms compared with the general population:</u> - 959 patients diagnosed with subsequent CNS tumor ranging from 4-262 per study - Each study reported increased incidence of subsequent CNS neoplasms among patients treated with CRT compared with the general population	Precision and generalizability of risk estimates were limited by lack of detailed information about CNS radiation therapy, small sample sizes or numbers of CNS tumor cases, less than 10 years of follow-up in some cohorts, or were from single institution cohorts.

childhood cancer survivors Treatment era: Ranging from 1940-2005 Follow-up: Ranging from 5-22.7 years	BMT recipients (n=1 study), ALL (n=5 studies), CNS neoplasms (n=1 study), leukemia, lymphoma, Hodgkin's disease (n=1 study), various types of childhood cancer (n=6 studies) Age at primary cancer diagnosis: Ranging from 0-21 years (1 study 1-67 years) Age at follow-up: Not reported Genetic predisposition: Not reported		- SIRs for subsequent CNS neoplasms (including gliomas and meningiomas) ranged from 9.5-52.3 - SIRs for subsequent gliomas ranged from 8.9-24.3 (n=3 studies) - SIRs for subsequent meningiomas ranged from 41.2-714.7 (n=3 studies) - AERs of subsequent CNS neoplasms ranged from 1.9-72.8 per 10,000 person-years Radiation exposure and subsequent CNS neoplasms: - Linear correlation of cumulative radiation dose with risk of subsequent (high-grade) gliomas, meningiomas and PNET (n=2 studies, see evidence tables Taylor 2010 and Neglia 2006) Median time interval to subsequent CNS neoplasms: - Latency time high-grade glioma ranged from 8-17.4 years (4 studies, n=141) - Latency time meningioma ranged from 10.7-23.1 years (7 studies, n=252) Incidence subsequent CNS neoplasms over time: - Increased rates of subsequent CNS neoplasms did not seem to plateau over time (no data reported)	Many studies examined only malignant neoplasms and excluded most or all meningiomas because they were considered to be benign. Unclear how CNS neoplasms were detected.

Abbreviations: AER, absolute excess risk; ALL, acute lymphoblastic leukemia; BMT, bone marrow transplant; CNS, central nervous system; CRT, cranial radiotherapy; PNET, primitive neuroectodermal tumor; SIR, standardized incidence ratio.

Who needs surveillance? At what age or time from exposure should surveillance be initiated? At what frequency should surveillance be performed?				
Bowers et al. Morbidity and mortality associated with meningioma after cranial radiotherapy: A report from the Childhood Cancer Survivor Study. J Clin Oncol 2017;35:1570-1576.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective cohort study Treatment era: 1970-1986	4,221 childhood cancer survivors diagnosed <21 years, treated with CRT <5 years of primary cancer diagnosis, who survived ≥5	CRT: 4,221 (100%) CRT dose: - Meningioma: 1.5-19.9 Gy: 23 (13.6%)	Survivors with subsequent meningioma: - All meningioma: n=199 in n=169 survivors - Benign meningioma: n=164 - Malignant meningioma: n=5	Unclear how CNS neoplasms were detected. No direct screening so true incidence might be underestimated.

Follow-up: - Meningioma: Median 22.8 (range 5.5-38) years - No meningioma: Median 25.7 (range 8.4-39) years	years after diagnosis Primary cancer diagnosis: - Meningioma: Leukemia (58.0%), CNS tumor (36.1%), other (5.9%) - No meningioma: Leukemia (62.6%), CNS tumor (25.1%), other (12.3%) Age at primary cancer diagnosis: - Meningioma: Median 4.0 (range 0-18) years - No meningioma: Median 5.0 (range 0-20) years Age at follow-up: - Meningioma: Median 35 (range 15-56) years - No meningioma: Median 32 (range 9-55) years Genetic predisposition: Not reported	20-29.9 Gy: 71 (42.0%) ≥30 Gy: 75 (44.4%) - No meningioma: 1.5-19.9 Gy: 1,214 (30.0%) 20-29.9 Gy: 1,409 (34.8%) ≥30 Gy: 1,416 (34.9%) Missing: 13 (0.3%) Chemotherapy: Not reported	Cumulative incidence subsequent meningioma: - 30-year: 5.8% (95% CI 4.8-6.8) - By age 40 years: 5.6% (95% CI 4.7-6.7) - By age 40 years males: 4.4% (95% CI 3.3-5.6) - By age 40 years females: 7.0% (95% CI 5.3-9.0) - By age 40 years 1-19.9 Gy CRT: 3.0% (95% CI 1.9-4.5) - By age 40 years 20-29.9 Gy CRT: 6.3% (95% CI 4.8-8.0) - By age 40 years ≥30 Gy CRT: 6.2% (95% CI 4.6-8.1) - By age 40 years 0-4 years at primary cancer diagnosis: 10.4% (95% CI 7.2-14.1) - By age 40 years 5-10 years at primary cancer diagnosis: 6.2% (95% CI 4.5-8.2) - By age 40 years 11-15 years at primary cancer diagnosis: 2.7% (95% CI 1.5-4.4) - By age 40 years 16-20 years at primary cancer diagnosis: 1.5% (95% CI 0.6-3.4) Hazard ratios of first subsequent meningioma in multivariable Cox regression analysis: - CRT dose 20-29.9 Gy vs. 1.5-19.9 Gy: 1.6 (95% CI 1.0-2.6) - CRT dose ≥30 Gy vs. 1.5-19.9 Gy: 2.6 (95% CI 1.6-4.2) *P* for trend <0.001 - Age at primary cancer diagnosis 0-5 years vs. 16-20 years: 1.6 (95% CI 0.8-3.2) - Age at primary cancer diagnosis 5-10 years vs. 16-20 years: 1.2 (95% CI 0.6-2.4) - Age at primary cancer diagnosis 11-15 years vs. 16-20 years: 0.9 (95% CI 0.4-2.0) *P* for trend = 0.076 - Sex female vs. male: 1.7 (95% CI 1.2-2.3) Time interval from primary cancer diagnosis to subsequent meningioma: - Median 22 (range 5-37) years Age at subsequent meningioma diagnosis: - Median 28 (range 7-50) years	Meningiomas were identified through self- or proxy report and confirmed by pathology reports if available or alternatively, by other medical records. Study design is limited by the integration of calendar dates from pathology reports or other medical records to determine participants' age at subsequent meningiomas diagnosis with the participants' self-reported chronological age at first onset of neurologic sequelae. Neurological outcomes: - 149 (88.2%) out of 169 survivors with meningioma reported at least one neurological sequela at some point 5 years from primary cancer diagnosis. - 66 (39%) reported seizures, 91 (53.8%) auditory-vestibularvisual deficits, 96 (56.8%) focal neurologic dysfunction and 91 (53.8%) severe headaches after the diagnosis of meningioma. - Adjusting for sex and CRT dose, survivors had an increased risk of neurologic sequelae within ± 6 months of meningioma diagnosis, including seizures (HR 10.0 (95% CI 7.0-15.3), auditory-vestibular-visual sensory deficits (HR 2.3 (95% CI 1.3-4.0), focal neurologic dysfunction (HR 4.9 (95% CI 3.2-7.5) and severe headaches (HR 3.2 (95% CI 1.9-5.4). Prognosis subsequent meningioma: - Median follow-up of survivors with a meningioma was 72 (range 3.8-395)

			Incidence subsequent meningioma over time: - Increased cumulative incidence of subsequent meningioma over time that did not seem to plateau (no data reported)	months - 22 (13%) out of 169 had died - 3-year overall survival: 95% (95% CI, 90% to 97%) - 5-year overall survival: 91% (95% CI, 85% to 95%) - 6 (27.3%) out of 22 deaths were attributed to a meningioma **Risk of bias:** - Selection bias: unclear how many patients were included in the original cohort of survivors. - Attrition bias: unclear for how many survivors follow-up data was complete. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: low risk, analyses were adjusted for CRT and follow-up.

Abbreviations: CNS, central nervous system; CRT, cranial radiotherapy.

Who needs surveillance? At what frequency should surveillance be performed?				
Cardous-Ubbink et al. Risk of second malignancies in long-term survivors of childhood cancer. Eur J Cancer 2007;43:351-362.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective cohort study Treatment era: 1966-1996 Follow-up: Median 16.8 (range 5-≥30) years	1,368 childhood cancer survivors <18 years at primary cancer diagnosis who survived ≥5 years after diagnosis Primary cancer diagnosis: Leukemia (24.5%), lymphoma (18.7%), Wilms tumor (14.0%), CNS tumor	Surgery only: 7.6% Chemotherapy only ± surgery: 48.0% Radiotherapy only ± surgery: 6.8% Chemotherapy and radiotherapy ± surgery:	SIRs subsequent CNS neoplasms: - Brain tumor (n=4): 10.8 (95% CI 2.93-27.6) - CNS tumor including benign meningioma (n=13): 40.1 (95% CI 21.4-68.6) - Meningioma (n=12): 41.2 (95% CI 21.3-71.9) AERs subsequent CNS neoplasms per 1,000 person-years: - Brain tumor: 0.21 - CNS tumor: 0.74	No radiotherapy and chemotherapy specifications. SIRs for meningioma increased with longer follow-up resulting in a SIR of 212 after ≥25 years of follow-up (data not shown). Unclear how CNS neoplasms were detected.

	(8.0%), bone tumor (8.6%), soft tissue sarcoma (10.7%), other (15.5%) Age at primary cancer diagnosis: Median 5.9 (range 0-18) years Age at follow-up: Range 5-≥30 years Genetic predisposition: Not reported	37.7%	- Meningioma: 0.69 Risk factors subsequent meningioma in multivariable Cox regression analysis: - Radiotherapy yes vs. no: HR could not be calculated as all 12 meningioma cases were treated with radiotherapy - Age at diagnosis per year: HR 1.03 (95% CI 0.90-1.18) - Sex female vs. male: HR 0.37 (95% CI 0.10-1.37) - Chemotherapy yes vs. no: HR 2.74 (95% CI 0.34-21.8) - Treatment era after October 1984 vs. before October 1984: HR 1.46 (95% CI 0.16-13.7) SIRs subsequent CNS neoplasms over time: - SIRs for meningioma increased with longer follow-up resulting in a SIR of 212 after ≥25 years of follow-up (no data reported)	No direct screening so true incidence might be underestimated. No information on absolute risk after radiotherapy exposure and no cumulative incidence data for CNS tumors or specifically for CNS tumors after radiotherapy. **Risk of bias:** - Selection bias: low risk, 1,368 out of 1,368 (100%) eligible survivors were included in the study. - Attrition bias: low risk, medical follow-up data available for 1,258 out of 1,368 (92.0%) survivors. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: low risk, analyses were adjusted for CRT and follow-up.

Abbreviations: AER, absolute excess risk; CNS, central nervous system; HR, hazard ratio; SIR, standardized incidence ratio.

Who needs surveillance? At what age or time from exposure should surveillance be initiated? At what frequency should surveillance be performed?				
Friedman et al. Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. J Natl Cancer Inst 2010;102:1083-95.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective cohort study Treatment era: 1970-1986 Follow-up: Mean 22.7 ± 6.8	14,359 childhood cancer survivors <21 years at primary cancer diagnosis who survived ≥5 years after diagnosis Primary cancer diagnosis: Leukemia (33.6%), CNS	Surgery only: 909 (6.3%) Radiotherapy only: 1514 (10.5%) Radiotherapy and chemotherapy:	CAYA cancer survivors with subsequent CNS neoplasms: - Glial neoplasms: n=53 - Medulloblastoma/PNET: n=6 - Meningioma: n=170 - Other: n=16 SIRs secondary malignant CNS neoplasms:	No radiotherapy details reported. CNS neoplasm cases came to diagnosis either by clinical symptomatic presentation or possibly screening but study cannot quantify these rates. **Risk of bias:**

years; 325,119 person-years of follow-up	tumor (13.1%), Hodgkin lymphoma (13.4%), non-Hodgkin lymphoma (7.5%), kidney neoplasms (8.7%), neuroblastoma (6.7%), bone and soft tissue neoplasms (17.0%), soft tissue sarcoma (8.7%), Ewing sarcoma (2.8%), osteosarcoma (5.1%), other bone neoplasms (0.4%) <u>Age at primary cancer diagnosis:</u> Mean 7.8 ± 5.8 years <u>Age at follow-up:</u> Median 30 (range 5-56) years <u>Genetic predisposition:</u> Not reported	7022 (48.9%) <u>Chemotherapy without radiotherapy:</u> 3091 (21.5%)	- All CNS neoplasms (n=77): 10.4 (95% CI 8.3-13.1) - Glial tumor (n=52): 8.9 (95% CI 6.8-11.7) - Medulloblastoma/PNET (n=6): 7.5 (95% CI 3.1-18.1) - Malignant meningioma (n=11): 87.8 (95% CI 26.5-291.4) <u>30-year cumulative incidence meningioma:</u> - 3.1% (95% CI 2.5-3.8) - Highest after primary diagnosis of CNS tumor or ALL <u>Risk ratio of meningioma in multivariable Poisson regression analysis:</u> - Radiotherapy yes vs. no: 16.6 (95% CI 5.2-52.6) - Sex female vs. male: 1.6 (95% CI 1.1-2.3) - Age at primary cancer diagnosis 5-9 years vs. 0-4 years: 0.7 (95% CI 0.5-1.1) - Age at primary cancer diagnosis 10-14 years vs. 0-4 years: 0.4 (95% CI 0.2-2.6) - Age at primary cancer diagnosis ≥15 years vs. 0-4 years: 0.6 (95% CI 0.3-1.1) - Treatment era 1975-1979 vs. 1970-1974: 0.8 (95% CI 0.5-1.3) - Treatment era 1980-1986 vs. 1970-1974: 0.4 (95% CI 0.3-0.7) - Primary cancer diagnosis CNS tumor vs. leukemia: 1.8 (95% CI 1.1-2.7) - Primary cancer diagnosis Hodgkin lymphoma vs. leukemia: 0.1 (95% CI 0.0-0.9) - Primary cancer diagnosis non-Hodgkin lymphoma vs. leukemia: 0.2 (95% CI 0.0-0.9) - Primary cancer diagnosis soft tissue tumor vs. leukemia: 0.2 (95% CI 0.1-0.7) - Primary cancer diagnosis bone tumor vs. leukemia: 0.1 (95% CI 0.1-1.5) - Splenectomy yes vs. no: 0.7 (95% CI 0.1-5.4) - Alkylating agent score 1 vs. 0: 0.8 (95% CI 0.5-1.4) - Alkylating agent score 2 vs. 0: 0.8 (95% CI 0.4-1.4) - Alkylating agent score 3 vs. 0: 0.4 (95% CI 0.1-1.2) - Anthracycline dose 1-100 mg/m^2 vs. none: 0.8 (95%	- <u>Selection bias:</u> high risk, 14,363 out of 20,626 (69.6%) eligible survivors were included in the study. - <u>Attrition bias:</u> low risk, medical follow-up data available for 14,359 out of 14,363 (99.9%) survivors. - <u>Detection bias:</u> unclear if the outcome assessors were blinded for important determinants related to the outcome. - <u>Confounding:</u> low risk, analyses were adjusted for CRT and follow-up.

			CI 0.3-2.1) - Anthracycline dose 101-300 mg/m^2 vs. none: 0.8 (95% CI 0.5-1.9) - Anthracycline dose ≥301 mg/m^2 vs. none: 0.5 (95% CI 0.2-1.2) - Epipodophyllotoxin dose 1-1000 mg/m^2 vs. none: 1.8 (95% CI 0.7-5.0) - Epipodophyllotoxin dose ≥4000 mg/m^2 vs. none: 1.7 (95% CI 0.6-4.3) - Platinum compounds 1-400 mg/m^2 vs. none: 4.0 (95% CI 1.5-11.1) - Platinum compounds 401-750 mg/m^2 vs. none: 1.8 (95% CI 0.2-14.8) - Platinum compounds ≥750 mg/m^2 vs. none: 0.0 <u>Median time interval from primary cancer diagnosis to secondary CNS tumor:</u> - All CNS neoplasms (n=77): 13.2 (range 6.0-32.7) years - Glial tumor (n=52): 11.7 (range 6.0-25.5) years - Medulloblastoma/PNET (n=6): 11.6 (range 8.0-14.6) years - Malignant meningioma (n=11): 22.9 (range 15.8-32.7) years <u>Incidence over time:</u> - Cumulative incidence of secondary CNS neoplasms increased over time (no data reported)	

Abbreviations: CNS, central nervous system; PNET, primitive neuroectodermal tumor; SIR, standardized incidence ratio.

Who needs surveillance? At what age or time from exposure should surveillance be initiated?				
Felicetti et al. Meningiomas after cranial radiotherapy for childhood cancer: a single institution experience. J Cancer Res Clin Oncol 2015; 141:1277-1282				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**

Retrospective cohort study Treatment era: 1974-1993 (for meningioma cases) Follow-up: Median 24.6 (range 13.2-36.8) yr	90 childhood cancer survivors <18 years at primary cancer diagnosis aged ≥18 years, treated with CRT Primary cancer diagnosis: ALL/non-Hodgkin lymphoma (48.9%), medulloblastoma (21.1%), ependymoma (7.8%), astrocytoma (6.7%), germinoma (4.4%), other (11.1%) Age at primary cancer diagnosis: <18 yr (58.9% <10 yr; 41.1% >10 yr) Age at follow-up: Range 18- >40 yr Genetic predisposition: Not reported	Whole brain radiotherapy: 90 (100%) Spinal radiotherapy: 30 (33.3%) CRT dose: 18-54 Gy Spinal radiotherapy dose: 18-47 Gy	Survivors with subsequent CNS meningioma: 15 (16.7%) Odds ratio of meningioma in multivariable Cox regression analysis: - Sex: 0.60 (95% CI 0.08-4.81) - Age <10 yr vs. ≥10 yr at primary cancer diagnosis: 0.86 (95% CI 0.18-4.04) - Radiation dose >30 Gy vs. ≤30 Gy: 0.95 (95% CI 0.28-3.24) - Non-meningioma secondary neoplasm yes vs. no: 1.24 (95% CI 1.06-17.22) Median time interval from primary cancer diagnosis to subsequent meningioma: 22.5 (range 12.2-34.3) yr	In four patients, meningioma was suspected on the basis of neurological symptoms (i.e., headache or seizures), whereas all other cases were discovered by MRI in asymptomatic patients. Multiple meningeal tumors were discovered in four CCS. RT dose was not significantly associated with the risk of meningioma. This may be influenced by the small number of included patients, but also by the fact that the lowest CRT dose was 18 Gy. Prognosis: Ten patients (66.6%) diagnosed with "suspected meningioma" on CT/MRI underwent surgery due to the large volume with mass effect or progressive enlargement of the lesion, or due to the onset of neurological symptoms. One patient died during anesthesia induction, due to cardiac arrhythmia. **Risk of bias:** - Selection bias: unclear how many patient from the original cohort were included in the study. - Attrition bias: low risk, medical follow-up data available for all survivors. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: low risk, analyses were adjusted for sex, age at primary cancer diagnosis and radiation dose.

Abbreviations: ALL, acute lymphoblastic leukemia; CRT, cranial radiotherapy.

Who needs surveillance? At what age or time from exposure should surveillance be initiated? At what frequency should surveillance be performed?				
Hijiya et al. Cumulative incidence of secondary neoplasms as a first event after acute lymphoblastic leukemia. JAMA 2007;297:1207-15.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective cohort study Treatment era: 1962-1998 Follow-up: Median 18.7 (range 2.4-41.3) years after ALL diagnosis; 29,179 person-years of follow-up	1,290 ALL survivors aged <21 years at primary cancer diagnosis of whom remained in complete remission ≥10 years after diagnosis Primary cancer diagnosis: ALL (100%) Age at primary cancer diagnosis: Not reported (0-21 years) Age at follow-up: Median 24.8 (range 6.1-52.5) years Genetic predisposition: Not reported	Not reported	CAYA cancer survivors with subsequent CNS neoplasms in first complete remission or after relapse: - Meningioma: n=24 - Glioblastoma multiforme: n=10 - Astrocytoma: n=9 - Oligodendroglioma: n=2 - Other: n=3 30-year cumulative incidence secondary CNS neoplasms in survivors in first complete remission: - All CNS neoplasms: 3.0% ± 0.59 - Excluding meningioma: 1.17% ± 0.25 SIRs secondary CNS neoplasms excluding meningioma in survivors in first complete remission: - CNS neoplasms (n=22): 31.8 (95% CI 19.7-47.6) - CRT/craniospinal radiotherapy (n=21): 45.8 (95% CI 26.0-64.2) - No CRT/craniospinal radiotherapy (n=1): 4.3 (95% CI 0.1-24.0) Risk factors secondary CNS neoplasms (n=10) in univariate regression analysis: - CRT yes (n=52) vs. no (n=101): 8-year cumulative incidence 11.5% ± 4.5 vs. 0% (p<0.001) - Defective TPMT (n=7) vs. wild-type TPMT (n=45) in patients treated with CRT: 8-year cumulative incidence 42.9% ± 20.6 vs. 6.7% ± 3.8 (p=0.06) Median time interval from primary cancer diagnosis to secondary CNS tumor in survivors in first complete remission:	CNS neoplasms detected by no direct imaging assessment; passive reporting or detection. Prognosis: 1 patient with meningioma died after developing hepatocellular carcinoma as a third neoplasm. **Risk of bias:** - Selection bias: low risk, 1,290 out of 1,290 (100%) eligible survivors were included in the study. - Attrition bias: low risk, medical follow-up data available (i.e. follow-up contact in the last 2 years) for 1,022 out of 1,290 (79.2%) survivors. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: low risk, analyses were adjusted for follow-up.

			- All CNS neoplasms (n=38): 11.9 (range 1.7-31.7) years - Meningioma (n=16): 20.6 (range 12.6-31.7) years - Other (n=22): 8.8 (range 1.7-14.1) years <u>Cumulative incidence secondary CNS neoplasms in survivors in first complete remission over time:</u> - 5-year: 0.05% ± 0.05 - 10-year: 0.8% ± 1.24 - 15-year: 1.24% ± 0.26 - 20-year: 1.87% ± 0.35 - 30-year: 3.0% ± 0.59 <u>Cumulative incidence secondary CNS neoplasms excluding meningioma in survivors in first complete remission over time:</u> - 5-year: 0.05% ± 0.05 - 10-year: 0.8% ± 0.2 - 15-year: 1.17% ± 0.25 - 20-year: 1.17% ± 0.25 - 30-year: 1.17% ± 0.25	

Abbreviations: ALL, acute lymphoblastic leukemia; CNS, central nervous system; SIR, standardized incidence ratio; CRT, cranial radiotherapy; TPMT, thiopurine methyltransferase.

Who needs surveillance? At what frequency should surveillance be performed?				
Inskip et al. New malignancies following childhood cancer in the United States, 1973-2002. Int J Cancer 2007;121:2233-40.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective cohort study <u>Treatment era:</u> 1973-2002 <u>Follow-up:</u> Median 6.3 (range 0.16-30.0) years;	25,965 childhood cancer survivors aged <18 years at primary cancer diagnosis who survived ≥2 months <u>Primary cancer diagnosis:</u> Leukemia (27.0%), Hodgkin lymphoma (7.2%), non-Hodgkin lymphoma (4.4%),	<u>Surgery:</u> 49.9% <u>Radiotherapy:</u> 37.1% <u>Chemotherapy:</u> 65.4%	<u>SIRs subsequent CNS neoplasms:</u> - Overall (n=51): 7.9 (p<0.05) - 5-year survivors treated with radiotherapy (n=27): 16.1 (p<0.05) - 5-year survivors treated without radiotherapy (n=10): 4.7 (p<0.05) - Primary diagnosis ALL (n=12): 9.0 (p<0.05) - Primary diagnosis Hodgkin lymphoma (n=3): 4.7 - Primary diagnosis non-Hodgkin lymphoma (n=1): 3.7	Unclear how many patients were treated with cranial radiotherapy. CNS neoplasms detected by no active detection. **Risk of bias:** - <u>Selection bias:</u> unclear how many patients were included in the original

820,000 person-years at risk	CNS neoplasms (18.5%), neuroblastoma (6.2%), retinoblastoma (2.4%), Wilms tumor (4.9%), bone tumors (5.6%), soft tissue sarcoma (7.4%), germ cell tumors (5.0%), other (11.4%) Age at primary cancer diagnosis: Median 8.2 years Age at follow-up: Maximum 47 years Genetic predisposition: Not reported		- Primary diagnosis astrocytoma (n=8): 12.6 (p<0.05) - Primary diagnosis PNET (n=8): 44.6 (p<0.05) - Primary diagnosis neuroblastoma (n=2): 5.3 - Primary diagnosis Wilms tumor (n=1): 2.5 - Primary diagnosis germ cell tumor (n=1): 2.7 EARs subsequent CNS neoplasms per 10,000 person-years: - Overall (n=51): 1.9 - 5-year survivors treated with radiotherapy (n=27): 4.2 - 5-year survivors treated without radiotherapy (n=10): 1.0 SIRs subsequent CNS neoplasms by time since primary cancer diagnosis: - 0.16-<1 years (n=4): 6.8 (p<0.05) - 1-4 years (n=9): 4.6 (p<0.05) - 5-9 years (n=17): 10.7 (p<0.05) - 10-14 years (n=10): 9.2 (p<0.05) - 15-19 years (n=5): 6.9 (p<0.05) - ≥20 years (n=6): 11.0 (p<0.05)	cohort of survivors. - Attrition bias: low risk, follow-up was complete for 89.1% of survivors. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: low risk, CRT analyses were adjusted for follow-up.

Abbreviations: ALL, acute lymphoblastic leukemia; CNS, central nervous system; EAR, excess absolute risk; PNET, primitive neuroectodermal tumor; SIR, standardized incidence ratio.

Who needs surveillance? At what age or time from exposure should surveillance be initiated? At what frequency should surveillance be performed?				
Kok et al. Risk of benign meningioma after childhood cancer in the DCOG-LATER cohort: contributions of radiation, exposed cranial volume, and age. Neuro-oncology 2018; 20:1-12				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Retrospective cohort study Treatment era: 1963-2001 Follow-up:	5,843 5-yr CCS diagnosed <18 year Primary cancer diagnosis: Meningioma: Leukemia 53.6%; Medulloblastoma 19.6%; Other CNS 13.4%; Other 13.4%	CRT: - Total group: 1,277 (21.9%) (including TBI) - Meningioma: Partial cranial volume: 14 (14.4%) Full cranial volume: 80 (82.5%)	Survivors with at least one subsequent benign meningioma: n=97 (1.7%) 40-yr cumulative incidence subsequent meningioma: - CRT: 12.4% (95% CI 9.8-15.2) - No CRT: 0.3% (95% CI 0.1-1.2) - 1-19 Gy: 5.6% (95% CI 2.3-11.0)	96 patients included in the analysis due to missing values. Only histologically confirmed subsequent benign meningiomas were included, so true incidence might be underestimated. Unclear how meningiomas were

Median 23.3 (range 5.0-52.2) yr since childhood cancer diagnosis 102,937 person-years at risk	Non-Meningioma: Leukemia 33.2%; Medulloblastoma 2.3%; Other CNS 10.7%; Other 53.9% <u>Age at primary cancer diagnosis:</u> Meningioma: 0-4y: 47.4% 5-9y: 26.8% 10-17y:25.8% No Meningioma: 0-4y: 45.2% 5-9y: 27.1% 10-17y: 27.7% <u>Age at follow-up:</u> Median: 30.6y (range 5.8-67.5) years Meningioma: <20y: 24.7% 20-29y: 48.5% 30-39y:25.8% 40+:1% No Meningioma: <20y: 36.7% 20-29y: 35.9% 30-39y:21.9% 40+:5.6% <u>Genetic predisposition:</u> 2 patients with meningioma had neurofibromatosis	- No meningioma: Partial cranial volume: 307 (5.3%) Full cranial volume: 876 (15.3%) <u>CRT dose</u> (including TBI)<u>:</u> - Meningioma: 1-19 Gy: 10 (10.3%) 20-39 Gy: 48 (49.5%) 40+ Gy: 35 (36.1%) - No meningioma: 1-19Gy: 314 (5.5%) 20-39 Gy: 397 (6.9%) 40+ Gy: 458 (8.0%) <u>Carboplatin:</u> - Meningioma: 6 (6.2%) - No meningioma: 400 (7%)	- 20-39 Gy: 13.1% (95% CI 9.6-7.1) - 40+ Gy: 9.4% (95% CI 6.3-13.3) - Age at primary cancer diagnosis 0-4 years: 5.2% (95% CI 3.7-7.1) - Age at primary cancer diagnosis 5-9 years: 4.3% (95% CI: 2.6-6.4) - Age at primary cancer diagnosis 10-17 years: 3.7% (95% CI 2.1-5.9) <u>Hazard ratios of first subsequent meningioma in multivariable Cox regression analysis:</u> - No CRT vs. CRT doses 1-19 Gy: 0.04 (95% CI 0.01-0.15) - CRT doses 20-39 Gy vs. 1-19 Gy: 1.66 (95% CI 0.83-3.33) - CRT doses 40+ Gy vs. 1-19 Gy: 2.81 (95% CI 1.30-6.08) - Linear dose-response among CRT-exposed individuals: excess relative risk/Gy 0.30 (95% CI 0.03-unknown) - Full CRT vs. partial CRT: 1.66 (95% CI 0.86-3.22) - Full CRT ≤25 Gy vs. partial CRT: 1.03 (95% CI 0.56-1.89) - Full CRT >25 Gy vs. partial CRT: 1.45 (95% CI 0.75-2.83) - No CRT vs. partial CRT: 0.01 (95% CI 0.00-0.05) - Carboplatin yes vs. no: 3.55 (95% CI 1.62-7.78) - No carboplatin dose-response relationship - Female vs. male: 1.36 (95% CI 0.91-2.04) - Age at childhood cancer diagnosis 0-4 yr vs. 10-17 yr: 2.38 (95% CI 1.39-4.07) - Age at childhood cancer diagnosis 5-9 yr vs. 10-17 yr: 1.09 (95% CI 0.62-1.91) - Time since childhood cancer diagnosis 20-29 yr vs. 5-19 yr: 2.18 (95% CI 1.13-4.23) - Time since childhood cancer diagnosis >30 yr vs. 5-	diagnosed. Tumors occurring during 1968‑1989 were not recorded reliably by PALGA. Therefore follow-up time since 1990. True cumulative incidence caused by left truncation is expected to be minimal, since most meningioma occur >20 year after childhood cancer. No significant modifications of the dose-response relationship by age at diagnosis, exposed cranial volume or sex were observed. **Risk of bias:** - <u>Selection bias:</u> low risk, study group consisted of 5843/6165 (94.8%) of the original cohort of childhood cancer survivors. - <u>Attrition bias:</u> low risk, for all survivors follow-up data was complete. - <u>Detection bias:</u> unclear if the outcome assessors were blinded for important determinants related to the outcome. - <u>Confounding:</u> low risk, analyses were adjusted for CRT dose, CRT volume, age at diagnosis, sex, carboplatin

			19 yr: 3.98 (95% CI 1.57-10.11) - Individual chemotherapy agents other than carboplatin (including methotrexate [57 exposed cases] and cisplatin [2 exposed cases]) were not associated with risk of meningioma Time interval from primary cancer diagnosis to subsequent meningioma: Median 24.9 (range 8.5-44.5) yr Incidence subsequent meningioma over time: Increased cumulative incidence over time that did not seem to plateau.	

Abbreviations: CNS, central nervous system; CRT, cranial radiotherapy.

Who needs surveillance?				
Little et al. Risks of brain tumour following treatment for cancer in childhood: modification by genetic factors, radiotherapy and chemotherapy. Int J Cancer 1998;78:269-275.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Cohort and nested case-control study Treatment era: Not reported Follow-up: Mean 15.1 (range 2.2-45.8) years; 63,309 person-years of follow-up	4,199 childhood cancer (non-leukemia) patients ≤18 years at primary cancer diagnosis 22 cases with a subsequent CNS tumor matched to 282 childhood cancer controls Primary cancer diagnosis: Wilms tumor (19.0%), neuroblastoma (13.1%), Hodgkin's disease (8.4%), non-Hodgkin lymphoma (10.6%), soft tissue sarcoma (12.9%), bone sarcoma (6.1%), CNS tumor (16.6%), gonadal tumor (3.4%),	CRT: Mean absorbed dose 6.2 (range 0.0-82.7) Gy Alkylating agents thought to deliver dose to the brain: carolysine, carboplatin, melphalan, procarbazine, thiothepa, cisplatin, cyclophosphamide, belustin, chlormethin, ifosdamide, carmustine; Mean dose 17.0 (range 0.0-421.2) mol/m^2 Alkylating agents unknown	Childhood cancer patients with subsequent CNS neoplasms: - Malignant brain neoplasms: n=12 - Benign/unspecified brain neoplasms: n=10 Relative risk of subsequent malignant brain tumors in univariate analysis: - Primary CNS tumor: 3.86 (95% CI 1.0-14.05) - Neurofibromatosis: >1000 (95% CI 6.53->1000) - Genetic syndromes other than neurofibromatosis: 0.00 (95% CI 0.00-10.09) - All genetic syndromes: 9.12 (95% CI 1.03-80.04) - After adjusting for the effects of first CNS tumor, the risk of subsequent brain tumor associated with neurofibromatosis remained statistically significant and the other way around (data not reported)	The total number of patients surviving their primary cancer is unknown. 4,400 patients were treated for childhood cancer; for 201 patients radiotherapy and chemotherapy doses were not available. Patients did not have to be in remission to be included in the subcohort. For each case up to 15 controls were selected from the subcohort and matched on age at diagnosis, sex, country of treatment and date of birth. Controls had to be free of any secondary tumor for a period at least as long as the interval between diagnosis of the first and secondary tumor in the corresponding

	thyroid cancer (0.8%), retinoblastoma (3.3%), other (5.8%) Age at primary cancer diagnosis: Mean 6.0 (range 0.0-16.9) years Age at follow-up: Not reported (median age at secondary CNS tumor diagnosis: range 8.0-41.2 years) Genetic predisposition: 170 (4.0%)	to deliver dose to the brain: amecytin, sparamustine, dacarbazine, estramustine, sarcolysine; Mean dose 0.5 (range 0.0-127.8) mol/m^2 Alkylating agents thought not to deliver dose to the brain: bleomycin, chloraminophen; Mean dose 0.1 (range 0.0-30.1) mol/m^2	Relative risk of subsequent benign/unspecified brain tumors in univariate analysis: - Primary CNS tumor: 18.45 (95% CI 3.12-353.12) - Neurofibromatosis: 10.25 (95% CI 0.39-267.62) - Genetic syndromes other than neurofibromatosis: 0.00 (95% CI 0.00-40.79) - All genetic syndromes: 6.71 (95% CI 0.23-196.20) Risk of subsequent brain tumors (malignant and benign) adjusted for background risk of neurofibromatosis and first CNS tumor in childhood cancer patients: - Radiotherapy linear dose-response (p=0.003), which was largely concentrated among the benign/unspecified brain tumors (data not reported) - Relative risk per unit dose was significantly higher for benign/unspecified brain tumors than for malignant brain tumors (data not reported) - After adjustment for chemotherapy the radiation dose-response remained significant (data not reported) - Chemotherapy adjusted for radiotherapy dose not significantly associated with brain tumors (p>0.05) Median age at secondary CNS tumor diagnosis: - Overall: Range 8.0-41.2 years	case. Genetic predisposition included neurofibromatosis (n=44), Fanconi's anaemia (n=1), xeroderma pigmentosum (n=3), multiple endocrine neoplasia type IIA (n=2) and IIB (n=3), Bloom's syndrome (n=1), tuberous sclerosis (n=2), Beckwith-Wiedemann syndrome (n=3), Li-Fraumeni syndrome (n=31), Klippel-Trenaunay syndrome (n=1) and bilateral retinioblastoma (n=80). Unclear how CNS neoplasms were detected. **Risk of bias:** - Selection bias: unclear how many patients were included in the original cohort of survivors. - Attrition bias: unclear for how many survivors follow-up data was complete. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: high risk, analyses were not adjusted for follow-up and CRT.

Abbreviations: CNS, central nervous system; CRT, cranial radiotherapy.

Who needs surveillance? At what age or time from exposure should surveillance be initiated? At what frequency should surveillance be performed?				
Löning et al. Secondary neoplasms subsequent to Berlin-Frankfurt-Munster therapy of acute lymphoblastic leukemia in childhood: significantly lower risk without cranial radiotherapy. Blood 2000;95:2770-5.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Prospective cohort study	5,006 ALL patients aged <21 years at primary cancer diagnosis	CRT: 77.2% Radiotherapy dose:	ALL survivors with secondary CNS neoplasms: - Gioblastoma: n=4 - Astrocytoma: n=4	The total number of patients surviving their primary cancer is unknown.

Treatment era: 1979-1995 Follow-up: Median 5.7 (range 1.5-18) years since primary cancer diagnosis; 28,605 person-years of follow-up	Primary cancer diagnosis: ALL (100%) Age at primary cancer diagnosis: Median 4.8 (range 0-20) years Age at follow-up: Not reported Genetic predisposition: Not reported	Median 12 (range 12-30) Gy via risk stratified protocols Cyclophosphamide: 100% Mean dose 3000 (range 2000-5000) mg/m^2 Anthracyclines: 100% Mean dose 240 (range 120-280) mg/m^2	- PNET: n=3 - Meningioma: n=2 15-year cumulative incidence secondary CNS neoplasms: - Overall: 1.0% (95% CI 0.4-1.8) - Patients treated with CRT: 1.3% - Patients treated without CRT: 0.1% - Patients aged <7 years: 1.5% (95% CI 0.2-2.7) - Patients aged ≥7 years: 0.1% (95% CI 0.0-0.3) (p=0.03 for age) SIR secondary CNS neoplasms: - 18.6 (95% CI 9.8-29.4) Median time interval from primary cancer diagnosis to secondary CNS tumor: - All CNS neoplasms: 7.9 (range 4-13) years Cumulative incidence secondary CNS neoplasms in survivors in first complete remission over time: - 5-year: 0.1% - 10-year: 0.4% - 15-year: 1.0% (95% CI 0.4-1.8)	Unclear how CNS neoplasms were detected. Prognosis: 7 (53.8%) out of 13 survivors with a subsequent CNS neoplasms have died. The median survival time for patients with CNS neoplasms was 14 months. **Risk of bias:** - Selection bias: unclear how many patients were included in the original cohort of survivors. - Attrition bias: unclear for how many survivors follow-up data was complete, probably all patients? - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: low risk, CRT analyses were adjusted for follow-up. High risk for age at treatment since there was no adjustment for CRT.

Abbreviations: ALL, acute lymphoblastic leukemia; CNS, central nervous system; CRT, cranial radiotherapy; PNET, primitive neuroectodermal tumor; SIR, standardized incidence ratio.

Who needs surveillance? At what frequency should surveillance be performed?				
Patterson et al. Growth hormone exposure as a risk factor for the development of subsequent neoplasms of the central nervous system: A report from the Childhood Cancer Survivors Study. J Clin Endocrinol Metab 2014;99:2030-2037.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective cohort study Treatment era: 1970-1986	12,098 childhood cancer survivors ≤21 years at primary cancer diagnosis; 338 patients with GH treatment and 11,760 patients without GH	CRT: - GH treated patients: 303 (89.6%) - GH untreated patients: 3974 (33.8%)	Survivors with subsequent CNS neoplasms: GH treated patients: - Meningioma: 10 (3.0%) - Glioma: 6 (1.8%) - Other: 0 (0.0%) GH untreated patients:	Patients treated with GH may have experienced more intensive surveillance for secondary neoplasms due to the CRT than patients not on GH treatment. However, the frequency of CNS imaging is not known.

Follow-up: <10 - ≥20 years	treatment Primary cancer diagnosis: Leukemia (29.9% GH, 33.8% non-GH), CNS tumor (48.8% GH, 11.5% non-GH), Hodgkin lymphoma (0.3% GH, 13.9% non-GH), non-Hodgkin lymphoma (3.0% GH, 7.5% non-GH), Wilms tumor (0.3% GH, 9.0% non-GH), neuroblastoma (4.7% GH, 6.8% non-GH), soft tissue sarcoma (12.4% GH, 8.6% non-GH), bone malignancies (0.6% GH, 8.8% non-GH) Age at primary cancer diagnosis: Range 0-21 years Age at follow-up: Range 0->40 years Genetic predisposition: Not reported	CRT dose: GH treated patients: - <10 Gy: 13 (3.8%) - 10-19.9 Gy: 32 (9.5%) - 20-29.9 Gy: 50 (14.8%) - 30-45 Gy: 36 (10.7%) - >45 Gy: 172 (50.9%) GH untreated patients: - <10 Gy: 370 (3.1%) - 10-19.9 Gy: 1168 (9.9%) - 20-29.9 Gy: 1303 (11.1%) - 30-45 Gy: 295 (2.5%) - >45 Gy: 838 (7.1%) Alkylating agents: - GH treated patients: 218 (64.5%) - GH untreated patients: 6060 (51.5%)	- Meningioma: 138 (1.2%) - Glioma: 49 (0.4%) - Other: 16 (0.1%) Rate ratios for meningioma in multivariable Poisson regression analysis: - GH treatment yes vs. no: 0.8 (95% CI 0.4-1.7) - Females vs. males: 1.8 (95% CI 1.3-2.6) - Age at primary cancer diagnosis 0-4 years vs. ≥15 years: 4.8 (95% 2.1-11.0) - Age at primary cancer diagnosis 5-9 years vs. ≥15 years: 2.6 (95% CI 1.2-5.5) - Age at primary cancer diagnosis 10-14 years vs. ≥15 years: 1.2 (95% CI 0.6-2.6) p<0.001 for age at primary cancer diagnosis - CRT ≤45 Gy and <10 years between CRT and CNS neoplasm vs. no CRT: 0.0 (95% CI 0.0-6.7) - CRT ≤45 Gy and 10-19 years between CRT and CNS neoplasm vs. no CRT: 23.1 (95% CI 9.9-53.7) - CRT ≤45 Gy and ≥20 years between CRT and CNS neoplasm vs. no CRT: 22.0 (95% CI 9.7-50.2) - CRT >45 Gy and <10 years between CRT and CNS neoplasm vs. no CRT: 55.1 (95% CI 15.3-198.1) - CRT >45 Gy and 10-19 years between CRT and CNS neoplasm vs. no CRT: 47.3 (95% CI 19.4-115.2) - CRT >45 Gy and ≥20 years between CRT and CNS neoplasm vs. no CRT: 58.5 (95% CI 25.5-134.2) p<0.001 for CRT by time since CRT - Intrathecal methotrexate yes vs. no: 1.3 (95% CI 0.8-2.0) - Estrogen and/or progesterone yes vs. no: 0.7 (95% CI 0.5-1.2) - Alkylating agents yes vs. no: 0.7 (95% CI 0.5-1.0) Rate ratios for glioma in multivariable Poisson regression analysis: - GH treatment yes vs. no: 1.9 (95% CI 0.7-4.8) - Females vs. males: 0.9 (95% CI 0.5-1.7) - Age at primary cancer diagnosis 0-4 years vs. ≥15	Unclear how CNS neoplasms were detected. GH treatment was self-reported and verified by medical records if doubt and when it remained doubtful this was excluded from analysis. Estrogen and/or progesterone exposure was determined by self-report. Prognosis: - 66 (30.1%) survivors died after the diagnosis of a subsequent CNS neoplasm; 7 had been treated with GH and 59 had not. - 4 of the GH treated subjects (all glioma) died due to complications of the CNS neoplasm. - None of the GH-treated survivors died of complications of a meningioma as a subsequent neoplasm. - 39 of the survivors without GH treatment died due to complication of a CNS subsequent neoplasm, of which 6 had meningioma, 26 had glioma, and 7 had another CNS neoplasm. - After adjustment for attained age at follow-up, sex, age at primary diagnosis, CRT dose, time since CRT, intrathecal methotrexate, estrogen and/or progesterone treatment, and alkylating agent exposure, the adjusted rate ratio for death due to any CNS subsequent neoplasm associated with GH exposure was 1.6 (95% CI 0.5- 4.9). **Risk of bias:** - Selection bias: high risk, 12,098 out of

			years: 2.0 (95% 0.5-7.8) - Age at primary cancer diagnosis 5-9 years vs. ≥15 years: 0.9 (95% CI 0.2-3.5) - Age at primary cancer diagnosis 10-14 years vs. ≥15 years: 1.8 (95% CI 0.6-5.6) p=0.22 for age at primary cancer diagnosis - CRT ≤45 Gy and <10 years between CRT and CNS neoplasm vs. no CRT: 7.9 (95% CI 2.7-23.0) - CRT ≤45 Gy and 10-19 years between CRT and CNS neoplasm vs. no CRT: 4.1 (95% CI 1.5-11.3) - CRT ≤45 Gy and ≥20 years between CRT and CNS neoplasm vs. no CRT: 1.5 (95% CI 0.3-6.3) - CRT >45 Gy and <10 years between CRT and CNS neoplasm vs. no CRT: 13.5 (95% CI 4.0-46.1) - CRT >45 Gy and 10-19 years between CRT and CNS neoplasm vs. no CRT: 13.4 (95% CI 4.8-37.6) - CRT >45 Gy and ≥20 years between CRT and CNS neoplasm vs. no CRT: 10.7 (95% CI 3.1-36.7) p<0.001 for CRT by time since CRT - Intrathecal methotrexate yes vs. no: 1.3 (95% CI 0.8-2.0) - Estrogen and/or progesterone yes vs. no: 0.7 (95% CI 0.5-1.2) - Alkylating agents yes vs. no: 0.7 (95% CI 0.5-1.0) <u>Rate ratios for any CNS neoplasm in multivariable Poisson regression analysis:</u> - GH treatment yes vs. no: 1.0 (95% CI 0.6-1.8) - Females vs. males: 1.6 (95% CI 1.2-2.2) - Age at primary cancer diagnosis 0-4 years vs. ≥15 years: 4.8 (95% 2.4-9.7) - Age at primary cancer diagnosis 5-9 years vs. ≥15 years: 2.5 (95% CI 1.3-4.7) - Age at primary cancer diagnosis 10-14 years vs. ≥15 years: 1.7 (95% CI 0.9-3.0) p<0.001 for age at primary cancer diagnosis - CRT ≤45 Gy and <10 years between CRT and CNS neoplasm vs. no CRT: 9.5 (95% CI 4.3-20.8) - CRT ≤45 Gy and 10-19 years between CRT and CNS	20,276 (59.7%) eligible survivors were included in the study. - <u>Attrition bias:</u> unclear for how many survivors follow-up data was complete, probably all patients? - <u>Detection bias:</u> unclear if the outcome assessors were blinded for important determinants related to the outcome. - <u>Confounding:</u> low risk, analyses were adjusted for CRT and follow-up.

			neoplasm vs. no CRT: 11.1 (95% CI 6.3-19.5) - CRT ≤45 Gy and ≥20 years between CRT and CNS neoplasm vs. no CRT: 9.9 (95% CI 5.5-17.5) - CRT >45 Gy and <10 years between CRT and CNS neoplasm vs. no CRT: 23.9 (95% CI 10.2-55.9) - CRT >45 Gy and 10-19 years between CRT and CNS neoplasm vs. no CRT: 24.9 (95% CI 13.6-45.8) - CRT >45 Gy and ≥20 years between CRT and CNS neoplasm vs. no CRT: 25.3 (95% CI 14.0-46.0) p<0.001 for CRT by time since CRT - Intrathecal methotrexate yes vs. no: 1.3 (95% CI 0.8-2.0) - Estrogen and/or progesterone yes vs. no: 0.7 (0.5-1.2) - Alkylating agents yes vs. no: 0.7 (0.5-1.0) <u>Cumulative incidence meningioma over time:</u> - Increased incidence of meningioma over time in patients treated with CRT, regardless of GH exposure	

Abbreviations: CNS, central nervous system; CRT, cranial radiotherapy; GH, growth hormone.

Who needs surveillance? At what age or time from exposure should surveillance be initiated? At what frequency should surveillance be performed?				
Remes et al. Radiation-Induced Meningiomas After Childhood Brain Tumor: A Magnetic Resonance Imaging Screening Study. JOAYA Oncol 2019; 1-9.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
<u>Study design</u> - Screened group: Prospective cohort study - Unscreened group: Retrospective cohort study <u>Treatment era:</u> - Screened group:	<u>Type and number of participants</u> - Screened group: 73 brain tumor survivors diagnosed at age ≤16 yr; treated with RT; age at the time of the study ≥16 yr; follow-up time since cessation of tumor therapy ≥5 yr; no progressive disease at the time of the study - Unscreened group: 569	<u>CRT:</u> - Screened group: 73 (100%) - Unscreened group: 569 (100%) <u>CRT Location:</u> - Screened group: *With meningioma:* Local: 4 (66.7%)	<u>Survivors with subsequent CNS neoplasms:</u> - Screened group: 6 (8.2%) meningioma - Unscreened group: 0 (0.0%) meningioma; 2 (0.35%) other CNS neoplasms (ganglioneuroma or ganglioneuroblastoma of posterior fossa and primitive neuroectodermal tumor) <u>Cumulative incidence subsequent meningioma:</u>	Primary tumor of patients with subsequent meningioma: ependymoma (n=3), medulloblastoma (n=1), meningioma (n=1), astrocytoma (n=1). In the screened group, secondary neoplasms were previously diagnosed in 3 of the 73 (4.1%) participants. Two subjects were operated because of meningiomas; one of them was found to have a relapse

1970-2008 - Unscreened group: 1963-2010 <u>Follow-up since primary cancer diagnosis:</u> - Screened group: Mean 19.9 ± 6.2 yr; *With meningioma*: Mean 23 ± 4.3 yr; *Without meningioma*: Mean 19.6 ± 6.2 - Unscreened group: Mean 11.8 ± 12.9 yr	unscreened brain tumor survivors diagnosed at age ≤16 yr, treated with RT, of whom 194 were alive <u>Primary cancer diagnosis:</u> Brain tumors <u>Age at primary cancer diagnosis:</u> - Screened group: Mean 8.4 ± 4.3 yr *With meningioma:* Mean 7.6 ± 4.9 yr *Without meningioma:* Mean 8.4 ± 4.2 yr - Unscreened group: Mean 7.6 ± 4.2 yr <u>Age at follow-up:</u> - Screened group: Mean 28.4 ± 6.8 yr *With meningioma:* Mean 32.2 ± 7.8 yr *Without meningioma:* Mean 28.1 ± 6.6 yr - Unscreened group: Mean 33.5 ± 10.1 yr <u>Genetic predisposition:</u> Not reported	Cranial or craniospinal: 2 (33.3%) *Without meningioma:* Local: 38 (56.7%) Cranial or craniospinal: 29 (43.3%) - Unscreened group: Not reported <u>CRT dose:</u> - Screened group: *With meningioma:* Mean 55 ± 2.5 Gy *Without meningioma:* Mean 51 ± 5.3 Gy - Unscreened group: Not reported <u>Chemotherapy:</u> - Screened group: 46 *With meningioma:* 4 (66.7%) *Without meningioma:* 42 (62.7%) - Unscreened group: 194 (34.1%) <u>Alkylating agents dose:</u> - Screened group: *With meningioma:* Mean 7,084 ± 7,830 mg/m^2 *Without meningioma:* Mean 6,332 ± 6,332 mg/m^2 - Unscreened group: Not reported <u>Previous or current GH</u>	- Screened group: At 20 years: 2% (95% CI 0.3-13.6) At 25 years: 10.2% (95% CI 3.9-25.1) - Unscreened group: Not reported <u>Growth hormone deficiency:</u> - Screened group: *With meningioma:* 6 (100%) *Without meningioma:* 28 (42.4%) *P*=0.009 - Unscreened group: Not reported <u>Odds ratio of subsequent meningioma in multivariable regression analysis</u>: - CRT dose: 1.43 (95% CI 1.04-1.96) - Whole-brain vs. local radiation: 43.3 (95% CI 1.75-1067.01) <u>Mean time interval from primary cancer diagnosis to subsequent meningioma in screened group:</u> 23 ± 4.3 yr <u>Cumulative incidence meningioma over time:</u> Incidence increased with increasing follow-up	in the study MRI. Another subject underwent two operations for three meningiomas before the study. One subject was followed up for a vestibular schwannoma, three meningiomas, and thickening of the optic nerves. Location of meningioma related to RT field in screened group: Whole-brain volume: 34.5 Gy n=1, 36 Gy n=2, 48 Gy n=1; In field border area: n=2 (<51.2 Gy and <54 Gy). The heterogeneity of the study population, and small number of SNs in clinical and register-based data, limits the statistical methods used in this study. Comparison of the observed rate of diagnosed meningioma in the screened versus the unscreened patients is subject to both lead-time and length-time biases. The following variables were tested in the multivariable model: age at diagnosis, follow-up time since the diagnosis of the primary tumor, radiation dose, measured levels of IGF-1, body mass index, sex, and mode of radiation therapy (local or whole brain with/without spinal radiation). **Risk of bias:** - <u>Selection bias:</u> high risk, 73 out of 127 (57%) of the eligible patients were included in the study. However, the group of participants did not differ statistically from non-participants with respect to patient, disease, or

		replacement therapy: - Screened group: *With meningioma:* 3 (50.0%) *Without meningioma:* 32 (47.8%) - Unscreened group: Not reported		treatment characteristics, but information on their current psychosocial status was lacking. - Attrition bias: low risk, all survivors in the study group underwent MRI screening. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: low risk, age at diagnosis, follow-up time since the diagnosis of the primary tumor, radiation dose, measured levels of IGF-1, body mass index, sex, and mode of radiation therapy were tested as potential variables in the model.

Abbreviations: CNS, central nervous system; CRT, cranial radiotherapy.

Who needs surveillance?

Reulen et al. Long-term risks of subsequent primary neoplasms among survivors of childhood cancer. JAMA 2011;22:2311-2319.

Study design Treatment era Years of follow-up	Participants	Treatment	Main outcomes	Additional remarks
Retrospective cohort study Treatment era: 1940-1991 Follow-up: Median 24.3 years; 369,910 person-years of follow-up	17,981 childhood cancer survivors <15 years at primary cancer diagnosis who survived ≥5 years after diagnosis Primary cancer diagnosis: CNS tumor, leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, neuroblastoma, retinoblastoma, Wilms tumor, bone tumor, soft tissue sarcoma, other	Unclear how many patients were treated with radiotherapy	Primary CNS tumor patients with subsequent CNS neoplasms: - Glioma: n=105 - Other CNS neoplasm: n=239 SIRs subsequent glioma: - Overall (n=105): 6.5 (95% CI 5.4-7.8) - Primary CNS tumor (n=50): 12.3 (95% CI 9.3-16.2) - Leukemia (n=27): 9.4 (95% CI 6.5-13.7) - Hodgkin lymphoma (n=4): 2.9 (95% CI 1.1-7.7) - Non-Hodgkin lymphoma (n=6): 6.5 (95% CI 2.9-14.6) - Neuroblastoma (n=2): 3.0 (95% CI 0.8-12.2) - Heritable retinoblastoma (n=3): 4.7 (95% CI 1.5-14.5)	Unclear how CNS neoplasms were detected. Potential overlap in patients with Taylor 2009 and 2010. **Risk of bias:** - Selection bias: low risk, 17,981 out of 17,981 (100%) eligible survivors were included in the study. - Attrition bias: low risk, medical follow-up data available for 17,981 out of 17,981 (100%) survivors. - Detection bias: unclear if the outcome

	(numbers not reported) <u>Age at primary cancer diagnosis:</u> Range 0-15 years <u>Age at follow-up:</u> 5-≥50 years <u>Genetic predisposition:</u> Not reported		- Nonheritable retinoblastoma (n=1): 1.3 (95% CI 0.2-8.9) - Wilms tumor (n=3): 2.2 (95% CI 0.7-7.0) - Bone tumor (n=2): 3.0 (95% CI 0.7-12.0) - Soft tissue sarcoma (n=4): 3.2 (95% CI 1.2-8.5) - Other tumor (n=3): 1.9 (95% CI 0.6-5.8) - Attained age 5-19 (n=40): 11.0 (95% CI 8.1-15.0) - Attained age 20-29 (n=29): 6.3 (95% CI 4.4-9.1) - Attained age 30-39 (n=26): 6.1 (95% CI 4.2-9.0) - Attained age 40-49 (n=6): 2.4 (95% CI 1.1-5.4) - Attained age ≥50 (n=4): 3.1 (95% CI 1.2-8.3) - Males (n=53): 5.7 (95% CI 4.3-7.4) - Females (n=52): 7.6 (95% CI 5.8-10.0) <u>AER subsequent glioma per 10,000 person-years:</u> - Overall: 2.4 (95% CI 1.9-2.9) <u>Relative risk (SIR) of subsequent glioma in multivariable Poison regression analysis:</u> - CRT yes vs. no: 5.5 (95% CI 2.4-12.3) - Chemotherapy yes vs. no: 1.3 (95% CI 0.7-2.5) - Age at primary cancer diagnosis 0-4 vs. 10-14 years: 1.8 (95% CI 1.0-3.3) - Age at primary cancer diagnosis 5-9 vs. 10-14 years: 1.1 (95% CI 0.6-2.1) - Attained age 5-19 vs. ≥50 years: 2.9 (95% CI 1.0-8.7) - Attained age 20-29 vs. ≥50 years: 1.5 (95% CI 0.5-4.4) - Attained age 30-39 vs. ≥50 years: 1.5 (95% CI 0.5-4.5) - Attained age 40-49) vs. ≥50 years: 0.8 (95% CI 0.2-2.8)	assessors were blinded for important determinants related to the outcome. - <u>Confounding:</u> low risk, analyses were adjusted for analyses were adjusted for CRT and follow-up.

Abbreviations: AER, absolute excess risk; CNS, central nervous system; CRT, cranial radiotherapy; SIR, standardized incidence ratio.

Who needs surveillance? At what age or time from exposure should surveillance be initiated? At what frequency should surveillance be performed?				
Rosso et al. Second malignant tumors after elective end of therapy for a first cancer in childhood: a multicenter study in Italy. Int J Cancer 1994;59:451-6.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective cohort study Treatment era: 1960-1986 Follow-up: Median 70.0 (range 0.1-300.8) months since end of treatment; 16,201 person-years of follow-up	3,196 childhood cancer survivors <16 years at primary cancer diagnosis Primary cancer diagnosis: ALL (52.1%), acute non-lymphoblastic leukemia (4.2%), Hodgkin disease (16.0%), non-Hodgkin lymphoma (7.1%), neuroblastoma (9.7%), Wilms tumor (10.7%) Age at primary cancer diagnosis: Median 4.9 (range 0-17.6) years Age at follow-up: Median 14.1 (1.1-36.2) years Genetic predisposition: Not reported	Radiotherapy and chemotherapy: 2353 (73.6%) Radiotherapy only: 61 (1.9%) Chemotherapy only: 726 (22.7%) Surgery only: 56 (1.8%) Radiotherapy dose: Median 24 (range 18-40) Gy	Childhood cancer survivors with subsequent CNS neoplasms: - Glioblastoma: n=4 - Astrocytoma: n=3 - Oligodendroglioma: n=1 - Brain lymphoma: n=1 - All occurred in ALL patients - All treated with 18-34 Gy CRT Cumulative incidence subsequent CNS neoplasms in ALL patients: - 5-year: 0.1% (95% CI 0.0-0.2) - 10-year: 1.9% (95% CI 0.5-3.2) SIR subsequent CNS tumor in ALL patients: - All CNS neoplasms (n=9): 58.9 (95% CI 26.8-111.8) Relative risk of subsequent CNS tumor in Cox regression analysis in ALL patients: - Age at diagnosis (NS) - Sex (NS) - Relapse of leukemia (NS) - CRT with methotrexate (unclear compared to what treatment): 32.1 (95% CI 8.5-121.5) Median time interval from primary cancer diagnosis to subsequent CNS tumor: - All CNS neoplasms: Range 1.1-8.8 years SIRs subsequent CNS neoplasms in ALL patients over time: - 0-4 year from end therapy (n=1): 9.3 (95% CI 0.2-	Number of eligible childhood survivors unclear, so impossible to judge about potential risk of selection bias. Unclear if multivariable or univariate analysis. Unclear how CNS neoplasms were detected. **Risk of bias:** - Selection bias: unclear how many patients were included in the original cohort of survivors. - Attrition bias: low risk, medical follow-up data available for 3,196 out of 3,211 (99.5%) survivors; for 2,469 (77.2%) of those known to be alive the last available information was obtained up to 3 years previously and for 517 (16.2%) the last information was obtained more than 3 years previously. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: unclear if analyses were adjusted for important confounding factors, most likely not.

			51.9) - 5-9 year from end therapy (n=8): 199.7 (95% CI 86.0-393.6)	

Abbreviations: ALL, acute lymphoblastic leukemia; CNS, central nervous system; NS, not significant; SIR, standardized incidence ratio.

Who needs surveillance?				
Sabin et al. Incidental detection of late subsequent intracranial neoplasms with magnetic resonance imaging among adult survivors of childhood cancer. J Cancer Surviv 2014;8:329-335.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective cohort study <u>Treatment era:</u> 1962-2001 <u>Follow-up:</u> Median 25.4 (range 12-46) yr since primary cancer diagnosis	219 childhood cancer survivors <25 yr at primary cancer diagnosis aged ≥18 yr who survived ≥10 yr after diagnosis and who underwent screening brain MRI <u>Primary cancer diagnosis:</u> ALL (74.9%), Hodgkin lymphoma (25.1%) <u>Age at primary cancer diagnosis:</u> Median 6.8 (range 0.5-19) yr <u>Age at follow-up:</u> Range 10- >50 yr <u>Genetic predisposition:</u> Not reported	<u>CRT:</u> 125/219 (57.1%), of whom all ALL survivors	<u>Survivors with subsequent CNS neoplasms:</u> - 19 (8.7%) had 31 incidentally detected subsequent intracranial neoplasms; 30 suggestive of meningioma - n=6 proven meningiomas after surgical resection - CRT: 18 (14.4%) - No CRT: 1 (1.1%) vestibular schwannoma within a cervical radiation field including the auditory canals <u>Prevalence of subsequent intracranial neoplasms among CRT vs. non-CRT survivors:</u> - <20 Gy: 4 (22.2%) vs. 64 (59.8%) - 20- <30 Gy: 14 (77.8%) vs. 42 (39.3%) - ≥30 Gy: 0 (0.0%) vs. 1 (0.9%) *P=0.0132* - Males: 7 (38.9%) vs. 51 (47.7%) - Females: 11 (61.1%) vs. 56 (52.3%) *P=0.6118* - Age at primary cancer diagnosis 0-4 yr: 12 (66.7%) vs. 73 (68.2%) - Age at primary cancer diagnosis 5-9 yr: 4 (22.2%) vs. 17 (15.9%) - Age at primary cancer diagnosis 10-14 yr: 2 (11.1%) vs. 15 (14.0%) - Age at primary cancer diagnosis 15-19 yr: 0 (0.0%) vs. 2 (1.9%) *P=0.8946*	Five of the survivors with subsequent neoplasms reported general symptoms such as headache or dizziness, not definitely related to the presence of a tumor. **Risk of bias:** - <u>Selection bias:</u> unclear how many patient from the original cohort were included in the study. - <u>Attrition bias:</u> low risk, medical follow-up data available for all survivors. - <u>Detection bias:</u> unclear if the outcome assessors were blinded for important determinants related to the outcome. - <u>Confounding:</u> high risk, only univariable analyses performed.

			- Time from diagnosis 10-19 yr: 0 (0.0%) vs. 2 (1.9%) - Time from diagnosis 20-29 yr: 4 (22.2%) vs. 75 (70.1%) - Time from diagnosis 30-39 yr: 11 (61.1%) vs. 24 (22.3%) - Time from diagnosis 40-49 yr: 3 (16.7%) vs. 6 (5.6%) *P=0.0015*	

Abbreviations: ALL, acute lymphoblastic leukemia; CRT, cranial radiotherapy.

Who needs surveillance?				
Salloum et al. Late morbidity and mortality among medulloblastoma survivors diagnosed across three decades: A report from the Childhood Cancer Survivor Study. J Clin Oncol 2019;731-740.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort study Treatment era: 1970-1990 Follow-up: Median 21 (range 5-44) yr since primary cancer diagnosis	997 childhood medulloblastoma survivors <21 yr at primary cancer diagnosis who survived ≥5 yr since diagnosis Primary cancer diagnosis: Medulloblastoma (100%) Age at primary diagnosis: Median 7 (range 0-21) yr Age at follow up: Mean 29 (range 6-60) yr Genetic predisposition: Not reported	Craniospinal radiation: - Total: 808 (81%) - RT only: 151 (18%) - High-risk multimodal therapy: 225 (27%) - Standard-risk multimodal therapy: 171 (21%) - Other: 284 (34%) Craniospinal radiation dose: - <30 Gy: 272 (32%) - ≥30 Gy: 536 (62%) Cisplatin: 479 (52%) Cisplatin cumulative dose: - 0-<200 mg/m^2: 53 (5%) - ≥200-<400 mg/m^2: 203 (20%) - ≥400 mg/m^2: 196 (20%) Carboplatin: 110 (12%)	Survivors with subsequent CNS neoplasms: - Astrocytoma: 6 (0.60%) - Other glioma: 2 (0.20%) - Benign meningioma: 24 (2.41%) 15-year cumulative incidence (95% CI) of subsequent CNS neoplasms by treatment era: *Menigioma:* - 1970s: 2.0% (0.6-5.4) - 1980s: 2.7% (1.3-4.8) - 1990s: 0.8% (0.2-2.2) *P*=0.11 *Astrocytoma:* - 1990s: 0.8% (0.3-1.9) *P*=0.14 15-year cumulative incidence (95% CI) of subsequent CNS neoplasms by treatment era: *Menigioma:* - Historical therapy (CRT only): 1.5% (0.3-4.7) - High-risk multimodal therapy: 1.0% (0.2-3.2) - Standard-risk multimodal therapy: 3.1% (1.0-7.4)	Subsequent neoplasms were ascertained through self- or proxy-report and confirmed by pathology report or, when not available, confirmed by death certificate or other medical records. Among 90 SNs confirmed, 78 were confirmed by pathology report, eight by medical records, and four on the basis of specificity of self-report. **Risk of bias:** - Selection bias: high risk, 997/1422 (70.1%) from the original cohort of survivors were included in the study group. - Attrition bias: low risk, medical follow-up data available for all survivors. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. Confounding: low risk, CRT analyses were adjusted for follow-up.

		Cyclophosphamide 356 (36%) Cyclophosphamide equivalent dose: - 0-<4.000 mg/m^2: 53 (5%) - ≥4.000-<8.000 mg/m^2: 89 (9%) - ≥8.000 mg/m^2: 436 (44%) Lomustine: 321 (57%) Vincristine: 625 (63%) Etoposide: 196 (20%)	*P*=0.24 *Astrocytoma:* - Historical therapy (CRT only): 0.7% (0.1-3.4) - High-risk multimodal therapy: 0 - Standard-risk multimodal therapy: 1.8% (0.5-4.7) *P*=0.13	

Abbreviations: CNS, central nervous system; CRT, cranial radiotherapy.

Who needs surveillance? At what age or time from exposure should surveillance be initiated?				
Schmiegelow et al. Second malignant neoplasms after treatment of childhood acute lymphoblastic leukemia. J Clin Oncol 2013;31:2469-2476.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective cohort study Treatment era: 1980-2007 Follow-up: Not reported	642 ALL survivors ≤21 years at primary cancer diagnosis with a secondary malignant neoplasm Primary cancer diagnosis: ALL (100%) Age at primary cancer diagnosis: Median 5.2 (50% range 3.2-	CNS radiation: At least 230 (35.8%) Epipodophyllotoxin: At least 185 (28.7%) Cyclophosphamide: At least 312 (48.6%)	ALL patients with secondary CNS neoplasms: - Meningioma: n=22 - Other CNS tumor: n=116 Secondary CNS neoplasms by primary cancer treatment in patients without HSCT: - CNS radiation: 97/109 (89.0%) - No CNS radiation: 12/111 (11.0%) - Epipodophyllotoxin:48/111 (43.2%) - No epipodophyllotoxin: 63/111 (56.8%) - Cyclophosphamide and CNS radiation: 76/108	The original cohort of childhood cancer survivors (including those patients without a secondary malignant neoplasm) is unclear. Unclear how CNS neoplasms were detected. Prognosis: Overall survival after non-meningioma brain tumor did not improve over time,

	10.3) years (total group); Median 4.2 (50% range 2.6-8.7) years (patients with secondary CNS neoplasms) Age at follow-up: Median 14.7 (50% range 11.0-19.2) years at secondary CNS neoplasm diagnosis Genetic predisposition: Not reported		(70.3%) - No cyclophosphamide and CNS radiation: 20/108 (18.5%) - Cyclophosphamide and no CNS radiation: 7/108 (6.5%) - No cyclophosphamide and no CNS radiation: 5/108 (4.6%) - 6-mercaptopurine and CNS radiation: 24/104 (23.1%) - No 6-mercaptopurine and CNS radiation: 68/104 (65.4%) - 6-mercaptopurine and no CNS radiation: 5/104 (4.8%) - No 6-mercaptopurine and no CNS radiation: 7/104 (6.7%) Median time interval from primary cancer diagnosis to secondary CNS tumor: - Meningioma: 16.2 (50% range 12.3-18.3) years - Other CNS tumor: 8.1 (50% range 6.5-9.8) years - CNS radiation vs. no radiation: 9.1 vs. 6.6 years (p=0.01) Median age at secondary CNS tumor diagnosis: - Overall: 14.7 (11.0-19.2) years - Meningioma: 16.2 (12.3-18.3) years - Other CNS tumor: 13.9 (10.5-16.5) years	with 5-year estimates of 19.6% ± 5.5% before 2000 and 16.6% ± 5.3% afterward (*P*=0.76). **Risk of bias:** - Selection bias: unclear how many patients were included in the original cohort of survivors. - Attrition bias: unclear for how many survivors follow-up data was complete. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: high risk, analyses were not adjusted for follow-up, but were stratified by CRT.

Abbreviations: ALL, acute lymphoblastic leukemia; CNS, central nervous system; HSCT, hematopoietic stem cell transplantation.

Who needs surveillance?				
Strodbeck et al. Risk of subsequent cancer following primary CNS tumor. J Neurooncol 2013;112:285-295.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective cohort study	5,456 primary CNS tumor patients ≤19 years at primary cancer diagnosis	Unclear how many pediatric patients were treated with CRT	Primary CNS tumor patients with subsequent CNS neoplasms: - Brain neoplasms: n=10	Unclear how CNS neoplasms were detected.

Treatment era: 1973-2009 Follow-up: Range 2 months - >10 years from primary cancer diagnosis	Primary cancer diagnosis: Pilocytic astrocytoma (21.4%), astrocytoma not otherwise specified (20.0%), astrocytoma grade II and III (7.5%), glioblastoma multiforme (5.7%), oligodendroglioma grade II and III (4.6%), ependymoma (9.3%), mixed glioma (2.2%), glioma not otherwise specified (4.4%), medulloblastoma/PNET (24.5%), meningioma (0.3%) Age at primary cancer diagnosis: Range 0-19 years Age at follow-up: Not reported Genetic predisposition: Not reported		- Cranial nerves/other nervous system neoplasms: n=2 Relative risk (SIR) of subsequent brain neoplasms among medulloblastoma/PNET patients by radiotherapy and latency time: - 1-5 years since primary cancer, radiotherapy (n=1): 13.91 (95% CI 0.35-77.48) - 1-5 years since primary cancer, no radiotherapy (n=0): 0 (95% CI 0-315.85) - 5-10 years since primary cancer, radiotherapy (n=3): 54.2 (95% CI 11.17-158.3) - 5-10 years since primary cancer, no radiotherapy (n=0): 0 (95% CI 0-456.67) - ≥10 years since primary cancer, radiotherapy (n=6): 59.59 (95% CI 21.87-129.7) - ≥10 years since primary cancer, no radiotherapy (n=0): 0 (95% CI 0-397.61) Relative risk (SIR) of subsequent cranial nerves/other nervous system neoplasms among medulloblastoma/PNET patients by radiotherapy and latency time: - ≥10 years since primary cancer, radiotherapy (n=2): 238.15 (95% CI 28.84-860.29) - ≥10 years since primary cancer, no radiotherapy (n=0): 0 (95% CI 0-5025.92) Mean time interval from primary cancer diagnosis to subsequent CNS tumor: - Brain neoplasms: 1-≥10 years - Cranial nerves/other nervous system neoplasms: ≥10 years	**Risk of bias:** - Selection bias: unclear how many patients were included in the original cohort of survivors. - Attrition bias: unclear for how many survivors follow-up data was complete. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: low risk, analyses were adjusted for follow-up.

Abbreviations: CNS, central nervous system; CRT, cranial radiotherapy; PNET, primitive neuroectodermal tumor; SIR, standardized incidence ratio.

Who needs surveillance?				
Swerdlow et al. Risk of Meningioma in European Patients Treated With Growth Hormone in Childhood: Results From the SAGhE Cohort. J Clin Edocrinol Metab 2019;10:658-664.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort study Treatment era: Not reported Follow-up: Total 154.795 person years at risk, mean 14.9 yr per patient since primary diagnosis (also including non-cancer patients)	10,403 patients treated with r-hGH below age 20 yr, of whom 1,830 childhood cancer survivors Primary cancer diagnosis: - CNS tumor: 1307 (12.6%) - Non-CNS solid tumor: 97 (0.9%) - Hematological malignancy: 426 (4.1%) Age at primary diagnosis: Not reported Age at follow up: Not reported Genetic predisposition: Individuals with certain conditions that are very strong predisposing factors for malignancy (e.g., type 1 NF, Fanconi syndrome) were excluded	Cranio(-spinal) radiotherapy: At least 1,165 (63.7%) childhood cancer survivors Chemotherapy: Not reported Surgery: Not reported	Survivors with subsequent meningioma: - Total: n=37 - Primary CNS tumor: n=29 - Primary hematological malignancy n=7 - Primary non-CNS solid tumor: n=1 - Cranio(-spinal) radiotherapy: n=30 SIR for subsequent meningiomas in cancer survivors treated with r-hGH: - Total: 466.3 (95% CI 337.8-643.5) - Male: 464.9 (95% CI 292.9-737.8) - Female: 467.6 (95% CI 298.3-733.1) - Primary CNS tumor: 533.7 (95% CI 370.9-768.0) - Primary hematological malignancy: 319.2 (95% CI 152.2-669.5 - Primary non-CNS solid tumor: 324.1 (95% CI 45.6-2300.6) - Cranio(-spinal) radiotherapy: 658.4 (95% CI 460.4-941.7) SIR for subsequent meningiomas in cancer survivors treated with radiotherapy and r-hGH: Age started GH treatment - 0-4 yr: 1401.5 (95% CI 197.4-9949.0) - 5-9 yr: 782.4 (95% CI 407.1-1503.7) - 10-14 yr: 644.7 (95% CI 411.2-1010.7) - 15-19 yr: 258.1 (95% CI 36.4-1832.1) *P trend = 0.21* Time since started GH treatment - 0-4 yr: 338.0 (95% CI 84.5-1351.4) - 5-9 yr: 197.5 (95% CI 49.4-789.5) - 10-14 yr: 1130.7 (95% CI 669.7-1909.2)	A subtle screening effect might have occurred if improvements in imaging technology over time had caused detection of some meningiomas in the cohort in recent years that were already present but undetected at the time of earlier, lower sensitivity imaging. **Risk of bias:** - Selection bias: high risk, 1830/3224 (57%) of the original cohort have been included in the study group of childhood cancer survivors. - Attrition bias: low risk, cancer incidence follow-up was via cancer registration and highly complete. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome - Confounding: low risk, SIRs were stratified by radiotherapy.

			- 15-19 yr: 857.0 (95% CI 461.1-1592.8) - ≥20 yr: 365.8 (95% CI 91.5-1462.5) *P trend = 0.26* Attained age - 0-9 yr: 0.0 (95% CI 0.0-12,296.3) - 10-19 yr: 487.2 (95% CI 218.9-1084.3) - 20-29 yr: 863.5 (95% CI 563.0-1324.4) - ≥30 yr: 346.7 (95% CI 111.8-1074.8) *P trend = 0.95* Duration of GH treatment - <3 yr: 547.5 (95% CI 273.8-1094.7) - 3-5 yr: 587.3 (95% CI 325.3-1060.5) - ≥6 yr: 998.9 (95% CI 553.2-1803.8) *P trend = 0.19* Mean GH dose - <20 mg/kg/d: 635.1 (95% CI 302.8-1332.2) - 20-29 mg/kg/d: 805.4 (95% CI 500.7-1295.6) - 30-39 mg/kg/d: 425.1 (95% CI 137.1-1318.1) - ≥40 mg/kg/d: 1297.5 (95% CI 182.8-9210.9) *P trend = 0.92* Cumulative GH dose - <25 mg/kg: 511.9 (95% CI 256.0-1023.7) - 25-49 mg/kg: 601.3 (95% CI 323.6-1117.6) - 50-99 mg/kg: 1286.0 (95% CI 712.2-2322.1) - ≥100 mg/kg: 0.0 (95% CI 0.0-4098.8) *P trend = 0.13*	

Abbreviations: CNS, central nervous system; r-hGH, recombinant growth hormone; SIR, standardized incidence ratio.

Who needs surveillance? At what age or time from exposure should surveillance be initiated? At what frequency should surveillance be performed?				
Taylor et al. Survival after second primary neoplasms of the brain or spinal cord in survivors of childhood cancer: results from the British Childhood Cancer Survivor Study. J Clin Oncol 2009;27:5781-5787. ***Taylor et al.*** Population-based risks of CNS tumors in survivors of childhood cancer: The British Childhood Cancer Survivor Study. J Clin Oncol 2010;28:5287-93.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective	17,980 childhood cancer	Radiotherapy:	Childhood cancer survivors with subsequent CNS	243 out of 247 cases were matched to

cohort and nested case-control study Treatment era: 1940-1991 Follow-up: Mean 17.3 years; 310,816 person-years of follow-up from 5-year survival	survivors <15 years at primary cancer diagnosis who survived ≥5 years after diagnosis 247 cases with a subsequent CNS tumor matched to 247 childhood cancer controls Primary cancer diagnosis: Leukemia (27.0%), CNS tumor (22.9%), genetic retinoblastoma (3.1%), nongenetic retinoblastoma (3.6%), lymphoma (12.3%), other (31.2%) Age at primary cancer diagnosis: Range 0-14 years Age at follow-up: Not reported Genetic predisposition: 26 (0.14%)	9223 (51.3%) No radiotherapy: 3835 (21.3%) Chemotherapy: 6633 (36.9%) No chemotherapy: 6038 (33.6%) *(Treatment data of total cohort)*	neoplasms: - Glioma: n=73 12 (16.4%) genetic predisposition - Meningioma: n=137 5 (3.6%) genetic predisposition - Schwannoma: n=16 5 (31.3%) genetic predisposition - PNET: n=9 0 (0.0%) genetic predisposition - Other: n=12 4 (33.3%) genetic predisposition 40-yr cumulative incidence subsequent CNS neoplasms: - Overall: 3.6% (95% CI 2.9-4.3) - Gliomas: 0.8% (95% CI 0.6-1.2) - Meningiomas: 2.3% (95% CI 1.8-3.0) - Patients treated with CNS radiotherapy: 9.1% (95% CI 7.9-11.7) - Gliomas in patients treated with CNS radiotherapy: 2.4% (95% CI 1.3-4.1) - Meningiomas in patients treated with CNS radiotherapy: 6.3% (95% CI 4.5-8.5) - Patients treated without CNS radiotherapy: 1.4% (95% CI 0.6-2.8) (p<0.001 radiotherapy) SIRs subsequent glioma: - All (n=73): 10.8 (95% CI 8.5-13.6) - Males (n=37): 9.0 (95% CI 6.4-12.5) - Females (n=36): 13.4 (95% CI 9.4-18.6) (p=0.09 sex) - Age at primary cancer diagnosis 0-4 years (n=34): 12.0 (95% CI 8.3-16.8) - Age at primary cancer diagnosis 5-9 years (n=21): 12.3 (95% CI 7.6-18.9) - Age at primary cancer diagnosis 10-14 years (n=18): 8.0 (95% CI 4.8-12.7) (p=0.31 age primary cancer diagnosis) - Radiotherapy (n=57): 14.3 (95% CI 10.9-18.7) - No radiotherapy (n=11): 6.1 (95% CI 3.1-11.0)	controls by age at primary cancer, sex, and time since primary cancer diagnosis. Unclear how CNS neoplasms were detected. Genetic risk includes known hereditary brain tumor syndromes neurofibromatosis types 1 and 2, Gorlin's syndrome, tuberous sclerosis, Von Hippel-Lindau syndrome, and any syndrome known to increase risk of brain or spinal cord tumors. Potential overlap in patients with Reulen 2011. **Risk of bias:** - Selection bias: low risk, 17,980 out of 17,981 (99.99%) eligible survivors were included in the study. - Attrition bias: low risk, medical follow-up data available for 17,980 out of 17,980 (100%) survivors. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: low risk, analyses were adjusted for CRT and follow-up; and cases well-matched to controls.

			(p=0.008 radiotherapy) - Chemotherapy (n=30): 15.3 (95% CI 10.3-21.9) - No chemotherapy (n=36): 10.2 (95% CI 7.1-14.1) (p=0.096 chemotherapy) <u>AERs subsequent glioma:</u> - All (n=73): 2.1 (95% CI 1.6-2.7) - Males (n=37): 1.9 (95% CI 1.2-2.7) - Females (n=36): 2.3 (95% CI 1.5-3.2) - Age at primary cancer diagnosis 0-4 years (n=34): 2.1 (95% CI 1.3-2.9) - Age at primary cancer diagnosis 5-9 years (n=21): 2.4 (95% CI 1.3-3.5) - Age at primary cancer diagnosis 10-14 years (n=18): 1.9 (95% CI 0.9-2.9) - Radiotherapy (n=57): 3.0 (95% CI 2.1-3.8) - No radiotherapy (n=11): 1.2 (95% CI 0.3-2.0) - Chemotherapy (n=30): 2.6 (95% CI 1.6-3.6) - No chemotherapy (n=36): 2.3 (95% CI 1.5-3.2) <u>ERRs subsequent glioma and PNET per Gy:</u> - Linear increase with increased cumulative radiotherapy dose: β 0.079 (95% CI 0.021-0.229) per Gy ($p<0.001$) - For intrathecal methotrexate, alkylating agents, anthracyclines, nonintrathecal antimetabolites, epipodophyllotoxins and vinca alkaloids no significant variations in ERR <u>ERRs subsequent meningioma per Gy:</u> - Linear increase with increasing radiotherapy dose: β 5.1 (95% CI 0.7-107.7) per Gy ($p<0.001$) - Linear increase with increasing radiotherapy dose and intrathecal methotrexate dose: β 2.2 (95% CI 0.1-64.4) per mg/m^2 ($p=0.015$) - For alkylating agents, anthracyclines, nonintrathecal antimetabolites, epipodophyllotoxins and vinca alkaloids no significant variations in ERR	

			Relative risk of subsequent glioma and PNET across different levels of radiotherapy exposure compared to no exposure (unadjusted): - 0.01-9.99 Gy: 0.5 (95% CI 0.2-1.5) - 10.0-19.99 Gy: 0.5 (95% CI 0.1-2.3) - 20.00-29.99 Gy: 2.6 (95% CI 0.9-8.0) - 30.00-39.99 Gy: 3.4 (95% CI 0.5-23.0) - ≥40.00 Gy: 4.4 (95% CI 1.2-16.4) Relative risk of subsequent meningioma across different levels of radiotherapy exposure compared to no exposure adjusted for intrathecal methotrexate: - 0.01-9.99 Gy: 1.8 (95% CI 0.8-39.3) - 10.0-19.99 Gy: 8.4 (95% CI 6.4-10.7) - 20.00-29.99 Gy: 51.6 (95% CI 5.5-69.5) - 30.00-39.99 Gy: 567.9 (95% CI 29.3-773.6) - ≥40.00 Gy: 479.1 (95% CI 25.0-657.2) Relative risk of subsequent meningioma across different levels of intrathecal methotrexate exposure compared to no exposure adjusted for radiotherapy: - 1-39 mg/m^2: 15.4 (95% CI 2.2-179.6) - 40-69 mg/m^2: 10.8 (95% CI 1.3-143.0) - ≥70 mg/m^2: 35.6 (95% CI 4.8-599.4) Mean time interval from primary cancer diagnosis to subsequent CNS tumor: - Glioma (n=73): 17.4 years - Low-grade glioma (n=31): 15.5 years - High-grade glioma (n=42): 18.7 years - Meningioma (n=137): 23.1 years - Low-grade meningioma (n=129): 23.5 years - High-grade meningioma (n=8): 15.9 years - Schwannoma (n=16): 20.0 years - PNET (n=9): 9.2 years SIRs subsequent glioma over time: - 0-4 years follow-up (n=27): 20.6 (95% CI 13.6-30.1) - 5-9 years follow-up (n=9): 7.5 (95% CI 3.4-14.3)	

			- 10-14 years follow-up (n=11): 11.0 (95% CI 5.5-19.7) - 15-19 years follow-up (n=11): 12.5 (95% CI 6.2-22.3) - 20-29 years follow-up (n=10): 7.2 (95% CI 3.5-13.3) - ≥30 years follow-up (n=5): 5.0 (95% CI 1.6-11.7) (p=0.0032) AERs subsequent glioma over time: - 0-4 years follow-up (n=27): 3.0 (95% CI 1.8-4.2) - 5-9 years follow-up (n=9): 1.0 (95% CI 0.3-1.8) - 10-14 years follow-up (n=11): 1.8 (95% CI 0.6-3.0) - 15-19 years follow-up (n=11): 2.6 (95% CI 0.9-4.2) - 20-29 years follow-up (n=10): 2.1 (95% CI 0.6-3.6) - ≥30 years follow-up (n=5): 2.6 (95% CI 0.0-5.5)	

Abbreviations: AER, absolute excess risk; CNS, central nervous system; ERR, excess relative risk; PNET, primitive neuroectodermal tumor; SIR, standardized incidence ratio.

Who needs surveillance? At what age or time from exposure should surveillance be initiated? At what frequency should surveillance be performed?				
Turcotte et al. Temporal Trends in Treatment and Subsequent Neoplasm Risk Among 5-Year Survivors of Childhood Cancer, 1970-2015. *JAMA*. 2017;317(8):814-824				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort study Treatment era 1970- 1999 Follow-up Mean 20.5±7.5 yr from primary cancer diagnosis; Person-years at risk: 374,638	23,603 childhood cancer survivors diagnosed <21 years Primary cancer diagnosis: Leukemia (39.4%), lymphoma (18.3%), CNS (15.7%), Wilms tumor (8.0%), bone cancer (7.4%), neuroblastoma (6.8%), rhabdomyosarcoma (4.3%) Age at primary diagnosis: Mean 7.7±6.0 yr	Any radiotherapy: 12,400 (53.1%) Radiotherapy dose: Median 26.0 Gy (interquartile range 18.0-45.0) Any chemotherapy: 17,978 (84.3%) Median cyclophosphamide equivalent dose: 7,395 mg/m^2 (interquartile range 3,218-1,2105) Median anthracycline dose:	Subsequent CNS neoplasms: - n=233 benign meningioma - n=7 malignant meningioma - n=82 glial tumors - n=7 medulloblastoma/PNET - n=11 other CNS neoplasms SIRs for subsequent CNS neoplasms: - Any malignant CNS tumor: 10.9 (95% CI 7.8-15.2) - Glial tumors: 11.0 (95% CI 9.0-13.4) - Medulloblastoma: 8.3 (95% CI 3.9-15.5) Reference absolute rates per 1000 person-years for meningioma: 0.16 (95% CI 0.06-0.41) Relative rates for subsequent meningioma in multivariable analysis:	Unclear how subsequent CNS neoplasms were detected. Subsequent neoplasms were identified via self- or next of-kin proxy report or death certificate and confirmed by pathology report or, when unavailable, death certificate, medical records, or both. Selected primary diagnoses, including retinoblastoma, germ cell tumor, and hepatoblastoma, were not included. Children with heritable retinoblastoma are at significant risk of subsequent neoplasms, and their exclusion may have resulted in underestimation of subsequent malignancy risk.

	Age at follow-up: Not reported Genetic predisposition: Not reported	186 mg/m^2 (interquartile range 105-320) Median epipodophyllotoxin dose: 2,000 mg/m^2 (interquartile range 1,000-4,688) Median platinum agent dose: 503 mg/m^2 (interquartile range 340-1,255)	- Maximum radiation treatment dose to any body region 0.1-10 Gy vs. none: 24.39 (95% CI 4.42-134.44) - Maximum radiation treatment dose to any body region 10.1-20 Gy vs. none: 14.77 (95% CI 5.89-37.03) - Maximum radiation treatment dose to any body region 20.1-30 Gy vs. none: 23.44 (95% CI 9.85-55.79) - Maximum radiation treatment dose to any body region 30.1-40 Gy vs. none: 10.91 (95% CI 3.60-33.05) - Maximum radiation treatment dose to any body region 40.1-50 Gy vs. none: 23.80 (95% CI 9.32-60.80) - Maximum radiation treatment dose to any body region ≥50.1 Gy vs. none: 34.93 (95% CI 14.20-85.93) - Cyclophosphamide equivalent dose 1-3999 mg/m^2 vs. none: 0.51 (95% CI 0.27-0.97) - Cyclophosphamide equivalent dose 4000-7999 mg/m^2 vs. none: 1.00 (95% CI 0.56-1.81) - Cyclophosphamide equivalent dose ≥8000 mg/m^2 vs. none: 0.54 (95% CI 0.34-0.88) - Anthracycline dose 1-100 mg/m^2 vs. none: 1.10 (95% CI 0.42-2.85) - Anthracycline dose 101-300 mg/m^2 vs. none: 0.59 (95% CI 0.32-1.10) - Anthracycline dose >300 mg/m^2 vs. none: 0.58 (95% CI 0.33-1.03) - Epipodophyllotoxin dose 1-1000 mg/m^2 vs. none: 1.88 (95% CI 0.78-4.51) - Epipodophyllotoxin dose 1001-4000 mg/m^2 vs. none: 1.15 (95% CI 0.34-3.87) - Epipodophyllotoxin dose >4000 mg/m^2 vs. none: 1.73 (95% CI 0.69-4.36) - Platinum dose 1-400 mg/m^2 vs. none: 2.93 (95% CI	Risk of bias - Selection bias: high risk, 32,603/35,923 (66%) of eligible survivors included in the study. - Attrition bias: unclear for how many survivors follow-up data was complete. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: low risk, analyses were adjusted for CRT and follow-up.

			1.37-6.27) - Platinum dose 401-750 mg/m^2 vs. none: 2.28 (95% CI 0.88-5.92) - Platinum dose >750 mg/m^2 vs. none: 3.12 (95% CI 0.92-10.59) - History of splenectomy yes vs. no: 0.10 (95% CI 0.02-0.42) - Female vs. male: 1.40 (95% CI 1.00-1.95) - Age at diagnosis 5-9 yr vs. 0-4 yr: 0.59 (95% CI 0.38-0.92) - Age at diagnosis 10-14 yr vs. 0-4 yr: 0.19 (95% CI 0.11-0.33) - Age at diagnosis ≥15 yr vs. 0-4 yr: 0.14 (95% CI 0.07-0.27) - Year of diagnosis per 5 yr: 0.93 (95% CI 0.86-1.00) <u>Time interval from primary cancer diagnosis to subsequent CNS neoplasm:</u> - Any: Median 10.9 (interquartile range 7.8-15.2) yr - Glial tumors: Median 9.4 (interquartile range 7.4-13.2) yr - Medulloblastoma: Median 9.2 (interquartile range 8.8-13.8) yr	

Abbreviations: CNS, central nervous system; CRT, cranial radiotherapy.

Who needs surveillance? At what age or time from exposure should surveillance be initiated? At what frequency should surveillance be performed?				
Vinchon et al. Radiation-induced tumors in children irradiated for brain tumor: a longitudinal study. Childs Nerv Syst 2011;27:445-453.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective cohort study <u>Treatment era:</u> 1970-2009	552 childhood brain tumor patients <18 years at primary cancer diagnosis <u>Primary cancer diagnosis:</u>	<u>Radiotherapy:</u> 522 (100%) <u>Radiotherapy dose:</u> Median 54.0 (range 36-68) Gy	<u>Brain tumor patients with subsequent CNS neoplasms:</u> - Overall: n=95 in 42 patients - Meningioma: n=26 - Malignant glioma: n=2 - Meningosarcoma: n=1	552 brain tumor patients included in the study; 193 died of progression of the primary tumor; 20 died of other causes, including 3 malignant radiation-induced neoplasms.

Follow-up of 309 survivors: Median 94.3 (range 0.6-27.1) months	Brain tumor (100%) Age at irradiation: Mean 8.3 (range 0.7-17.8) years Age at follow-up: Not reported Neurofibromatosis type 1: 39 (7.5%)		- Cavernoma: n=60 - Thyroid tumor: n=6 Cumulative incidence subsequent CNS neoplasms in meningioma survivors: - 5-year: 0.1% - 10-year: 1.8% - 20-year: 28.9% - 5-year max. radiotherapy dose ≥52.5 Gy vs. <52.5 Gy: 0.0% vs. 0.0% - 10-year max. radiotherapy dose ≥52.5 Gy vs. <52.5 Gy: 5.1% vs. 0.0% - 20-year max. radiotherapy dose ≥52.5 Gy vs. <52.5 Gy: 29.5% vs. 19.1% p=0.035 for radiotherapy dose - 5-year male vs. female: 0.0% vs. 0.0% - 10-year male vs. female: 2.7% vs. 0.1% - 20-year male vs. female: 24.0% vs. 18.6% p=0.071 for gender - 5-year <8.1 years vs. >8.1 years: 0.0% vs. 1.1% - 10-year <8.1 years vs. >8.1 years: 0.9% vs. 3.0% - 20-year <8.1 years vs. >8.1 years: 25.2% vs. 13.2% p=0.60 for age at primary cancer diagnosis	6 patients were diagnosed with a secondary thyroid tumor. Unclear how CNS neoplasms were detected. Imaging is mentioned but unclear if this was for surveillance or for symptoms. **Risk of bias:** - Selection bias: unclear how many patients were included in the original cohort of survivors. - Attrition bias: unclear for how many survivors follow-up data was complete. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: low risk, CRT analyses were adjusted for follow-up; high risk for other analyses since no adjustment for CRT.

Abbreviations: CNS, central nervous system.

Who needs surveillance? At what age or time from exposure should surveillance be initiated?				
Walter et al. Secondary brain tumors in children treated for acute lymphoblastic leukemia in St Jude Children's Research Hospital. J Clin Oncol 1998;16:3761-3767.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective cohort study Treatment era: 1967-1988	1,612 ALL patients ≤18 years at primary cancer diagnosis Primary cancer diagnosis: ALL (100%)	Based on St Jude ALL research program studies V-XI (1967-1988) CRT: - None: 361 (22.4%)	ALL survivors with subsequent CNS neoplasms: - Overall: n=22 in 21 patients - Glioblastoma multiforme: n=4 - Anaplastic astrocytoma: n=2 - Other high-grade glioma: n=4 - Low-grade oligodendroglioma: n=1	Unclear how CNS neoplasms were detected. In the abstract the authors mentioned that the proportion of low-grade tumors in their study is probably higher than in other samples because of the exhaustive long-term follow-up

Follow-up: Median 15.9 (range 5.5-29.9) years	Age at primary cancer diagnosis: 0-5 years: n=946 >5 years: n=666 Age at follow-up: Not reported Genetic predisposition: Not reported	- 10-21 Gy: 386 (23.9%) - >21-30 Gy: 793 (49.2%) - >30 Gy*: 62 (3.8%) Chemotherapy: methotrexate, epipodophyllotoxins, cytarabine, hydrocortisone Intrathecal chemotherapy administrations**: - None: n=119 - 1-10: n=839 - >10: n=654 Treatment by era: - 1967-1979 (n=826): Majority 24 Gy CRT and intrathecal methotrexate - 1979-1983 (n=428): 24 Gy CRT for high-risk patients and 18 Gy or no CRT for low-risk patients, and intrathecal methotrexate and epipodophyllotoxins - 1984-1988 (n=358): 18 Gy CRT for higher risk patients and 24 Gy for CNS leukemia, and triple intrathecal chemotherapy (methotrexate, hydrocortisone, cytarabine) replaced single-agent methotrexate - Patients with isolated	- Meningioma: n=11 in 10 patients 20-yr cumulative incidence subsequent CNS neoplasms in ALL patients: - Overall: 1.39% (95% CI 0.63-2.15) - 0 Gy vs. 10-21 Gy vs. >21-30 Gy vs. >30 Gy CRT: 0% vs. 1.03% vs. 1.65% vs. 3.23%; p=0.015 - CNS ALL vs. other ALL: 4.17 % vs. 1.25%; p=0.002 - Age 0-5 years vs. >5 years at primary cancer diagnosis: 1.98 % vs. 0.53%; p=0.104 - Males vs. females: 1.35% vs. 1.45%; p=0.474 - 0 vs. 1-10 vs. >10 intrathecal administrations: 0.84% vs. 1.6% vs. 0.96%; p=0.234 20-yr cumulative incidence subsequent high-grade CNS neoplasms in ALL patients: - 0 Gy vs. 10-21 Gy vs. >21-30 Gy vs. >30 Gy CRT: 0% vs. 1.03% vs. 0.76% vs. 3.23%; p=0.043 - CNS ALL vs. other ALL: 2.78 % vs. 0.60%; p=0.014 - Age 0-5 years vs. >5 years at primary cancer diagnosis: 1.08 % vs. 0.15%; p=0.045 - males vs. females: 0.76% vs. 0.63%; p=0.803 - 0 vs. 1-10 vs. >10 intrathecal administration: 0 % vs. 0.74% vs. 0.81%; p=0.625 Risk factors subsequent CNS tumor in stratified analysis in ALL patients: - CRT dose significant prognostic factor for subsequent CNS tumor after adjustment for CNS disease at primary ALL diagnosis (p=0.038; no effect measure reported) - Primary diagnosis of CNS ALL significant prognostic factor for subsequent CNS tumor after adjustment for radiation dose (p=0.007; no effect measure reported) Time interval from primary cancer diagnosis to subsequent CNS tumor: - Overall (n=22 neoplasms in 21 patients): Mean 12.6	evaluation. *Patients who had CRT at doses >30 Gy most likely represent the group who had both initial CRT (18 or 24 Gy) and later craniospinal axis radiation for an isolated cranial relapse. These patients have a worse prognosis/life expectancy owing to the relapse, and thus less patient-years at risk to develop a CNS tumor years/decades later. In theory one would expect risk estimates to be underestimated (death = competing risk). In this study, survival rates of the cohort by RT dose group are not reported. It is possible but not certain that the risk is overestimated in the high-dose group. **Intrathecal chemotherapy administrations: methotrexate only for cohort treated 1967-1983 and triple-agent (methotrexate, hydrocortisone, cytarabine) for patients treated 1984-1988 (Protocol XI). Prognosis: - 11 out of 11 (100%) patients with low-grade neoplasms (n=10 with meningioma and n=1 with low-grade oligodendroglioma) are alive with a median survival of 2.5 (range 0.5-10) years after subsequent CNS tumor diagnosis. - 8 out of 10 (80.0%) patients with high-grade neoplasms have died with a median survival of 7 (range 0.1-25) months after subsequent CNS tumor diagnosis. - 2 out of 10 (20.0%) patients with high-

		CNS relapse craniospinal radiotherapy and systemic chemotherapy with or without intrathecal chemotherapy	(range 5.9-29) years - Meningioma (n=11): Median 19 years - High-grade glioma (n=10): Median 9.1 years Cumulative incidence subsequent CNS neoplasms over time: - Meningioma (n=11): cumulative incidence increases over a follow-up time of 30 years since diagnosis - High-grade glioma (n=10): cumulative incidence increased over a follow-up time of 14 years since diagnosis and remained stable after longer follow-up	grade neoplasms are alive with survival 5 months and 7.8 years after subsequent CNS tumor diagnosis, respectively. **Risk of bias:** - Selection bias: unclear how many patients were included in the original cohort of survivors. - Attrition bias: low risk, 97.1% of surviving ALL patients have been contacted in 2 years before the analysis, but numbers not reported. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: low risk for CRT analyses, because adjustment for follow-up; high risk for other analyses because no adjustment for CRT.

Abbreviations: ALL, acute lymphoblastic leukemia; CNS, central nervous system; CRT, cranial radiotherapy.

Who needs surveillance? At what age or time from exposure should surveillance be initiated? At what frequency should surveillance be performed?				
Neglia et al. New primary neoplasms of the central nervous system in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Natl Cancer Inst 2006;98:1528-37.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Nested case-control study Treatment era: 1970-1986 Follow-up: Range 5 - ≥15 years since primary cancer diagnosis	14,361 childhood cancer survivors <21 years at primary cancer diagnosis who survived ≥5 years after diagnosis 116 cases with a subsequent CNS tumor matched to 464 childhood cancer survivor controls	**Cases** Radiotherapy: 107 (92.2%) Surgery only: 1 (0.9%) Radiotherapy only: 1 (0.9%)	CAYA cancer survivors with subsequent CNS neoplasms: - Glioma: n=40 - Meningioma: n=66 - PNET: n=6 - CNS lymphoma: n=1 - Other: n=3 SIRs subsequent glioma: - All (n=40): 8.66 (95% CI 6.24-11.6)	Cases and controls were matched by age at primary cancer, sex, and time since primary cancer diagnosis. Unclear how many patients were treated with cranial radiotherapy. Risk factor analyses were adjusted for primary cancer diagnosis; all chemotherapy data were adjusted for

	Primary cancer diagnosis of cases: Leukemia (51.7%), CNS tumor (31.0%), Hodgkin lymphoma (8.8%), non-Hodgkin lymphoma (4.3%), Wilms tumor (0.9%), neuroblastoma (1.7%), soft tissue sarcoma (4.3%), bone tumors (1.7%) Age at primary cancer diagnosis: Range 0-20 years Age at follow-up: Range 5-40 years Genetic predisposition: Not reported	Chemotherapy only: 1 (0.9%) Surgery and radiotherapy: 23 (19.8%) Surgery and chemotherapy: 3 (2.6%) Radiotherapy and chemotherapy: 27 (23.3%) Surgery, radiotherapy and chemotherapy: 56 (48.3%) **Controls** Radiotherapy: 309 (66.6%) Surgery only: 30 (6.5%) Radiotherapy only: 0 (0.0%) Chemotherapy only: 26 (5.6%) Surgery and radiotherapy: 48 (10.3%) Surgery and chemotherapy: 64 (13.8%) Radiotherapy and	- Males (n=26): 9.64 (95% CI 6.39-13.8) - Females (n=14): 7.28 (95% CI 4.10-11.8) - Age at primary cancer diagnosis 0-4 years (n=25): 14.5 (95% CI 9.56-21.0) - Age at primary cancer diagnosis 5-9 years (n=7): 7.48 (95% CI 3.21-14.5) - Age at primary cancer diagnosis 10-14 years (n=6): 6.24 (95% CI 2.48-12.6) - Age at primary cancer diagnosis 15-20 years (n=2): 1.99 (95% CI 0.33-6.16) - Radiotherapy and chemotherapy (n=31): 12.9 (95% CI 8.88-18.0) - Radiotherapy only (n=7): 11.2 (95% CI 4.8-21.6) - Chemotherapy only (n=1): 1.01 (95% CI 0.06-4.46) - No radiotherapy or chemotherapy (n=1): 2.9 (95% CI 0.17-12.8) EARs subsequent glioma per 10,000 person-years: - All (n=40): 19.3 (95% CI 13.2-26.8) - Males (n=26): 24.5 (95% CI 15.3-36.4) - Females (n=14): 13.7 (95% CI 6.79-23.6) - Age at primary cancer diagnosis 0-4 years (n=25): 31.9 (95% CI 20.2-47.2) - Age at primary cancer diagnosis 5-9 years (n=7): 15.0 (95% CI 5.11-31.1) - Age at primary cancer diagnosis 10-14 years (n=6): 13.6 (95% CI 3.83-30.2) - Age at primary cancer diagnosis 15-20 years (n=2): 3.07 (95% CI -2.06-15.9) - Radiotherapy and chemotherapy (n=31): 29.6 (95% CI 19.6-42.2) - Radiotherapy only (n=7): 27.5 (95% CI 10.3-55.6) - Chemotherapy only (n=1): 0.03 (95% CI -2.36-8.66) - No radiotherapy or chemotherapy (n=1): 4.96 (95% CI -2.17-30.7) Risk factors glioma in conditional logistic regression analysis adjusted for primary cancer diagnosis: - Radiotherapy yes vs. no: OR 6.78 (95% CI 1.54-29.7)	radiation dose. With adjustment for radiotherapy dose, type of primary cancer was not significantly associated with the risk of subsequent CNS neoplasms. Unclear how CNS neoplasms were detected. **Risk of bias:** - Selection bias: high risk, 14,361 out of 20,720 (69.3%) eligible survivors were included in the study. - Attrition bias: unclear for how many survivors follow-up data was complete, probably all patients? - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: low risk, analyses were adjusted for follow-up; and cases well-matched to controls.

		<u>chemotherapy:</u> 63 (13.6%) <u>Surgery, radiotherapy and chemotherapy:</u> 198 (42.7%)	- Radiotherapy 1-9.9 Gy vs. <1 Gy: OR 0.0 (95% CI 0.0-5.17) - Radiotherapy 10-19.9 Gy vs. <1 Gy: OR 7.61 (95% CI 1.49-38.8) - Radiotherapy 20-29.9 Gy vs. <1 Gy: OR 6.68 (95% CI 1.47-30.3) - Radiotherapy 30-44.9 Gy vs. <1 Gy: OR 21.0 (95% CI 3.11-142.3) - Radiotherapy >45 Gy vs. <1 Gy: OR 17.5 (95% CI 2.86-107.5) - Alkylating agents yes vs. no: OR 1.10 (95% CI 0.45-2.66) - Anthracyclines yes vs. no: OR 0.90 (95% CI 0.37-2.20) - Epipodophyllotoxins yes vs. no: OR 2.43 (95% CI 0.63-9.32) - Platinum agents yes vs. no: OR 1.99 (95% CI 0.20-19.8) - 6-mercaptopurine or 6-thioguanine yes vs. no: OR 0.75 (95% CI 0.13-4.45) <u>Risk factors meningioma in conditional logistic regression analysis adjusted for primary cancer diagnosis:</u> - Radiotherapy yes vs. no: OR 9.94 (95% CI 2.17-45.6) - Radiotherapy 1-9.9 Gy vs. <1 Gy: OR 0.0 (95% CI 0.0-15.8) - Radiotherapy 10-19.9 Gy vs. <1 Gy: OR 12.0 (95% CI 1.42-100.7) - Radiotherapy 20-29.9 Gy vs. <1 Gy: OR 21.6 (95% CI 3.13-149.3) - Radiotherapy 30-44.9 Gy vs. <1 Gy: OR 96.3 (95% CI 10.32-899.3) - Radiotherapy >45 Gy vs. <1 Gy: OR 58.0 (95% CI 6.02-559.0) - Alkylating agents yes vs. no: OR 0.85 (95% CI 0.34-2.09) - Anthracyclines yes vs. no: OR 0.33 (95% CI 0.11-1.04)	

			- Epipodophyllotoxins yes vs. no: OR 2.19 (95% CI 0.29-16.7) - Platinum agents yes vs. no: OR 3.07 (95% CI 0.17-55.7) - 6-mercaptopurine or 6-thioguanine yes vs. no: OR 1.37 (95% CI 0.26-7.21) <u>ERRs subsequent glioma per Gy:</u> - All: 0.33 (95% CI 0.07-1.71) - Males: 0.48 (95% CI -0.48-1.43) - Females: 0.23 (95% CI -0.25-0.71) - Age <5 years at exposure: 0.64 (95% CI 0.12-5.66) - Age 5-10 years at exposure: 0.10 (95% CI -0.2-0.39) - Age 10-20 years at exposure: 0.15 (95% CI -0.23-0.52) <u>ERRs subsequent meningioma per Gy:</u> - All: 1.06 (95% CI 0.21-8.15) - Males: 3.99 (95% CI not reliable) - Females: 0.41 (95% CI -0.49-1.32) - Age <5 years at exposure: 0.75 (95% CI 0.11-6.59) - Age 5-10 years at exposure: 1.99 (95% CI 0.28-21.12) - Age 10-20 years at exposure: 1.36 (95% CI 0.10-30.69) <u>Median time interval from primary cancer diagnosis to subsequent CNS tumor:</u> - All CNS neoplasms (n=116): 14 (range 5-28) years - Glioma (n=40): 9 years - Meningioma (n=66): 17 years <u>Median age at subsequent CNS tumor diagnosis:</u> - All CNS neoplasms: 20.5 years - Glioma: 15.0 years - Meningioma 25.5 years <u>Incidence subsequent CNS neoplasms over time:</u> - 21 out of 40 (52.5%) gliomas occurred 5-10 years after primary cancer diagnosis; 4 out of 40 (0.1%)	

			occurred >15 years - 47 out of 66 (71.2%) meningiomas occurred >15 years after primary cancer diagnosis <u>SIRs subsequent glioma over time:</u> - 5-9 years from primary cancer diagnosis (n=21): 13.9 (95% CI 8.79-20.8) - 10-14 years from primary cancer diagnosis (n=15): 11.2 (95% CI 6.43-17.8) - 15-20 years from primary cancer diagnosis (n=3): 3.04 (95% CI 0.76-7.88) - ≥20 years from primary cancer diagnosis (n=1): 1.28 (95% CI 0.07-5.63) <u>EARs subsequent glioma per 10,000 person-years over time:</u> - 5-9 years from primary cancer diagnosis (n=21): 30.8 (95% CI 18.5-47.0) - 10-14 years from primary cancer diagnosis (n=15): 23.9 (95% CI 12.8-39.5) - 15-20 years from primary cancer diagnosis (n=3): 5.25 (95% CI -0.63-17.7) - ≥20 years from primary cancer diagnosis (n=1): 0.90 (95% CI -3.00-14.9) <u>ERRs subsequent glioma per Gy over time:</u> - 5-9 years from exposure: 0.45 (95% CI -0.46-1.36) - 10-14 years from exposure: 0.18 (95% CI -0.2-0.56) <u>ERR subsequent meningioma per Gy over time:</u> - 5-9 years from exposure: 0.05 (95% CI -0.14-0.25) <u>ERRs subsequent CNS tumor per Gy over time:</u> - 5-9 years from exposure: 0.39 (95% CI 0.08-2.33) - 10-14 years from exposure: 0.45 (95% CI -0.1-2.97) - >15 years from exposure: 2.07 (95% CI 0.36-39.3)	

Abbreviations: CNS, central nervous system; EAR, excess absolute risk; ERR, excess relative risk; PNET, primitive neuroectodermal tumor; SIR, standardized incidence ratio.

At what age or time from exposure should surveillance be initiated?				
Banerjee et al. Radiation-induced meningiomas: A shadow in the success story of childhood leukemia. Neuro-Oncology 2009;11:534-549.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Retrospective cohort study Treatment era: Not reported Follow-up: >10 yr	60 ALL survivors treated with CRT who are >10 yr post-treatment and aged >18 yr at follow-up Primary cancer diagnosis: ALL (100%) Age at primary cancer diagnosis: Meningioma cases: Range 1-8 yr Age at follow-up: Not reported Genetic predisposition: Not reported	No treatment data available of cohort of survivors CRT dose of meningioma cases: Range 21-46 Gy	Survivors with subsequent meningioma: 11 (22.4%) Time interval from primary cancer diagnosis to subsequent meningioma: Range 14-34 yr	As a part of different research projects, the patients have been followed with brain MRI since 1991, although the follow-up has not been systematic. Four patients presented with neurological symptoms: one with generalized seizures, and the others with headache and visual disturbances. Three patients had multiple meningiomas. The meningiomas were significantly larger in diameter if diagnosed at time of symptomatology (mean, 51 mm vs. 23 mm; *p*=0.001) Prognosis: None of the patients have died yet, and except for three patients, the postoperative morbidity has been low. **Risk of bias:** - Selection bias: unclear how many patients were included in the original cohort of survivors. - Attrition bias: low risk, for 49 (81.7%) patients follow-up was complete. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: not applicable, only latency time reported.

Abbreviations: ALL, acute lymphoblastic leukemia; CRT, cranial radiotherapy.

At what age or time from exposure should surveillance be initiated?				
Bilginer et al. De novo formation of brain tumors in pediatric population following therapeutic cranial irradiation. Childs Nerv Syst 2015;31:893-899.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective cohort study Treatment era: 2000-2012 Follow-up: >2 years since primary cancer diagnosis	6 patients ≤18 years at primary cancer diagnosis treated with radiotherapy who survived >2 years since primary cancer diagnosis and developed a secondary neoplasm in the radiotherapy field Primary cancer diagnosis: ALL (16.7%), non-Hodgkin lymphoma (16.7%), pilocytic astrocytoma (33.3%), craniopharyngioma (16.7%), astrocytoma (16.7%) Age at primary cancer diagnosis: Mean 7.3 (range 4-12) years Age at follow-up: Mean 18 (range 10-28) years Genetic predisposition: 0 (0%)	CRT: 6 (100%) CRT dose: 18-54 Gy	Survivors with subsequent CNS neoplasms: - Meningeal sarcoma: n=1 - High-grade glial tumor: n=2 - High-grade malignant mesenchymal tumor: n=1 - High-grade medulloblastoma: n=2 Mean time interval from radiotherapy to subsequent CNS neoplasm: - Overall (n=6): 9.5 (range 5-18) years - Meningeal sarcoma (n=1): 18 years - High-grade glial tumor (n=2): 6 and 11 years - High-grade malignant mesenchymal tumor (n=1): 9 years - High-grade medulloblastoma (n=2): 5 and 8 years	The total number of patients surviving their primary cancer is unknown. CNS neoplasms detected by symptoms. **Risk of bias:** - Selection bias: unclear how many patients were included in the original cohort of survivors. - Attrition bias: unclear for how many survivors follow-up data was complete. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: not applicable, only latency time reported.

Abbreviations: ALL, acute lymphoblastic leukemia; CRT, cranial radiotherapy.

At what age or time from exposure should surveillance be initiated?				
Felice et al. Second Neoplasms in Children Following a Treatment for Acute Leukemia and/or Lymphoma: 29 Years of Experience in a Single Institution in Argentina. Journal of pediatric hematology oncology 2017; 39: 406-4012.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Retrospective cohort study Treatment era: 1987-2016 Follow-up: From 17 patients who achieved complete remission of secondary neoplasm and stayed alive: Median 110 (range 4-276) months	3,321 patients with childhood acute leukemia or lymphoma Primary cancer diagnosis: Acute leukemia (85%), lymphoma (15%) Age at primary cancer diagnosis: Median 6 (range 1-16) yr Age at follow-up: Not reported Genetic predisposition: No genetic/molecular studies for ruling-out genetic predisposition to develop cancer were performed to any patient. However, no phenotypic stigmata were detected in any case.	No treatment data available of cohort of survivors Treatment among survivors with a subsequent CNS neoplasm: - Chemotherapy: 5 - Radiotherapy: 4 - HSCT: 1 patient with glioblastoma multiforme with relapsed NHL	Survivors with subsequent CNS neoplasms: - 3 glioblastoma multiforme - 1 meningioma - 1 PNET Time interval from primary cancer diagnosis to subsequent CNS tumor: Median 112 (range 37-236) months	Unclear how CNS neoplasms were detected. Prognosis: - 1/1 (100%) with meningioma alive and in complete remission for 178 months - 4/4 (100%) with glioblastoma multiforma and PNET died **Risk of bias:** - Selection bias: unclear how many patients were included in the original cohort of survivors. - Attrition bias: unclear for how many patients follow-up was complete. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: not applicable, only latency time reported.

Abbreviations: CNS, central nervous system; CRT, cranial radiotherapy.

At what age or time from exposure should surveillance be initiated? At what frequency should surveillance be performed?				
Galloway et al. Analysis of dose at the site of second tumor formation after radiotherapy to the central nervous system. Int J Radiation Oncology Biol Phys 2012;82:90-94. ***Galloway et al.*** Second tumors in pediatric patients treated with radiotherapy to the central nervous system. Am J Clin Oncol 2012;35:279-283.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective cohort study Treatment era: 1963-2006 Follow-up: Median 4.7 (range 0.1-45.4) years	370 childhood cancer survivors ≤19 years at CRT Primary cancer diagnosis: Glioma (31.5%), ALL/AML (26.3%), medulloblastoma (17.0%), ependymoma (11.2%), germinoma (3.8%), nongerminomatous germ cell tumor (10.1%) Age at radiotherapy: Median 8.1 (range 0.2-19.0) years Age at follow-up: Median 21.2 (range 2.4-59.9) years Genetic predisposition: 6 (1.6%) with a known diagnosis of neurofibromatosis	CRT: 370 (100%) Radiation volumes: - Part of the brain: 172 (47%) - Whole brain: 79 (21%) - Craniospinal axis: 119 (32%) Radiation dose (28% Cobalt): - Tumor bed: median 53.1 (range 6-75.6) Gy - Craniospinal axis: median 30 (range 12-45.6 Gy) Chemotherapy: 210 (56.6%)	Survivors with secondary neoplasms: - Meningioma: n=10 - Glioma: n=4 - Sarcoma: n=1 - Thyroid tumor: n=1 Cumulative incidence secondary neoplasms: - 10-year: 3% - 15-year: 4% - 20-year: 8% - 25-year: 19% - 30-year: 24% Secondary neoplasms by radiation field and brain dose: - Whole brain field: 9 (56%) - Marginal to target volume: 2 (12.5%) - Whole brain field margin, boost field: 2 (12.5%) - Boost field: 2 (12.5%) - Distant to target volume: 1 (6%) - <20 Gy: 1 (6%) - 20-36 Gy: 13 (81%) - >45 Gy: 2 (12.5%) Risk factors for secondary neoplasms in univariate analysis: - Radiation volume to the brain (p=0.36) - Age at primary treatment (p=0.58) - Radiotherapy dose (p=0.11) Median time interval from primary cancer treatment to secondary CNS tumor:	Two patients developed a third tumor at 3.6 and 9.5 years after treatment for their secondary tumor and 22.0 and 32.7 years after treatment for their primary tumor, respectively. Six patients with a known diagnosis of neurofibromatosis did not develop a secondary tumor. Multivariable analysis was not performed due to the small number of events. Unclear how CNS neoplasms were detected. Prognosis: - Deaths from tumor recurrence was greater than from second tumor until 20 years when the rate of death between late recurrences of the primary second tumor was essentially equal (although small numbers (n=8)). - 63% of secondary primary neoplasms were meningiomas and for these there was an 89% 5-year survival. **Risk of bias:** - Selection bias: unclear how many patients were included in the original cohort of survivors. - Attrition bias: low risk, 81% of

			- Overall: 18.9 years - Meningioma: 22 years - Glioma: 15 years Median age at secondary CNS tumor diagnosis: - Overall: 24 (range 10-39) years	presumed living patients have been contacted within last 5 years before the analysis, but numbers not reported. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: high risk, analyses were not adjusted for follow-up and CRT.

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CNS, central nervous system; CRT, cranial radiotherapy.

At what age or time from exposure should surveillance be initiated? At what frequency should surveillance be performed?

Goshen et al. High incidence of meningioma in cranial irradiated survivors of childhood acute lymphoblastic leukemia. Pediatr Blood Cancer 2007;49:294-297.

Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective cohort study Treatment era: 1974-1997 Follow-up: ≥5 years after diagnosis or relapse	210 childhood ALL and non-Hodgkin lymphoma survivors who survived ≥5 years after diagnosis or relapse Primary cancer diagnosis: ALL (±90%), non-Hodgkin lymphoma (±10%) Age at primary cancer diagnosis: Age at follow-up: Not reported; Median 28.7 (range 20-39) at meningioma diagnosis Genetic predisposition: No neurofibromatosis type 1 or 2 among survivors with meningioma	CRT: 88 (41.9%) CRT dose: - 18 Gy: 36 (40.9%) - 24 Gy: 46 (52.3%) - ≥24 Gy: 6 (6.8%)	Survivors with subsequent meningioma: - Total: 16 (7.6%) - ALL: n=14 - Non-Hodgkin lymphoma: n=2 - 24 Gy CRT: n=14 - 18 Gy CRT: n=1 - No CRT: n=1 Median time interval from primary cancer diagnosis to subsequent meningioma: 21 (range 10-29) yr Cumulative incidence meningioma over time since CRT: - 10-year: 1.5% ± 1.4 - 15-year: 6.3% ± 3.5 - 20-year: 14.8% ± 5.7 - 25-year: 53.8% ± 11.6	Follow-up included cranial imaging with MRI or CT with contrast agents every 3-6 years in 76 survivors (86%) or at longer intervals in 12. Imaging studies were also performed in 74 of the 122 non-irradiated survivors (61%). One meningioma patient had clinical symptoms (seizures). **Risk of bias:** - Selection bias: low risk, 210 out of 223 (94.2%) eligible survivors were included in the study. - Attrition bias: low risk, medical follow-up data complete for all survivors in the study group. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: not applicable, only latency time reported.

Abbreviations: ALL, acute lymphoblastic leukemia; CRT, cranial radiotherapy.

At what age or time from exposure should surveillance be initiated?				
Hudson et al. Clinical ascertainment of health outcomes among adults treated for childhood cancer. JAMA 2013;22:2371-2381.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective cohort study Treatment era: 1962-2001 Follow-up: Median 25.1 (range 10.9-47.9) years from diagnosis	1,713 childhood cancer survivors <25 years at primary cancer diagnosis aged ≥18 years and who survived ≥10 years after diagnosis Primary cancer diagnosis: Leukemia (47.3%), Hodgkin lymphoma (12.7%), non-Hodgkin lymphoma (4.6%), CNS tumors (8.2%), sarcoma (11.2%), germ cell tumor (1.2%), neuroblastoma (3.7%), Wilms tumor (5.5%), other (5.6%) Age at primary cancer diagnosis: Median 6.0 (range 0.0-24.0) years Age at follow-up: Median 32.0 (range 18.0-60.0) years Genetic predisposition: Not reported	Radiotherapy: 1108 (64.7%) Anthracyclines: 1001 (58.4%) Alkylating agents: 1068 (62.4%) Platinum agents: 152 (8.9%) Glucocorticoids: 964 (56.3%) Epipodophyllotoxins: 694 (40.5%) Antimetabolites: 994 (58.0%)	Survivors with subsequent CNS neoplasms: - Meningioma: n=63 - Other CNS neoplasm: n=10 Median time interval from primary cancer diagnosis to subsequent CNS tumor: - Overall: 25.1 (interquartile range 19.0-33.1) years - Meningioma: 26.6 (interquartile range 20.3-33.5) years - Other CNS neoplasm: 9.6 (interquartile range 5.5-23.4) years	CNS neoplasms detected by risk-based screening (history, physical examination, further examination) in 12 patients (meningioma) a median of 32.9 (interquartile range 31.5-36.2) years from primary cancer diagnosis. **Risk of bias:** - Selection bias: high risk, 1,837 out of 2,843 (64.4%) eligible survivors were included in the study. - Attrition bias: low risk, medical follow-up data available for 1,713 out of 1,837 (93.2%) survivors. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: not applicable, only latency time reported.

Abbreviations: ALL, acute lymphoblastic leukemia; CNS, central nervous system.

At what age or time from exposure should surveillance be initiated?				
Lee et al. Irradiation-induced secondary tumors following pediatric central nervous system tumors: experiences of a single institute in Taiwan (1975-2013). Int J Radiat Oncol Biol Phys 2018;101:1243-1252.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective cohort study Treatment era: 1975-2013 Follow-up: Mean 21 years for survivors since primary cancer diagnosis	681 CNS tumor survivors ≤18 years at primary cancer diagnosis treated with CRT who survived ≥5 years since primary cancer diagnosis Primary cancer diagnosis: CNS tumor (100%) of whom 128 (19%) medulloblastoma Age at primary cancer diagnosis: Mean 8.8 (range 3-16.5) years Age at follow-up: Not reported Genetic predisposition: Neurofibromatosis-related disease was excluded	CRT: 681 (100%) CRT dose: Median 52.5 Gy Chemotherapy: Not reported	Survivors with subsequent CNS neoplasms: - Meningioma: n=13 - High-grade glioma: n=6 Mean time interval from primary cancer diagnosis to subsequent CNS neoplasm: - Meningioma: 19.7 (range 12.2-33) years - High-grade glioma: 10.8 (range 4.1-20.3) years	Unclear how CNS neoplasms were detected. Prognosis: - 3 out of 13 (23.1%) patients with meningioma died during follow-up; 10-yr survival: 76.9%. - All 6 patients with high-grade glioma died after aggressive multimodality treatment after a mean period of 9.5 (range 4-15) months. **Risk of bias:** - Selection bias: unclear how many survivors from the original cohort were included in the study group. - Attrition bias: unclear for how many survivors of the total study group follow-up data was complete (for 99 out of 128 (77.3%) medulloblastoma patients follow-up was complete). - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: not applicable, only latency time reported.

Abbreviations: CNS, central nervous system; CRT, cranial radiotherapy.

At what age or time from exposure should surveillance be initiated?				
Ning et al. Evidence of high mortality in long term survivors of childhood medulloblastoma. J Neurooncol 2015;122:321-327.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective cohort study Treatment era: 1973-2003 Follow-up: Mean 16 (range 5.0-35.7) years	455 medulloblastoma survivors ≤19 years at primary cancer diagnosis who survived ≥5 years since primary cancer diagnosis Primary cancer diagnosis: Medulloblastoma (100%) Age at primary cancer diagnosis: Median 7.0 years Age at follow-up: Not reported Genetic predisposition: Not reported	CRT: 455 (100%) Chemotherapy: Not reported (most probably 100%)	Survivors with subsequent CNS neoplasms: - Glioblastoma: n=3 - Anaplastic astrocytoma: n=2 - Low-grade glioma: n=2 - Other: n=2 SIR for subsequent CNS neoplasms: - Overall: 53.9 (95% CI 26.9-96.5) Mean time interval from primary cancer diagnosis to subsequent CNS neoplasm: - Overall: 14.4 years	Unclear how CNS neoplasms were detected. **Risk of bias:** - Selection bias: low risk, 455 out of 455 eligible survivors included in the study. - Attrition bias: unclear for how many survivors follow-up data was complete. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: not applicable, only latency time reported.

Abbreviations: CNS, central nervous system; CRT, cranial radiotherapy; SIR, standardized incidence ratio.

At what age or time from exposure should surveillance be initiated?				
Tsui et al. Subsequent neoplasms in survivors of childhood central nervous system tumors: risk after modern multimodal therapy. Neuro Oncol 2015;17:448-456.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective cohort study Treatment era: 1985-2012	2,779 childhood brain tumor patients Primary cancer diagnosis: Glioma/astrocytoma	CRT only: 654 (23.5%) CRT and chemotherapy: 1448 (52.1%)	Survivors with subsequent CNS neoplasms: - Glioma: n=23 - Malignant meningioma: n=1 - Non-malignant meningioma: n=13 - Medulloblastoma: n=1	Unclear how CNS neoplasms were detected. Children with a known cancer predisposition syndrome accounted for

Follow-up: Median 4.5 (range 0.1-28.2) years from primary cancer diagnosis	(48.2%), medulloblastoma/PNET (21.5%), ependymoma (12.1%), craniopharyngioma (5.5%), atypical teratoid rhabdoid tumor (4.0%), other CNS tumor (8.7%) Age at primary cancer diagnosis: <5 - ≥10 years Age at follow-up: Not reported Genetic predisposition: Not reported (patients with genetic predisposition syndromes excluded from multivariable analyses)	Chemotherapy only: 185 (6.7%)	- Fibrous histiocytoma: n=1 - Dysembryoplastic neuroepithelial tumor: n=2 SIRs for subsequent CNS neoplasms: - Overall (excluding non-malignant meningioma): 49.7 (95% CI 33.1-71.9) - Glioma: 57.2 (95% CI 36.2-85.8) - Medulloblastoma: 18.7 (95% CI 0.2-104.0) Median time interval from primary cancer diagnosis to subsequent CNS neoplasm: - Overall (excluding non-malignant meningioma): 7.3 years - Glioma: 7.2 years - Non-malignant meningioma: 11.1 years - Medulloblastoma: 5.0 years - Others: 12.1 years	22% of the population who developed secondary neoplasms (SNs). Among the 81 survivors, 3 children with Gorlin syndrome developed 11 SNs, 9 children with neurofibromatosis type 1 developed 11 SNs, and 1 SN each was developed by 2 children with Li–Fraumeni syndrome, 1 child with neurofibromatosis type 2, and 1 child each with Lynch syndrome, familial adenomatous polyposis, and Fanconi anemia. **Risk of bias:** - Selection bias: unclear how many patients were included in the original cohort of survivors. - Attrition bias: unclear for how many survivors follow-up data was complete. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: not applicable, only latency time reported.

Abbreviations: ALL, acute lymphoblastic leukemia; CNS, central nervous system; CRT, cranial radiotherapy; SIR, standardized incidence ratio.

At what age or time from exposure should surveillance be initiated?				
Ueda et al. Therapy related secondary malignancies after treatment for secondary malignancy: Cases from a single institution. Journal of Nippon Medical School 2019; 86: 207-214.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort study Treatment era: 1980-2014 Follow-up: Median 7 yr, mean 10 yr, maximum 33 yr from primary cancer diagnosis	275 childhood cancer survivors <15 years at primary cancer diagnosis who survived >1 yr Primary cancer diagnosis: All types of childhood cancer Age at primary cancer diagnosis: Not reported Age at follow-up: Not reported; Median 29 yr at meningioma diagnosis Genetic predisposition: Not reported	*Treatment of study group not reported* CRT dose for primary malignancy Meningioma cases: 18Gy: n=2 24Gy: n=2 Second malignancy infield or out of field: Meningioma cases: In field: n=4 Chemotherapy: Meningioma cases: Cyclophosfamide n=2 Daunorubicin n=2	Survivors with secondary meningioma: 4 (1.5%) (all ALL survivors) Median time interval from primary cancer diagnosis to subsequent meningioma: 26.5 (range 20-29) yr	Routine brain MRIs were performed every 2 or 3 years for all survivors who had received CRT. All meningioma's were diagnosed by MRI. Prognosis: 4/4 (100%) alive at end of follow-up. **Risk of bias:** - Selection bias: low risk, 275 of 328 (84%) eligible survivors were included in the study. - Attrition bias: low risk, 53 of 328 (16.2%) were excluded because there was a lack of follow-up data or follow-up <1 yr. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: not applicable, only latency time reported.

Abbreviations: ALL, acute lymphoblastic leukemia; CRT, cranial radiotherapy.