Summary of findings tables, grading of the evidence and detailed conclusions of evidence CNS neoplasms

Key question: Does early diagnosis result in better outcome?

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
1.a. Prognosis of subsequent glioma (n=4 studies)	Lee 2019	681 CNS tumor survivors	21.0	100%	6 high-grade glioma	Survival: 0% alive 6/6 (100%) died after aggressive multimodality treatment after a mean period of 9.5 (range 4-15) months	SB: unclear AB: unclear DB: unclear
	Felice 2017	3.321 childhood acute leukemia or lymphoma patients	Not reported	Not reported (4 patients with a subsequent neoplasm had radiotherapy, not further specified)	3 glioblastoma multiforme	Survival: 3/3 (100%) with glioblastoma multiforme died	SB: unclear AB: unclear DB: unclear
	Taylor 2010	17,980 CCS	17.3 (>5 - …)	51.% (radiotherapy, not further specified)	73 glioma: 27 low-grade, 41 high-grade	5-yr relative survival (95% CI): High-grade: 4.9% (0.8-14.6); Low grade: 38.9% (22.1-55.4); p<0.001; Hazard ratio (95% CI) Mortality from all causes high-grade vs. low-grade: 3.15 (1.58-6.28)	SB: low risk AB: low risk DB: unclear
	Walter 1998	1,612 childhood ALL patients	15.9 (5.5-29.9)	77.6%	10 glioma: 4 glioblastoma multiforme, 2 anaplastic astrocytoma, 4 other high-grade glioma	Survival: 8/10 (80.0%) died; 2/10 (20.0%) alive; Median survival time dead: 7 (range 0.1-25) months; Survival time survivors: 5 months and 7.8 yr, respectively	SB: unclear AB: low risk DB: unclear

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 1/4, unclear in 3/4; Attrition bias low in 2/4, unclear in 2/4; Detection bias unclear in 4/4
Consistency:	0	No important inconsistency, although survival varies among the studies
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, small number of events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		The 5-year survival rate of subsequent glioma ranges from 0% (high-grade glioma) to 38.9% (low-grade glioma) in CAYA cancer survivors.

	(4 studies; 23,594 participants; 92 events)						

Abbreviations: AB, attrition bias; ALL, acute lymphoblastic leukemia; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; DB, detection bias; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
1.b. Prognosis of subsequent meningioma (n=10 studies)	Ueda 2019	275 CCS	7 (…-33)	Not reported (4 patients with a subsequent neoplasm had CRT)	4 meningioma	4/4 (100%) alive at end of follow-up	SB: low risk AB: low risk DB: unclear
	Lee 2018	681 CNS tumor survivors	21.0	100%	13 meningioma	10-yr survival: 76.9% 3/13 (23.1%) patients with meningioma died during follow-up	SB: unclear AB: unclear DB: unclear
	Bowers 2017	4,221 CCS	22.8 (5.5-38.0)	100%	169 meningioma	5-yr overall survival (95% CI): 91.0% (85.0-95.0); 22/169 (13.0%) died, 6 attributed to meningioma; Median survival time survivors: 6.0 (0.3-32.9) yr	SB: unclear AB: unclear DB: unclear
	Felice 2017	3.321 childhood acute leukemia or lymphoma patients	Not reported	Not reported (4 patients with a subsequent neoplasm had radiotherapy, not further specified)	1 meningioma	Survival: 1/1 meningioma case stayed alive and in complete remission for 178 months	SB: unclear AB: unclear DB: unclear
	Brignardello 2015	49 CCS	≥5	91.8%	10 meningioma	4/10 (40.0%) underwent neurosurgery due to onset of neurological symptoms or to progressive enlargement of the lesion; 2 operated meningiomas showed complete recovery; Non-operated meningiomas followed-up with regular MRI scans, 1 recently showed tumor progression requiring neurosurgery	SB: unclear AB: low risk DB: unclear
	Felicetti 2015	90 CCS	24.6 (13.2-36.8)	100%	15 meningioma	Survival: 14/15 (93.3%)	SB: unclear AB: low risk DB: unclear
	Galloway 2012	370 CCS	4.7 (0.1-45.4)	100%	10 meningioma	5-yr survival: 89%	SB: unclear AB: low risk

							DB: unclear
	Taylor 2010	17,980 CCS	17.3 (>5 - …)	51.% (radiotherapy, not further specified)	137 meningioma: 129 low-grade, 8 high-grade	5-yr relative survival (95% CI): High-grade: 57.3% (17.2-84.0); Low grade: 84.3% (76.5-90.0); p=0.09; Hazard ratio (95% CI) Mortality from all causes high-grade vs. low grade: 4.95 (1.37-17.92)	SB: low risk AB: low risk DB: unclear
	Banerjee 2009	60 ALL survivors	>10 yr	100%	11 meningioma	11 (100%) alive at end of follow-up	SB: unclear AB: low risk DB: unclear
	Walter 1998	1,612 childhood ALL patients	15.9 (5.5-29.9)	77.6%	10 meningioma, 1 low-grade oligodendroglioma	Survival: 11/11 (100%) alive; Median survival time: 2.5 (range 0.5-10) yr	SB: unclear AB: low risk DB: unclear
GRADE assessment:							
Study design:	+4	Retrospective cohort studies					
Study limitations:	-1	Some limitations: Selection bias low in 2/10, unclear in 8/10; Attrition bias low in 7/10, unclear in 3/10; Detection bias unclear in 10/10					
Consistency:	0	No important inconsistency, although survival varies among the studies					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-1	Some imprecision, four studies had very small number of events					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	No dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊕⊖⊖ LOW					
Conclusion:		The 5-year survival rate of subsequent meningioma ranges from 57.3% to 100% in CAYA cancer survivors. (10 studies; 28,659 participants; 380 events)					

Abbreviations: AB, attrition bias; ALL, acute lymphoblastic leukemia; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CNS, central nervous system; DB, detection bias; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
1.c. Prognosis of subsequent CNS neoplasms (all different types)* (n=4 studies)	Patterson 2014	12,098 CAYA cancer survivors	<10-≥20	35.4%	219: 55 glioma, 148 meningioma, 16 other	Survival: 66/219 (30.1%) died; 153/219 (69.9%) alive; Rate ratio (95% CI) for death GH exposure yes vs. no: 1.6 (0.5- 4.9)	SB: high risk AB: unclear DB: unclear
	Schmiegelow 2013	642 CAYA ALL survivors	NM	At least 35.8%	138: 22 meningioma, 116 other CNS tumor	5-yr overall survival non-meningioma brain tumors: 19.6% ± 5.5% before 2000; 16.6% ± 5.3% after 2000; p=0.76	SB: unclear AB: unclear DB: unclear

	Bhatia 2002	8,831 CAYA ALL survivors	5.5 (0-16.1)	38%	19: 9 glioblastoma multiforme, 4 anaplastic astrocytoma, 3 PNET, 1 medulloblastoma, 2 meningioma	Survival: 11/19 (57.9%) died; 8/19 alive (42.1%)	SB: unclear AB: low risk DB: unclear
	Löning 2000	5,006 CAYA ALL patients	5.7 (1.5-18)	77.2%	13: 4 glioblastoma, 4 astrocytoma, 3 PNET, 2 meningioma	Survival: 7/13 (53.8%) died; 6/13 alive (46.2%); Median survival time: 14 months	SB: unclear AB: unclear DB: unclear

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias high in 1/4, unclear in 3/4; Attrition bias low in 1/4, unclear in 3/4; Detection bias unclear in 4/4
Consistency:	0	No important inconsistency, although survival varies among the studies
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, three studies had very small number of events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		The 5-year survival rate of subsequent CNS neoplasms (different types)* ranges from 16.6% to 69.9% in CAYA cancer survivors. (4 studies; 26,577 participants; 389 events)

Abbreviations: AB, attrition bias; ALL, acute lymphoblastic leukemia; CAYA, childhood, adolescent and young adult; CNS, central nervous system; DB, detection bias; NM, not mentioned; PNET, primitive neuroectodermal tumor; SB, selection bias; yr, year.
* Studies including different types of subsequent CNS neoplasms, not making a distinction between glioma, meningioma and other types.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
2.a. Early detection of subsequent meningioma (n=1 study)	Co 2019	Screened group: 70 ALL survivors Unscreened group: 106 CCS	Screened group: 27 (19-33) Unscreened group: 29 (23-37)	100%	Screened group: 15 meningioma Unscreened group: 9 meningioma	*Meningioma 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,	SB: unclear AB: low risk DB: unclear CF: low risk

			2 subtotal resection *P*=0.52 *Post-operative complications* Screened group: 0 major, 2 minor; Unscreened group: 1 major, 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
GRADE assessment:			
Study design:	+4	Retrospective cohort studies	
Study limitations:	-1	Some limitations: Selection bias unclear in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1	
Consistency:	0	Not applicable (one study)	
Directness:	0	Results are direct, population and outcomes broadly generalizable	
Precision:	-2	Important imprecision, small number of events and only 1 study	
Publication bias:	0	Unlikely	
Effect size:	0	No large magnitude of effect	
Dose-response:	0	No dose response relationship	
Plausible confounding:	0	No plausible confounding	
Quality of evidence:		⨁⊖⊖⊖ VERY LOW	
Conclusion:		There were small, but non-significant differences between screened versus unscreened CAYA cancer survivors related to meningioma size, extent of resection and persistent morbidity. (1 study; 176 participants; 24 events)	

Abbreviations: AB, attrition bias; ALL, acute lymphoblastic leukemia; CF, confounding; DB, detection bias; SB, selection bias; yr, year.

PICO 3-6: No studies identified

Key question: Who needs surveillance?

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
1.a. Risk subsequent glioma after cranial radiotherapy (n=4 studies)	Patterson 2014	12,098 CAYA cancer survivors	<10-≥20	35.4%	55 glioma	Rate ratio (95% CI) CRT ≤45 Gy and fup <10 yr vs. no CRT: 7.9 (2.7-23.0); CRT >45 Gy and fup <10 yr vs. no CRT: 13.5 (4.0-46.1)	SB: high risk AB: unclear DB: unclear CF: low risk
	Reulen 2011	17,981 CCS	24.3 (>5 - …)	Unclear how many patients were treated with CRT	105 glioma	Relative risk (95% CI) CRT yes vs. no: 5.5 (2.4-12.3)	SB: low risk AB: low risk DB: unclear CF: low risk
	Taylor 2010	17,980 CCS	17.3 (>5 - …)	51.% (radiotherapy, not further specified)	73 glioma	Standardized incidence ratio (95% CI) CNS radiotherapy: 14.3 (95% CI 10.9-18.7); No CNS radiotherapy: 6.1 (95% CI 3.1-11.0); p=0.008	SB: low risk AB: low risk DB: unclear CF: low risk
	Neglia 2006	14,361 CAYA cancer survivors (116 cases matched to 464 controls)	>5-≥15	71.7% (radiotherapy, not further specified)	40 glioma	Odds ratio (95% CI) Radiotherapy yes vs. no (unclear how many patients were treated with CRT): 6.78 (1.54-29.7)	SB: high risk AB: unclear DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 2/4, high in 2/4; Attrition bias low in 2/4, unclear in 2/4; Detection bias unclear in 4/4; Confounding low in 4/4
Consistency:	0	No important inconsistency, all show effect of CRT
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	+1	Large magnitude of effect
Dose-response:	+1	Dose response relationship as higher doses are associated with an increased risk as compared to lower doses
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊕ HIGH
Conclusion:		Increased risk of subsequent glioma after radiotherapy exposing the brain/spinal cord in CAYA cancer survivors. (4 studies significant effect; 62,420 participants; 273 events)

Abbreviations: AB, attrition bias; ALL, acute lymphoblastic leukemia; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CNS, central nervous system; CRT, cranial radiotherapy; DB, detection bias; fup, follow-up; NM, not mentioned; SB, selection bias; yr, year.

Subgroup	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
1.b. Risk subsequent meningioma after cranial radiotherapy (n=10 studies)	Salloum 2019	997 medulloblastoma survivors	21 (range 5-44)	81%	24 benign meningioma	15-year cumulative incidence (95% CI) 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) *P*=0.24	SB: high risk AB: low risk DB: unclear CF: low risk
	Swerdlow 2019	1,830 CCS treated with GH	Total 154.795 person years at risk, mean 14.9 yr per patient	63.7%	37 meningioma	Standardized incidence ratio (95% CI) in CCS treated with GH and CRT: 658.4 (460.4-941.7)	SB: high risk AB: low risk DB: unclear CF: low risk
	Kok 2018	5,843 CCS	28.3 (5.0-52.2)	21.9%	96 benign meningioma	40-yr cumulative incidence (95% CI) CRT: 12.4% (9.8-15.2); No CRT: 0.3% (0.1-1.2); Hazard ratio (95% CI) No CRT vs. 1-19 Gy CRT: 0.04 (0.01-0.15)	SB: low risk AB: low risk DB: unclear CF: low risk
	Bowers 2017	4,221 CCS	22.8 (5.5-38.0)	100%	169 meningioma	30-year cumulative incidence (95% CI): 5.8% (4.8-6.8); Hazard ratio (95% CI) CRT dose 20-29.9 Gy vs. 1.5-19.9 Gy: 1.6 (1.0-2.6); CRT dose ≥30 Gy vs. 1.5-19.9 Gy: 2.6 (1.6-4.2) *P* for trend <0.001	SB: unclear AB: unclear DB: unclear CF: low risk
	Turcotte 2017	23,603 CCS	20.5±7.5	53.1% (any radiotherapy, not further specified)	233 benign meningioma, 7 malignant meningioma	Relative rate (95% CI) Maximum radiation treatment dose to any body region 0.1-10 Gy vs. none: 24.39 (4.42-134.44); 10.1-20 Gy vs. none: 14.77 (5.89-37.03); 20.1-30 Gy vs. none: 23.44 (9.85-55.79); 30.1-40 Gy vs. none: 10.91 (3.60-33.05); 40.1-50 Gy vs. none: 23.80 (9.32-60.80); ≥50.1 Gy vs. none:	SB: high risk AB: unclear DB: unclear CF: low risk

						34.93 (14.20-85.93)	
	Patterson 2014	12,098 CAYA cancer survivors	<10-≥20	35.4%	148 meningioma	Rate ratio (95% CI) CRT ≤45 Gy and fup ≥20 yr vs. no CRT: 22.0 (9.7-50.2); CRT >45 Gy and fup ≥20 yr vs. no CRT: 58.5 (25.5-134.2)	SB: high risk AB: unclear DB: unclear CF: low risk
	Sabin 2014	219 childhood ALL and non-Hodgkin lymphoma survivors	25.4 (range 12-46)	57.1%	19 had 31 incidentally detected subsequent intracranial neoplasms; 30 suggestive of meningioma	Prevalence among CRT vs. non-CRT survivors <20 Gy: 4 (22.2%) vs. 64 (59.8%); 20- <30 Gy: 14 (77.8%) vs. 42 (39.3%); ≥30 Gy: 0 (0%) *P=0.0132*	SB: unclear AB: low risk DB: unclear CF: high risk
	Friedman 2010	14,359 CAYA cancer survivors	22.7 ± 6.8	59.4% (radiotherapy, not further specified)	170 meningioma	Risk ratio (95% CI) Radiotherapy yes vs. no (unclear how many patients were treated with CRT): 16.6 (5.2-52.6)	SB: high risk AB: low risk DB: unclear CF: low risk
	Cardous-Ubbink 2007	1,368 CCS	16.8 (5-≥30)	44.5% (radiotherapy, not further specified)	12 meningioma	Hazard ratio could not be calculated as all 12 meningioma cases were treated with radiotherapy (unclear how many patients were treated with CRT)	SB: low risk AB: low risk DB: unclear CF: low risk
	Neglia 2006	14,361 CAYA cancer survivors (116 cases matched to 464 controls)	>5-≥15	71.7% (radiotherapy, not further specified)	66 meningioma	Odds ratio (95% CI) Radiotherapy yes vs. no (unclear how many patients were treated with CRT): 9.94 (2.17-45.6)	SB: high risk AB: unclear DB: unclear CF: low risk

GRADE assessment:

Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 2/10, high in 6/10, unclear in 2/10; Attrition bias low in 6/10, unclear in 4/10; Detection bias unclear in 10/10; Confounding low in 9/10, high in 1/10
Consistency:	0	No important inconsistency, all show effect of CRT
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	+1	Large magnitude of effect
Dose-response:	+1	Dose response relationship as higher doses are associated with an increased risk as compared to lower doses
Plausible confounding:	0	No plausible confounding

Quality of evidence: ⊕⊕⊕⊕ HIGH

Conclusion: Increased risk of subsequent meningioma after radiotherapy exposing the brain/spinal cord in CAYA cancer survivors.
(10 studies significant effect; 78,899 participants; 981 events)

Abbreviations: AB, attrition bias; ALL, acute lymphoblastic leukemia; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CNS, central nervous system; CRT, cranial radiotherapy; DB, detection bias; fup, follow-up; GH, growth hormone; NM, not mentioned; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
1.c. Risk subsequent CNS neoplasms (all different types*) after cranial radiotherapy (n=12 studies)	Patterson 2014	12,098 CAYA cancer survivors	<10-≥20	35.4%	219: 55 glioma, 148 meningioma, 16 other	Rate ratio (95% CI) CRT ≤45 Gy and fup ≥20 yr vs. no CRT: 9.9 (5.5-17.5); CRT >45 Gy and fup ≥20 yr vs. no CRT: 25.3 (14.0-46.0)	SB: high risk AB: unclear DB: unclear CF: low risk
	Schmiegelow 2013	642 CAYA ALL survivors	NM	At least 35.8%	138: 22 meningioma, 116 other CNS tumor	Incidence/prevalence in survivors without HSCT CNS radiotherapy: 89.0%; No CNS radiotherapy: 11.0%; No p-value reported	SB: unclear AB: unclear DB: unclear CF: high risk
	Strodbeck 2013	1,338 childhood medullobastoma/ PNET patients	(0.2 - >10)	NM	10: 10 brain neoplasms (not further specified)	Standardized incidence ratio (95% CI) CRT and fup ≥10 yr: 59.59 (21.87-129.7); No CRT and fup ≥10 yr: 0 (0-397.61); No p-value reported	SB: unclear AB: unclear DB: unclear CF: low risk
	Taylor 2010	17,980 CCS	17.3 (>5 - …)	51.% (radiotherapy, not further specified)	247: 73 glioma, 16 schwannoma, 9 PNET, 137 meningioma, 12 other	40-yr cumulative incidence (95% CI) CNS radiotherapy: 9.1% (7.9-11.7); No CNS radiotherapy: 1.4% (0.6-2.8); p<0.001	SB: low risk AB: low risk DB: unclear CF: low risk
	Armstrong 2009	1,877 CAYA primary CNS tumor survivors	19.6 (5.1-34.6)	57.8%	20: 15 astrocytoma/glial tumor, 4 malignant meningioma, 1 medulloblastoma/PNET	25-yr cumulative incidence (95% CI) No CRT: 1.0% (0-2.3); CRT <50 Gy: 5.2% (2.1-8.3); CRT ≥50 Gy: 7.1% (4.5-9.6); No p-value reported	SB: high risk AB: low risk DB: unclear CF: low risk
	Hijiya 2007	1,290 CAYA ALL survivors	18.7 (2.4-41.3)	NM	22: 10 glioblastoma multiforme, 9 astrocytoma, 2 oligodendroglioma, 1 other	Standardized incidence ratio (95% CI) CRT: 45.8 (26.0-64.2); No CRT: 4.3 (0.1-24.0); 8-yr cumulative incidence CRT: 11.5%; No CRT: 0%; p<0.001	SB: low risk AB: low risk DB: unclear CF: low risk
	Inskip 2007	25,965 CAYA cancer survivors	6.3 (0.16-30.0)	37.1% (radiotherapy, not	51: Not further specified	Absolute excess risk per 10,000 person-years	SB: unclear AB: low risk

				further specified)		Radiotherapy: 4.2; No radiotherapy: 1.0; No p-value reported	DB: unclear CF: low risk
	Bhatia 2002	8,831 CAYA ALL survivors	5.5 (0-16.1)	38%	19: 9 glioblastoma multiforme, 4 anaplastic astrocytoma, 3 PNET, 1 medulloblastoma, 2 meningioma	Relative risk (95% CI) CRT yes vs. no: 2.4 (1.1-5.2)	SB: unclear AB: low risk DB: unclear CF: low risk
	Löning 2000	5,006 CAYA ALL patients	5.7 (1.5-18)	77.2%	13: 4 glioblastoma, 4 astrocytoma, 3 PNET, 2 meningioma	15-yr cumulative incidence CRT: 1.3%; No CRT: 0.1%; No p-value reported	SB: unclear AB: unclear DB: unclear CF: low risk
	Little 1998	4,199 CCS (22 cases matched to 282 controls)	15.1 (2.2-45.8)	NM	22: 12 malignant brain neoplasm, 10 benign/unspecified brain neoplasm	NM Linear dose-response p=0.003	SB: unclear AB: unclear DB: unclear CF: low risk
	Walter 1998	1,612 childhood ALL patients	15.9 (5.5-29.9)	77.6%	22: 4 glioblastoma multiforme, 2 anaplastic astrocytoma, 4 other high-grade glioma, 1 low-grade oligodendroglioma, 11 meningioma	20-yr cumulative incidence No CRT: 0.0%; CRT 10-21 Gy: 1.03%; CRT >21-30 Gy: 1.65%; CRT >30 Gy: 3.23%; p=0.015	SB: unclear AB: low risk DB: unclear CF: low risk
	Rosso 1994	3,196 CCS	5.8 (0.0-25.1)	75.5% (radiotherapy, not further specified)	9: 4 glioblastoma, 3 astrocytoma, 1 oligodendroglioma, 1 brain lymphoma	Relative risk (95% CI) in ALL survivors CRT with methotrexate (unclear compared to what treatment): 32.1 (8.5-121.5)	SB: unclear AB: low risk DB: unclear CF: unclear

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 2/12, high in 2/12, unclear in 8/12; Attrition bias low in 7/12, unclear in 5/12; Detection bias unclear in 12/12; Confounding low in 10/12, high in 1/12, unclear in 1/12
Consistency:	0	No important inconsistency, all show effect of CRT
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	+1	Large magnitude of effect
Dose-response:	+1	Dose response relationship as higher doses are associated with an increased risk as compared to lower doses
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊕ HIGH
Conclusion:		Increased risk of subsequent CNS neoplasms (different types)* after radiotherapy exposing the brain/spinal cord in CAYA cancer survivors.

(12 studies significant effect; 84,034 participants; 792 events)							

Abbreviations: AB, attrition bias; ALL, acute lymphoblastic leukemia; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CNS, central nervous system; CRT, cranial radiotherapy; DB, detection bias; fup, follow-up; HSCT, hematopoietic stem cell transplant; NM, not mentioned; PNET, primitive neuroectodermal tumor; SB, selection bias; yr, year.
* Studies including different types of subsequent CNS neoplasms, not making a distinction between glioma, meningioma and other types.

PICOs 1.1.a t/m 1.3.c (photon/proton/MIBG): No studies identified, all included studies photon therapy.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
2.a. Risk subsequent glioma after higher vs. lower dose cranial radiotherapy (n=3 studies)	Patterson 2014	12,098 CAYA cancer survivors	<10-≥20	35.4%	55 glioma	Rate ratio (95% CI) CRT ≤45 Gy and fup <10 yr vs. no CRT: 7.9 (2.7-23.0); CRT >45 Gy and fup <10 yr vs. no CRT: 13.5 (4.0-46.1); p<0.001	SB: high risk AB: unclear DB: unclear CF: low risk
	Taylor 2010	17,980 CCS (247 cases matched to 247 controls)	17.3 (>5 - …)	51.% (radiotherapy, not further specified)	73 glioma	Relative risk (95% CI) 0.01-9.99 Gy vs. 0 Gy: 0.5 (0.2-1.5); 10.0-19.99 Gy vs. 0 Gy: 0.5 (0.1-2.3); 20.00-29.99 Gy vs. 0 Gy: 2.6 (0.9-8.0); 30.00-39.99 Gy vs. 0 Gy: 3.4 (0.5-23.0); ≥40.00 Gy vs. 0 Gy: 4.4 (1.2-16.4); Excess relative risk per Gy: β 0.079 (0.021-0.229); p<0.001	SB: low risk AB: low risk DB: unclear CF: low risk
	Neglia 2006	14,361 CAYA cancer survivors (116 cases matched to 464 controls)	>5-≥15	71.7% (radiotherapy, not further specified)	40 glioma	Odds ratio (95% CI) 1-9.9 Gy vs. <1 Gy: 0.0 (0.0-5.17); 10-19.9 Gy vs. <1 Gy: 7.61 (1.49-38.8); 20-29.9 Gy vs. <1 Gy: 6.68 (1.47-30.3); 30-44.9 Gy vs. <1 Gy: 21.0 (3.11-142.3); >45 Gy vs. <1 Gy: 17.5 (2.86-107.5); Excess relative risk per Gy:	SB: high risk AB: unclear DB: unclear CF: low risk

			β 0.33 (0.07-1.71) (unclear how many patients were treated with CRT)
GRADE assessment:			
Study design:	+4	Retrospective cohort studies	
Study limitations:	-1	Some limitations: Selection bias low in 1/3, high in 2/3; Attrition bias low in 1/3, unclear in 2/3; Detection bias unclear in 3/3; Confounding low in 3/3	
Consistency:	0	No important inconsistency, all show effect of higher CRT dose	
Directness:	0	Results are direct, population and outcomes broadly generalizable	
Precision:	0	No important imprecision, high total number of patients and events	
Publication bias:	0	Unlikely	
Effect size:	+1	Large magnitude of effect	
Dose-response:	+1	Dose response relationship as higher doses are associated with an increased risk as compared to lower doses	
Plausible confounding:	0	No plausible confounding	
Quality of evidence:		⊕⊕⊕⊕ HIGH	
Conclusion:		Increased risk of subsequent glioma after higher doses of radiotherapy exposing the brain/spinal cord in CAYA cancer survivors. (3 studies significant effect; 44,439 participants; 168 events)	

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CRT, cranial radiotherapy; DB, detection bias; fup, follow-up; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
2.b. Risk subsequent meningioma after higher vs. lower dose cranial radiotherapy (n=10 studies)	Remes 2019	642 childhood brain tumor survivors	19.9	100%	6 meningioma	Odds ratio (95% CI) CRT dose: 1.43 (1.04-1.96)	SB: high risk AB: low risk DB: unclear CF: low risk
	Kok 2018	5,843 CCS	28.3 (5.0-52.2)	21.9%	96 benign meningioma	Hazard ratio (95% CI) No CRT vs. 1-19 Gy CRT: 0.04 (0.01-0.15); 20-39 Gy CRT vs. 1-19 Gy CRT: 1.66 (0.83-3.33); 40+ Gy CRT vs. 1-19 Gy CRT: 2.81 (1.30-6.08); Linear dose-response among CRT-exposed patients: excess relative risk/Gy 0.30 (95% CI 0.03-unknown)	SB: low risk AB: low risk DB: unclear CF: low risk
	Bowers 2017	4,221 CCS	22.8 (5.5-38.0)	100%	169 meningioma	Hazard ratio (95% CI) CRT dose 20-29.9 Gy vs. 1.5-19.9 Gy: 1.6 (1.0-2.6); CRT dose ≥30 Gy vs. 1.5-19.9 Gy: 2.6 (1.6-4.2) *P* for trend <0.001	SB: unclear AB: unclear DB: unclear CF: low risk

	Turcotte 2017	23,603 CCS	20.5±7.5	53.1% (any radiotherapy, not further specified)	233 benign meningioma, 7 malignant meningioma	Relative rate (95% CI) Maximum radiation treatment dose to any body region 0.1-10 Gy vs. none: 24.39 (4.42-134.44); 10.1-20 Gy vs. none: 14.77 (5.89-37.03); 20.1-30 Gy vs. none: 23.44 (9.85-55.79); 30.1-40 Gy vs. none: 10.91 (3.60-33.05); 40.1-50 Gy vs. none: 23.80 (9.32-60.80); ≥50.1 Gy vs. none: 34.93 (14.20-85.93)	SB: high risk AB: unclear DB: unclear CF: low risk
	Felicetti 2015	90 CCS	24.6 (range 13.2-36.8)	100%	15 meningioma	Odds ratio (95% CI) Radiation dose >30 Gy vs. ≤30 Gy: 0.95 (0.28-3.24)	SB: unclear AB: low risk DB: unclear CF: low risk
	Patterson 2014	12,098 CAYA cancer survivors	<10-≥20	35.4%	148 meningioma	Rate ratio (95% CI) CRT ≤45 Gy and fup ≥20 yr vs. no CRT: 22.0 (9.7-50.2); CRT >45 Gy and fup ≥20 yr vs. no CRT: 58.5 (25.5-134.2); p<0.001	SB: high risk AB: unclear DB: unclear CF: low risk
	Sabin 2014	219 childhood ALL and non-Hodgkin lymphoma survivors	25.4 (range 12-46)	57.1%	19 had 31 incidentally detected subsequent intracranial neoplasms; 30 suggestive of meningioma	Prevalence among CRT vs. non-CRT survivors <20 Gy: 4 (22.2%) vs. 64 (59.8%); 20- <30 Gy: 14 (77.8%) vs. 42 (39.3%); ≥30 Gy: 0 (0%) *P=0.0132*	SB: unclear AB: low risk DB: unclear CF: high risk
	Vinchon 2011	552 childhood brain tumor patients	94.3 (0.6-27.1)	100%	26 meningioma	5-yr cumulative incidence Max. CRT dose ≥52.5 Gy vs. <52.5 Gy: 0.0% vs. 0.0%; 10-yr cumulative incidence Max. CRT dose ≥52.5 Gy vs. <52.5 Gy: 5.1% vs. 0.0%; 20-yr cumulative incidence Max. CRT dose ≥52.5 Gy vs. <52.5 Gy: 29.5% vs. 19.1%; p=0.035	SB: unclear AB: unclear DB: unclear CF: low risk
	Taylor 2010	17,980 CCS (247 cases	17.3 (>5 - …)	51.% (radiotherapy, not	137 meningioma	Relative risk (95% CI) 0.01-9.99 Gy vs. 0 Gy:	SB: low risk AB: low risk

		matched to 247 controls)		further specified)		1.8 (0.8-39.3); 10.0-19.99 Gy vs. 0 Gy: 8.4 (6.4-10.7); 20.00-29.99 Gy vs. 0 Gy: 51.6 (5.5-69.5); 30.00-39.99 Gy vs. 0 Gy: 567.9 (29.3-773.6); ≥40.00 Gy vs. 0 Gy: 479.1 (25.0-657.2); Excess relative risk per Gy: β 5.1 (0.7-107.7); p<0.001	DB: unclear CF: low risk
	Neglia 2006	14,361 CAYA cancer survivors (116 cases matched to 464 controls)	>5-≥15	71.7% (radiotherapy, not further specified)	66 meningioma	Odds ratio (95% CI) 1-9.9 Gy vs. <1 Gy: 0.0 (0.0-15.8); 10-19.9 Gy vs. <1 Gy: 12.0 (1.42-100.7); 20-29.9 Gy vs. <1 Gy: 21.6 (3.13-149.3); 30-44.9 Gy vs. <1 Gy: 96.3 (10.32-899.3); >45 Gy vs. <1 Gy: 58.0 (6.02-559.0); Excess relative risk per Gy: 1.06 (0.21-8.15) (unclear how many patients were treated with CRT)	SB: high risk AB: unclear DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 2/10, high in 4/10, unclear in 4/10; Attrition bias low in 5/10, unclear in 5/10; Detection bias unclear in 10/10; Confounding low in 9/10, high in 1/10
Consistency:	0	No important inconsistency, all show effect of higher CRT dose
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	+1	Large magnitude of effect
Dose-response:	+1	Dose response relationship as higher doses are associated with an increased risk as compared to lower doses
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊕ HIGH
Conclusion:		Increased risk of subsequent meningioma after higher doses of radiotherapy exposing the brain/spinal cord in CAYA cancer survivors. (10 studies significant effect; 79,609 participants; 922 events)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CRT, cranial radiotherapy; DB, detection bias; fup, follow-up; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
2.c. Risk subsequent CNS neoplasms (all different types*) after higher vs. lower dose cranial radiotherapy (n=5 studies)	Bhatia 2012	8,831 CAYA ALL survivors	5.5 (0-16.1)	38%	19: 9 glioblastoma multiforme, 4 anaplastic astrocytoma, 3 PNET, 1 medulloblastoma, 2 meningioma	Relative risk (95% CI) CRT 18 Gy vs. 0 Gy: 2.1 (0.7-3.6); CRT 24 Gy vs. 0 Gy: 4.2 (0.5-37.7)	SB: unclear AB: low risk DB: unclear CF: low risk
	Patterson 2014	12,098 CAYA cancer survivors	<10-≥20	35.4%	219: 55 glioma, 148 meningioma, 16 other	Rate ratio (95% CI) CRT ≤45 Gy and fup ≥20 yr vs. no CRT: 9.9 (5.5-17.5); CRT >45 Gy and fup ≥20 yr vs. no CRT: 25.3 (14.0-46.0); p<0.001	SB: high risk AB: unclear DB: unclear CF: low risk
	Little 1998	4,199 CCS (22 cases matched to 282 controls)	15.1 (2.2-45.8)	NM	22: 12 malignant brain neoplasm, 10 benign/unspecified brain neoplasm	NM Linear dose-response p=0.003	SB: unclear AB: unclear DB: unclear CF: low risk
	Armstrong 2009	1,877 CAYA primary CNS tumor survivors	19.6 (5.1-34.6)	57.8%	20: 15 astrocytoma/glial tumor, 4 malignant meningioma, 1 medulloblastoma/PNET	25-yr cumulative incidence (95% CI) No CRT: 1.0% (0-2.3); CRT <50 Gy: 5.2% (2.1-8.3); CRT ≥50 Gy: 7.1% (4.5-9.6); No p-value reported	SB: high risk AB: low risk DB: unclear CF: low risk
	Walter 1998	1,612 childhood ALL patients	15.9 (5.5-29.9)	77.6%	22: 4 glioblastoma multiforme, 2 anaplastic astrocytoma, 4 other high-grade glioma, 1 low-grade oligodendroglioma, 11 meningioma	20-yr cumulative incidence No CRT: 0.0%; CRT 10-21 Gy: 1.03%; CRT >21-30 Gy: 1.65%; CRT >30 Gy: 3.23%; p=0.015 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)	SB: unclear AB: low risk DB: unclear CF: low risk

GRADE assessment:

Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias high in 2/5, unclear in 3/5; Attrition bias low in 3/5, unclear in 2/5; Detection bias unclear in 5/5; Confounding low in 5/5
Consistency:	0	No important inconsistency, all show effect of higher CRT dose
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of events
Publication bias:	0	Unlikely

Effect size:	+1	Large magnitude of effect
Dose-response:	+1	Dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊕ HIGH
Conclusion:		Increased risk of subsequent CNS neoplasms (different types)* after higher doses of radiotherapy exposing the brain/spinal cord in CAYA cancer survivors. (5 studies significant effect; 28,617 participants; 302 events)

Abbreviations: AB, attrition bias; ALL, acute lymphoblastic leukemia; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CNS, central nervous system; CRT, cranial radiotherapy; DB, detection bias; fup, follow-up; NM, not mentioned; PNET, primitive neuroectodermal tumor; SB, selection bias; yr, year.
* Studies including different types of subsequent CNS neoplasms, not making a distinction between glioma, meningioma and other types

PICOs 2.1.a t/m 2.3.c (photon/proton/MIBG): No studies identified, all included studies photon therapy.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
3.a. Risk subsequent glioma after alkylating agents (n=2 studies)	Patterson 2014	12,098 CAYA cancer survivors	<10-≥20	35.4%	55 glioma	Rate ratio (95% CI) Alkylating agents yes vs. no: 0.7 (0.5-1.0)	SB: high risk AB: unclear DB: unclear CF: low risk
	Neglia 2006	14,361 CAYA cancer survivors (116 cases matched to 464 controls)	>5-≥15	71.7% (radiotherapy, not further specified)	40 glioma	Odds ratio (95% CI) Alkylating agents yes vs. no: 1.10 (0.45-2.66)	SB: high risk AB: unclear DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Retrospective cohort studies					
Study limitations:	-1	Some limitations: Selection bias high in 2/2; Attrition bias unclear in 2/2; Detection bias unclear in 2/2; Confounding low in 2/2					
Consistency:	0	No important inconsistency, both studies show non-significant effects					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	0	No important imprecision, high number of events and narrow confidence intervals					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	No dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊕⊕⊖ MODERATE					
Conclusion:		No significant effect of alkylating agents on the risk of subsequent glioma in CAYA cancer survivors. (2 studies no significant effect; 26,459 participants; 95 events)					

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CF, confounding; DB, detection bias; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
3.b. Risk subsequent meningioma after alkylating agents (n=4 studies)	Turcotte 2017	23,603 CCS	20.5±7.5	53.1% (any radiotherapy, not further specified)	233 benign meningioma, 7 malignant meningioma	Relative rate (95% CI) Cyclophosphamide equivalent dose 1-3999 mg/m^2 vs. none: 0.51 (0.27-0.97); Cyclophosphamide equivalent dose 4000-7999 mg/m^2 vs. none: 1.00 (0.56-1.81); Cyclophosphamide equivalent dose ≥8000 mg/m^2 vs. none: 0.54 (0.34-0.88)	SB: high risk AB: unclear DB: unclear CF: low risk
	Patterson 2014	12,098 CAYA cancer survivors	<10-≥20	35.4%	148 meningioma	Rate ratio (95% CI) Alkylating agents yes vs. no: 0.7 (0.5-1.0)	SB: high risk AB: unclear DB: unclear CF: low risk
	Friedman 2010	14,359 CAYA cancer survivors	22.7 ± 6.8	59.4% (radiotherapy, not further specified)	170 meningioma	Risk ratio (95% CI) Alkylating agent score 1 vs. 0: 0.8 (0.5-1.4); Alkylating agent score 2 vs. 0: 0.8 (0.4-1.4); Alkylating agent score 3 vs. 0: 0.4 (0.1-1.2)	SB: high risk AB: low risk DB: unclear CF: low risk
	Neglia 2006	14,361 CAYA cancer survivors (116 cases matched to 464 controls)	>5-≥15	71.7% (radiotherapy, not further specified)	66 meningioma	Odds ratio (95% CI) Alkylating agents yes vs. no: 0.85 (0.34-2.09)	SB: high risk AB: unclear DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias high in 4/4; Attrition bias low in 1/4, unclear in 3/4; Detection bias unclear in 4/4; Confounding low in 4/4
Consistency:	-1	Some inconsistency, 1 study showed no increased risk after alkylating agents and 3 studies showed non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		No increased risk of alkylating agents on the risk of subsequent meningioma in CAYA cancer survivors. (1 study significant effect, 3 studies no significant effect; 64,421 participants; 624 events)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CF, confounding; DB, detection bias; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
3.c. Risk subsequent CNS neoplasms (all different types*) after alkylating agents (n=2 studies)	Patterson 2014	12,098 CAYA cancer survivors	<10-≥20	35.4%	219: 55 glioma, 148 meningioma, 16 other	Rate ratio (95% CI) Alkylating agents yes vs. no: 0.7 (0.5-1.0)	SB: high risk AB: unclear DB: unclear CF: low risk
	Bhatia 2002	8,831 CAYA ALL survivors	5.5 (0-16.1)	38%	19: 9 glioblastoma multiforme, 4 anaplastic astrocytoma, 3 PNET, 1 medulloblastoma, 2 meningioma	Relative risk (95% CI) 1-2000 mg/m^2 cyclophosphamide vs. none: 0.7 (0.2-2.6); >2000 mg/m^2 cyclophosphamide vs. none: 0.9 (0.3-2.9)	SB: unclear AB: low risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Retrospective cohort studies					
Study limitations:	-1	Some limitations: Selection bias high in 1/2, unclear in 1/2; Attrition bias low in 1/2, unclear in 1/2; Detection bias unclear in 2/2; Confounding low in 2/2					
Consistency:	0	No important inconsistency, all studies show non-significant effects					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	0	No important imprecision, high total number of events					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	No dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊕⊕⊖ MODERATE					
Conclusion:		No significant effect of alkylating agents on the risk of subsequent CNS neoplasms (different types)* in CAYA cancer survivors. (2 studies no significant effect; 20,929 participants; 238 events)					

Abbreviations: AB, attrition bias; ALL, acute lymphoblastic leukemia; CAYA, childhood, adolescent and young adult; CF, confounding; CNS, central nervous system; DB, detection bias; HSCT, hematopoietic stem cell transplant; NM, not mentioned; PNET, primitive neuroectodermal tumor; SB, selection bias; yr, year.
* Studies including different types of subsequent CNS neoplasms, not making a distinction between glioma, meningioma and other types.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
4.a. Risk subsequent glioma after antimetabolites (n=2 studies)	Patterson 2014	12,098 CAYA cancer survivors	<10-≥20	35.4%	55 glioma	Rate ratio (95% CI) Intrathecal methotrexate yes vs. no: 1.3 (0.8-2.0)	SB: high risk AB: unclear DB: unclear CF: low risk
	Neglia 2006	14,361 CAYA cancer survivors (116 cases matched to 464 controls)	>5-≥15	71.7% (radiotherapy, not further specified)	40 glioma	Odds ratio (95% CI) 6-mercaptopurine or 6-thioguanine yes vs. no: 0.75 (0.13-4.45)	SB: high risk AB: unclear DB: unclear CF: low risk
GRADE assessment:							

Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias high in 2/2; Attrition bias unclear in 2/2; Detection bias unclear in 2/2; Confounding low in 2/2
Consistency:	0	No important inconsistency, both studies show non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⨀ MODERATE
Conclusion:		No significant effect of antimetabolites on the risk of subsequent glioma in CAYA cancer survivors (2 studies no significant effect; 26,459 participants; 95 events)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CF, confounding; DB, detection bias; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
4.1.a. Risk subsequent glioma after methotrexate (n=1 study)	Patterson 2014	12,098 CAYA cancer survivors	<10-≥20	35.4%	55 glioma	Rate ratio (95% CI) Intrathecal methotrexate yes vs. no: 1.3 (0.8-2.0)	SB: high risk AB: unclear DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Retrospective cohort studies					
Study limitations:	-1	Some limitations: Selection bias high in 1/1; Attrition bias unclear in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1					
Consistency:	0	Not applicable (1 study)					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-1	Some imprecision, only one study, but narrow confidence intervals					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	No dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⨁⨁⨀⨀ LOW					
Conclusion:		No significant effect of intrathecal methotrexate on the risk of subsequent glioma in CAYA cancer survivors (1 study no significant effect; 12,098 participants; 55 events)					

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CF, confounding; DB, detection bias; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
4.2.a. Risk subsequent glioma after 6-mercaptopurine or 6-thioguanine (n=1 study)	Neglia 2006	14,361 CAYA cancer survivors (116 cases matched to 464 controls)	>5-≥15	71.7% (radiotherapy, not further specified)	40 glioma	Odds ratio (95% CI) 6-mercaptopurine or 6-thioguanine yes vs. no: 0.75 (0.13-4.45)	SB: high risk AB: unclear DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Retrospective cohort studies					
Study limitations:	-1	Some limitations: Selection bias high in 1/1; Attrition bias unclear in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1					
Consistency:	0	Not applicable (1 study)					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-1	Some imprecision, only one study, but narrow confidence intervals					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	No dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊕⊖⊖ LOW					
Conclusion:		No significant effect of 6-mercaptopurine or 6-thioguanine on the risk of subsequent glioma in CAYA cancer survivors (1 study no significant effect; 14,361 participants; 40 events)					

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CF, confounding; DB, detection bias; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
4.b. Risk subsequent meningioma after antimetabolites (n=4 studies)	Kok 2018	5,843 CCS	28.3 (5.0-52.2)	21.9%	96 benign meningioma	Methotrexate not significantly associated (57 exposed cases) (no effect measure reported)	SB: low risk AB: low risk DB: unclear CF: low risk
	Patterson 2014	12,098 CAYA cancer survivors	<10-≥20	35.4%	148 meningioma	Rate ratio (95% CI) Intrathecal methotrexate yes vs. no: 1.3 (0.8-2.0)	SB: high risk AB: unclear DB: unclear CF: low risk
	Taylor 2010	17,980 CCS	17.3 (>5 - …)	51.% (radiotherapy, not further specified)	137 meningioma	Relative risk (95% CI) Intrathecal methotrexate 1-39 mg/m^2 vs. 0 mg/m^2: 15.4 (2.2-179.6); Intrathecal methotrexate 40-69 mg/m^2 vs. 0 mg/m^2: 10.8 (1.3-143.0); Intrathecal methotrexate ≥70 mg/m^2 vs. 0 mg/m^2: 35.6 (4.8-599.4);	SB: low risk AB: low risk DB: unclear CF: low risk

						Excess relative risk with increasing radiotherapy dose per mg/m^2: β 2.2 (0.1-64.4); p=0.015	
	Neglia 2006	14,361 CAYA cancer survivors (116 cases matched to 464 controls)	>5-≥15	71.7% (radiotherapy, not further specified)	66 meningioma	Odds ratio (95% CI) 6-mercaptopurine or 6-thioguanine yes vs. no: 1.37 (0.26-7.21)	SB: high risk AB: unclear DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Retrospective cohort studies					
Study limitations:	-1	Some limitations: Selection bias low in 2/4, high in 2/4; Attrition bias low in 2/4, unclear in 2/4; Detection bias unclear in 4/4; Confounding low in 4/4					
Consistency:	-1	Some inconsistency, 1 study shows significantly increased risk after intrathecal methotrexate, 2 studies shows non-significant effect of (intrathecal) methotrexate and 1 study shows non-significant effect 6-mercaptopurine or 6-thioguanine					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-1	Some imprecision, large number of events, but the study that showed an effect had very broad confidence intervals					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	No dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊖⊖⊖ VERY LOW					
Conclusion:		Increased risk of subsequent meningioma after intrathecal methotrexate in CAYA cancer survivors (1 study significant effect, 2 studies no significant effect; 35,921 participants; 381 events), but no significant effect 6-mercaptopurine or 6-thioguanine on the risk of subsequent meningioma in CAYA cancer survivors. (1 study no significant effect, 14,361 participants, 66 events)					

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
4.1.b. Risk subsequent meningioma after methotrexatae (n=3 studies)	Kok 2018	5,843 CCS	28.3 (5.0-52.2)	21.9%	96 benign meningioma	Methotrexate not significantly associated (57 exposed cases) (no effect measure reported)	SB: low risk AB: low risk DB: unclear CF: low risk
	Patterson 2014	12,098 CAYA cancer survivors	<10-≥20	35.4%	148 meningioma	Rate ratio (95% CI) Intrathecal methotrexate yes vs. no: 1.3 (0.8-2.0)	SB: high risk AB: unclear DB: unclear CF: low risk
	Taylor 2010	17,980 CCS	17.3 (>5 - …)	51.% (radiotherapy, not further specified)	137 meningioma	Relative risk (95% CI) Intrathecal methotrexate 1-39 mg/m^2 vs. 0 mg/m^2: 15.4 (2.2-179.6); Intrathecal methotrexate 40-69 mg/m^2 vs. 0 mg/m^2: 10.8 (1.3-143.0); Intrathecal methotrexate ≥70 mg/m^2	SB: low risk AB: low risk DB: unclear CF: low risk

						vs. 0 mg/m^2: 35.6 (4.8-599.4); Excess relative risk with increasing radiotherapy dose per mg/m^2: β 2.2 (0.1-64.4); p=0.015	
GRADE assessment:							
Study design:	+4	Retrospective cohort studies					
Study limitations:	-1	Some limitations: Selection bias low in 2/3, high in 1/3; Attrition bias low in 2/3, unclear in 1/3; Detection bias unclear in 3/3; Confounding low in 3/3					
Consistency:	-1	Some inconsistency, 1 study shows significantly increased risk after intrathecal methotrexate, 2 studies show non-significant effects of (intrathecal) methotrexate					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-1	Some imprecision, since only 1 study shows significant effect of intrathecal methotrexate and had very broad confidence intervals					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	No dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊖⊖⊖ VERY LOW					
Conclusion:		Increased risk of subsequent meningioma after intrathecal methotrexate in CAYA cancer survivors. (1 study significant effect, 2 studies no significant effect; 35,921 participants; 381 events)					

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
4.2.b. Risk subsequent meningioma after 6-mercaptopurine or 6-thioguanine (n=1 study)	Neglia 2006	14,361 CAYA cancer survivors (116 cases matched to 464 controls)	>5-≥15	71.7% (radiotherapy, not further specified)	66 meningioma	Odds ratio (95% CI) 6-mercaptopurine or 6-thioguanine yes vs. no: 1.37 (0.26-7.21)	SB: high risk AB: unclear DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Retrospective cohort studies					
Study limitations:	-1	Some limitations: Selection bias high in 1/1; Attrition bias unclear in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1					
Consistency:	0	Not applicable (1 study)					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-2	Important imprecision, only one study and with small number of events					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	No dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊖⊖⊖ VERY LOW					
Conclusion:		No significant effect 6-mercaptopurine or 6-thioguanine on the risk of subsequent meningioma in CAYA cancer survivors. (1 study no significant effect, 14,361 participants, 66 events)					

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
4.c. Risk subsequent CNS neoplasms (all different types*) after antimetabolites (n=1 study)	Patterson 2014	12,098 CAYA cancer survivors	<10-≥20	35.4%	219: 55 glioma, 148 meningioma, 16 other	Rate ratio (95% CI) Intrathecal methotrexate yes vs. no: 1.3 (0.8-2.0)	SB: high risk AB: unclear DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Important limitations: Selection bias high in 1/1; Attrition bias unclear in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1
Consistency:	0	N/A (1 study)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, only 1 study
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨀⨀ LOW
Conclusion:		No significant effect of intrathecal methotrexate on the risk of subsequent CNS neoplasms (different types)* in CAYA cancer survivors. (1 study no significant effect; 12,098 participants; 219 events)

Abbreviations: AB, attrition bias; ALL, acute lymphoblastic leukemia; CAYA, childhood, adolescent and young adult; CF, confounding; CNS, central nervous system; DB, detection bias; HSCT, hematopoietic stem cell transplant; NM, not mentioned; SB, selection bias; yr, year.
* Studies including different types of subsequent CNS neoplasms, not making a distinction between glioma, meningioma and other types.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
5.a. Risk subsequent glioma after epipodophyllotoxins (n=1 study)	Neglia 2006	14,361 CAYA cancer survivors (116 cases matched to 464 controls)	>5-≥15	71.7% (radiotherapy, not further specified)	40 glioma	Odds ratio (95% CI) Epipodophyllotoxins yes vs. no: 2.43 (0.63-9.32)	SB: high risk AB: unclear DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias high in 1/1; Attrition bias unclear in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1
Consistency:	0	Not applicable (1 study)
Directness:	0	Results are direct, population and outcomes broadly generalizable

Precision:	-2	Important imprecision, only one study and low total number of events and wide confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		No significant effect of epipodophyllotoxins on the risk of subsequent glioma in CAYA cancer survivors. (1 study no significant effect; 14,361 participants; 40 events)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CF, confounding; DB, detection bias; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
5.b. Risk subsequent meningioma after epipodophyllotoxins (n=3 studies)	Turcotte 2017	23,603 CCS	20.5±7.5	53.1% (any radiotherapy, not further specified)	233 benign meningioma, 7 malignant meningioma	Relative rate (95% CI) Epipodophyllotoxins 1-1000 mg/m^2 vs. none: 1.88 (0.78-4.51); Epipodophyllotoxins 1001-4000 mg/m^2 vs. none: 1.15 (0.34-3.87); Epipodophyllotoxins >4000 mg/m^2 vs. none: 1.73 (0.69-4.36)	SB: high risk AB: unclear DB: unclear CF: low risk
	Friedman 2010	14,359 CAYA cancer survivors	22.7 ± 6.8	59.4% (radiotherapy, not further specified)	170 meningioma	Risk ratio (95% CI) Epipodophyllotoxins 1-1000 mg/m^2 vs. none: 1.8 (0.7-5.0); Epipodophyllotoxins ≥4000 mg/m^2 vs. none: 1.7 (0.6-4.3)	SB: high risk AB: low risk DB: unclear CF: low risk
	Neglia 2006	14,361 CAYA cancer survivors (116 cases matched to 464 controls)	>5-≥15	71.7% (radiotherapy, not further specified)	66 meningioma	Odds ratio (95% CI) Epipodophyllotoxins yes vs. no: 2.19 (0.29-16.7)	SB: high risk AB: unclear DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Retrospective cohort studies					
Study limitations:	-1	Some limitations: Selection bias high in 3/3; Attrition bias low in 1/3, unclear in 2/3; Detection bias unclear in 3/3; Confounding low in 3/3					
Consistency:	0	No important inconsistency, all studies show non-significant effects					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	0	No important imprecision, high total number of patients and events					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	No dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊕⊕⊖ MODERATE					
Conclusion:		No significant effect of epipodophyllotoxins on the risk of subsequent meningioma in CAYA cancer survivors. (3 studies no significant effect; 52323 participants; 476 events)					

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CF, confounding; DB, detection bias; SB, selection bias; yr, year.

PICO 5.c.: no studies

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
6.a. Risk subsequent glioma after anthracyclines (n=1 study)	Neglia 2006	14,361 CAYA cancer survivors (116 cases matched to 464 controls)	>5-≥15	71.7% (radiotherapy, not further specified)	40 glioma	Odds ratio (95% CI) Anthracyclines yes vs. no: 0.90 (0.37-2.20)	SB: high risk AB: unclear DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Retrospective cohort studies					
Study limitations:	-1	Some limitations: Selection bias high in 1/1; Attrition bias unclear in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1					
Consistency:	0	Not applicable (1 study)					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-1	Some imprecision: only 1 study and low number of events, but narrow confidence intervals					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	No dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊕⊖⊖ LOW					
Conclusion:		No significant effect of anthracyclines on the risk of subsequent glioma in CAYA cancer survivors. (1 study no significant effect; 14,361 participants; 40 events)					

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CF, confounding; DB, detection bias; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
6.b. Risk subsequent meningioma after anthracyclines (n=3 studies)	Turcotte 2017	23,603 CCS	20.5±7.5	53.1% (any radiotherapy, not further specified)	233 benign meningioma, 7 malignant meningioma	Relative rate (95% CI) Anthracyclines 1-100 mg/m^2 vs. none: 1.10 (0.42-2.85) Anthracyclines 101-300 mg/m^2 vs. none: 0.59 (0.32-1.10) Anthracyclines >300 mg/m^2 vs. none: 0.58 (0.33-1.03)	SB: high risk AB: unclear DB: unclear CF: low risk
	Friedman 2010	14,359 CAYA cancer survivors	22.7 ± 6.8	59.4% (radiotherapy, not further specified)	170 meningioma	Risk ratio (95% CI) Anthracyclines 1-100 mg/m^2 vs. none: 0.8 (0.3-2.1); Anthracyclines 101-300 mg/m^2 vs. none:	SB: high risk AB: low risk DB: unclear CF: low risk

						0.8 (0.5-1.9); Anthracyclines ≥301 mg/m^2 vs. none: 0.5 (0.2-1.2)	
	Neglia 2006	14,361 CAYA cancer survivors (116 cases matched to 464 controls)	>5-≥15	71.7% (radiotherapy, not further specified)	66 meningioma	Odds ratio (95% CI) Anthracyclines yes vs. no: 0.33 (0.11-1.04)	SB: high risk AB: unclear DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Retrospective cohort studies					
Study limitations:	-1	Some limitations: Selection bias high in 3/3; Attrition bias low in 1/3, unclear in 2/3; Detection bias unclear in 3/3; Confounding low in 3/3					
Consistency:	0	No important inconsistency, all studies show non-significant effects					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	0	No important imprecision, high total number of patients and events					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	No dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊕⊕⊖ MODERATE					
Conclusion:		No significant effect of anthracyclines on the risk of subsequent meningioma in CAYA cancer survivors. (3 studies no significant effect; 52323 participants; 476 events)					

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CF, confounding; DB, detection bias; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
6.c. Risk subsequent CNS neoplasms (all different types*) after anthracyclines (n=1 study)	Bhatia 2002	8,831 CAYA ALL survivors	5.5 (0-16.1)	38%	19: 9 glioblastoma multiforme, 4 anaplastic astrocytoma, 3 PNET, 1 medulloblastoma, 2 meningioma	Relative risk (95% CI) Anthracyclines 11-200 mg/m^2 vs. none: 0.6 (0.2-1.9); Anthracyclines >200 mg/m^2 vs. none: 1.8 (0.5-6.5)	SB: unclear AB: low risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Retrospective cohort studies					
Study limitations:	-1	Some limitations: Selection bias unclear in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1					
Consistency:	0	Not applicable (1 study)					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-1	Some imprecision: only 1 study and low number of events, but narrow confidence intervals					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	No dose response relationship					

Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		No significant effect of anthracyclines on the risk of subsequent CNS neoplasms (different types)* in CAYA cancer survivors. (1 study no significant effect; 8,831 participants; 19 events)

Abbreviations: AB, attrition bias; ALL, acute lymphoblastic leukemia; CAYA, childhood, adolescent and young adult; CF, confounding; CNS, central nervous system; DB, detection bias; PNET, primitive neuroectodermal tumor; SB, selection bias; yr, year.
* Studies including different types of subsequent CNS neoplasms, not making a distinction between glioma, meningioma and other types.

Subgroup	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
7.a. Risk subsequent glioma after platinum agents (n=1 study)	Neglia 2006	14,361 CAYA cancer survivors (116 cases matched to 464 controls)	>5-≥15	71.7% (radiotherapy, not further specified)	40 glioma	Odds ratio (95% CI) Platinum agents yes vs. no: 1.99 (0.20-19.8)	SB: high risk AB: unclear DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias high in 1/1; Attrition bias unclear in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1
Consistency:	0	Not applicable (1 study)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, only 1 study and small total number of events and wide confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		No significant effect of platinum agents on the risk of subsequent glioma in CAYA cancer survivors. (1 study no significant effect; 14,361 participants; 40 events)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CF, confounding; DB, detection bias; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
7.b. Risk subsequent meningioma after platinum agents (n=4 studies)	Kok 2018	5,843 CCS	28.3 (5.0-52.2)	21.9%	96 benign meningioma	Hazard ratio (95% CI) Carboplatin yes vs. no: 3.55 (1.62-7.78); No carboplatin dose-response relationship; Cisplatin not significantly associated (2 exposed cases) (no effect measure reported)	SB: low risk AB: low risk DB: unclear CF: low risk

	Turcotte 2017	23,603 CCS	20.5±7.5	53.1% (any radiotherapy, not further specified)	233 benign meningioma, 7 malignant meningioma	Relative rate (95% CI) Platinum agents 1-400 mg/m^2 vs. none: 2.93 (1.37-6.27); Platinum agents 401-750 mg/m^2 vs. none: 2.28 (0.88-5.92); Platinum dose >750 mg/m^2 vs. none: 3.12 (0.92-10.59)	SB: high risk AB: unclear DB: unclear CF: low risk
	Friedman 2010	14,359 CAYA cancer survivors	22.7 ± 6.8	59.4% (radiotherapy, not further specified)	170 meningioma	Risk ratio (95% CI) Platinum agents 1-400 mg/m^2 vs. none: 4.0 (1.5-11.1); Platinum agents 401-750 mg/m^2 vs. none: 1.8 (0.2-14.8) Platinum agents ≥750 mg/m^2 vs. none: 0.0	SB: high risk AB: low risk DB: unclear CF: low risk
	Neglia 2006	14,361 CAYA cancer survivors (116 cases matched to 464 controls)	>5-≥15	71.7% (radiotherapy, not further specified)	66 meningioma	Odds ratio (95% CI) Platinum agents yes vs. no: 3.07 (0.17-55.7)	SB: high risk AB: unclear DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Retrospective cohort studies					
Study limitations:	-1	Some limitations: Selection bias low ¼, high in 3/4; Attrition bias low in 2/4, unclear in 2/4; Detection bias unclear in 4/4; Confounding low in 4/4					
Consistency:	-1	Some inconsistency, 1 study shows non-significant effect, 1 study shows a significant effect of carboplatin and 2 studies show significant effect of platinum agents <400 mg/m^2 and non-significant effects of platinum agents >400 mg/m^2					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-1	Some imprecision, high total number of events, but wide confidence intervals					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	No dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊖⊖⊖ VERY LOW					
Conclusion:		Increased risk of meningioma after platinum agents in CAYA cancer survivors. (3 studies significant effect, 1 study no significant effect; 58,16628,720 participants; 572 events)					

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CF, confounding; DB, detection bias; SB, selection bias; yr, year.

PICO 7.c.: no studies

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
8.a. Risk subsequent glioma after	Reulen 2011	17,981 CCS	24.3 (>5 - …)	Unclear how many patients were treated with CRT	105 glioma	Relative risk (95% CI) Chemotherapy yes vs. no: 1.3 (0.7-2.5)	SB: low risk AB: low risk DB: unclear

chemotherapy not further specified (n=2 studies)							CF: low risk
	Taylor 2010	17,980 CCS	17.3 (>5 - …)	51.% (radiotherapy, not further specified)	73 glioma	Standardized incidence ratio (95% CI) Chemotherapy: 15.3 (10.3-21.9); No chemotherapy: 10.2 (7.1-14.1); p=0.096	SB: low risk AB: low risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Retrospective cohort studies					
Study limitations:	-1	Some limitations: Selection bias low in 2/2; Attrition bias low in 2/2; Detection bias unclear in 2/2; Confounding low in 1/2, high in 1/2					
Consistency:	0	No important inconsistency, both studies show non-significant effects					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	0	No important imprecision, high total number of patients and events					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	No dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊕⊕⊖ MODERATE					
Conclusion:		No significant effect of chemotherapy (not further specified) on the risk of subsequent glioma in CAYA cancer survivors. (2 studies no significant effect; 35,961 participants; 178 events)					

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CRT; cranial radiotherapy; DB, detection bias; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
8.b. Risk subsequent meningioma after chemotherapy not further specified (n=1 study)	Cardous-Ubbink 2007	1,368 CCS	16.8 (5-≥30)	44.5% (radiotherapy, not further specified)	12 meningioma	Hazard ratio (95% CI) Chemotherapy yes vs. no: 2.74 (0.34-21.8)	SB: low risk AB: low risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Retrospective cohort studies					
Study limitations:	0	No serious limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1					
Consistency:	0	Not applicable (1 study)					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-2	Important imprecision, only 1 study and small total number of events					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	No dose response relationship					
Plausible confounding:	0	No plausible confounding					

Quality of evidence:	⊕⊕⊖⊖ LOW
Conclusion:	No significant effect of chemotherapy (not further specified) on the risk of subsequent meningioma in CAYA cancer survivors. (1 study no significant effect; 1,368 participants; 12 events)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
8.c. Risk subsequent CNS neoplasms (all different types*) after chemotherapy not further specified (n=1 study)	Little 1998	4,199 CCS (22 cases matched to 282 controls)	15.1 (2.2-45.8)	NM	22: 12 malignant brain neoplasm, 10 benign/unspecified brain neoplasm	Chemotherapy yes vs. no was not significantly associated with the risk of subsequent CNS neoplasms (no effect measure reported)	SB: unclear AB: unclear DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias unclear in 1/1; Attrition bias unclear in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1
Consistency:	0	Not applicable (1 study)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, only 1 study and small total number of events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding

Quality of evidence:	⊕⊖⊖⊖ VERY LOW
Conclusion:	No significant effect of chemotherapy (not further specified) on the risk of subsequent CNS neoplasms (different types)* in CAYA cancer survivors. (1 study no significant effect; 4,199 participants; 22 events)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CNS, central nervous system; DB, detection bias; NM, not mentioned; SB, selection bias; yr, year.

* Studies including different types of subsequent CNS neoplasms, not making a distinction between glioma, meningioma and other types.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
9.a. Risk subsequent glioma by age at primary cancer treatment	Patterson 2014	12,098 CAYA cancer survivors	<10-≥20	35.4%	55 glioma	Rate ratio (95% CI) 0-4 yr vs. ≥15 yr: 2.0 (0.5-7.8); 5-9 yr vs. ≥15 yr: 0.9 (0.2-3.5); 10-14 yr vs. ≥15 yr: 1.8 (0.6-5.6); p=0.22	SB: high risk AB: unclear DB: unclear CF: low risk

(n=4 studies)	Reulen 2011	17,981 CCS	24.3 (>5 - …)	Unclear how many patients were treated with CRT	105 glioma	Relative risk (95% CI) 0-4 yr vs. 10-14 yr: 1.8 (1.0-3.3); 5-9 yr vs. 10-14 yr: 1.1 (0.6-2.1)	SB: low risk AB: low risk DB: unclear CF: low risk
	Taylor 2010	17,980 CCS	17.3 (>5 - …)	51.% (radiotherapy, not further specified)	73 glioma	Standardized incidence ratio (95% CI) 0-4 yr: 12.0 (8.3-16.8); 5-9 yr: 12.3 (7.6-18.9); 10-14 yr: 8.0 (4.8-12.7) p=0.31	SB: low risk AB: low risk DB: unclear CF: low risk
	Neglia 2006	14,361 CAYA cancer survivors (116 cases matched to 464 controls)	>5-≥15	71.7% (radiotherapy, not further specified)	40 glioma	Standardized incidence ratio (95% CI) 0-4 yr: 14.5 (9.56-21.0); 5-9 yr: 7.48 (3.21-14.5); 10-14 yr: 6.24 (2.48-12.6); 15-20 yr: 1.99 (0.33-6.16); No p-value reported	SB: high risk AB: unclear DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 2/4, high in 2/4; Attrition bias low in 2/4, unclear in 2/4; Detection bias unclear in 4/4; Confounding low in 4/4
Consistency:	-1	Some inconsistency, 1 study shows significant effect of younger age at primary cancer treatment, 1 study shows effect of younger age at primary cancer treatment (unclear if significant), 2 studies show non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		Increased risk of subsequent glioma in CAYA cancer survivors treated at a younger age. (1 study significant effect, 3 studies no significant effect; 62,420 participants; 273 events)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CRT, cranial radiotherapy; DB, detection bias; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
9.b. Risk subsequent meningioma by age at primary cancer treatment (n=7 studies)	Kok 2018	5,843 CCS	28.3 (5.0-52.2)	21.9%	96 benign meningioma	Hazard ratio (95% CI) Age at primary cancer diagnosis 0-4 yr vs. 10-17 yr: 2.38 (1.39-4.07); Age at primary cancer diagnosis 5-9 yr vs. 10-17 yr: 1.09 (0.62-1.91)	SB: low risk AB: low risk DB: unclear CF: low risk
	Bowers 2017	4,221 CCS	22.8 (5.5-38.0)	100%	169 meningioma	Hazard ratio (95% CI) Age at primary cancer diagnosis 0-5 yr vs. 16-20 yr: 1.6 (0.8-3.2);	SB: unclear AB: unclear DB: unclear

						Age at primary cancer diagnosis 5-10 yr vs. 16-20 yr: 1.2 (0.6-2.4) Age at primary cancer diagnosis 11-15 yr vs. 16-20 yr: 0.9 (95% CI 0.4-2.0) *P* for trend = 0.076	CF: low risk
	Turcotte 2017	23,603 CCS	20.5±7.5	53.1% (any radiotherapy, not further specified)	233 benign meningioma, 7 malignant meningioma	Relative rate (95% CI) Age at primary cancer diagnosis 5-9 yr vs. 0-4 yr: 0.59 (0.38-0.92); Age at primary cancer diagnosis 10-14 yr vs. 0-4 yr: 0.19 (0.11-0.33); Age at primary cancer diagnosis ≥15 yr vs. 0-4 yr: 0.14 (0.07-0.27); Year of diagnosis per 5 yr: 0.93 (0.86-1.00)	SB: high risk AB: unclear DB: unclear CF: low risk
	Felicetti 2015	90 CCS	24.6 (range 13.2-36.8)	100%	15 meningioma	Odds ratio (95% CI) Age at primary cancer diagnosis <10 yr vs. ≥10 yr: 0.86 (0.18-4.04)	SB: unclear AB: low risk DB: unclear CF: low risk
	Patterson 2014	12,098 CAYA cancer survivors	<10-≥20	35.4%	148 meningioma	Rate ratio (95% CI) 0-4 yr vs. ≥15 yr: 4.8 (2.1-11.0); 5-9 yr vs. ≥15 yr: 2.6 (1.2-5.5); 10-14 yr vs. ≥15 yr: 1.2 (0.6-2.6); p<0.001	SB: high risk AB: unclear DB: unclear CF: low risk
	Friedman 2010	14,359 CAYA cancer survivors	22.7 ± 6.8	59.4% (radiotherapy, not further specified)	170 meningioma	Risk ratio (95% CI) 5-9 yr vs. 0-4 yr: 0.7 (0.5-1.1); 10-14 yr vs. 0-4 yr: 0.4 (0.2-2.6); ≥15 yr vs. 0-4 yr: 0.6 (0.3-1.1)	SB: high risk AB: low risk DB: unclear CF: low risk
	Cardous-Ubbink 2007	1,368 CCS	16.8 (5-≥30)	44.5% (radiotherapy, not further specified)	12 meningioma	Hazard ratio (95% CI) Age at diagnosis per year: 1.03 (0.90-1.18)	SB: low risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 2/7, high in 2/7, unclear in 3/7; Attrition bias low in 4/7, unclear in 3/7; Detection bias unclear in 7/7; Confounding low in 7/7
Consistency:	-1	Some inconsistency, 3 studies show significant effect of younger age at primary cancer treatment, 4 studies show non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW

Conclusion:	Increased risk of subsequent meningioma in CAYA cancer survivors treated at a younger age. (3 studies significant effect, 4 studies no significant effect; 61,582 participants; 850 events)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
9.c. Risk subsequent CNS neoplasms (all different types*) by age at primary cancer treatment (n=5 studies)	Patterson 2014	12,098 CAYA cancer survivors	<10-≥20	35.4%	219: 55 glioma, 148 meningioma, 16 other	Rate ratio (95% CI) 0-4 yr vs. ≥15 yr: 4.8 (2.4-9.7); 5-9 yr vs. ≥15 yr: 2.5 (1.3-4.7); 10-14 yr vs. ≥15 yr: 1.7 (0.9-3.0); p<0.001	SB: high risk AB: unclear DB: unclear CF: low risk
	Bhatia 2002	8,831 CAYA ALL survivors	5.5 (0-16.1)	38%	19: 9 glioblastoma multiforme, 4 anaplastic astrocytoma, 3 PNET, 1 medulloblastoma, 2 meningioma	Relative risk (95% CI) >5 yr vs. 0-5 yr: 0.6 (0.2-1.5)	SB: unclear AB: low risk DB: unclear CF: low risk
	Löning 2000	5,006 CAYA ALL patients	5.7 (1.5-18)	77.2%	13: 4 glioblastoma, 4 astrocytoma, 3 PNET, 2 meningioma	15-yr cumulative incidence (95% CI) <7 yr: 1.5% (0.2-2.7); ≥7 yr: 0.1% (0.0-0.3); p=0.03	SB: unclear AB: unclear DB: unclear CF: high risk
	Walter 1998	1,612 childhood ALL patients	15.9 (5.5-29.9)	77.6%	22: 4 glioblastoma multiforme, 2 anaplastic astrocytoma, 4 other high-grade glioma, 1 low-grade oligodendroglioma, 11 meningioma	20-yr cumulative incidence (95% CI) 0-5 yr: 1.98%; >5 yr: 0.53%; p=0.104	SB: unclear AB: low risk DB: unclear CF: high risk
	Rosso 1994	3,196 CCS	5.8 (0.0-25.1)	75.5% (radiotherapy, not further specified)	9: 4 glioblastoma, 3 astrocytoma, 1 oligodendroglioma, 1 brain lymphoma	Age at primary cancer diagnosis was not significantly associated with the risk of subsequent CNS tumors (no effect measure reported)	SB: unclear AB: low risk DB: unclear CF: unclear

GRADE assessment:

Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias high in 1/5, unclear in 4/5; Attrition bias low in 3/5, unclear in 2/5; Detection bias unclear in 5/5; Confounding low in 2/5, high in 2/5, unclear in 1/5
Consistency:	-1	Some inconsistency, 2 studies show significant effect of younger age at primary cancer treatment, 3 studies show non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect

Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		Increased risk of subsequent CNS neoplasms (different types)* in CAYA cancer survivors treated at a younger age. (2 studies significant effect, 3 studies no significant effect; 30,743 participants; 282 events)

Abbreviations: AB, attrition bias; ALL, acute lymphoblastic leukemia; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CNS, central nervous system; DB, detection bias; PNET, primitive neuroectodermal tumor; SB, selection bias; yr, year.
* Studies including different types of subsequent CNS neoplasms, not making a distinction between glioma, meningioma and other types.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
10.a. Risk subsequent glioma by gender (n=4 studies)	Patterson 2014	12,098 CAYA cancer survivors	<10-≥20	35.4%	55 glioma	Rate ratio (95% CI) Females vs. males: 0.9 (0.5-1.7)	SB: high risk AB: unclear DB: unclear CF: low risk
	Reulen 2011	17,981 CCS	24.3 (>5 - …)	Unclear how many patients were treated with CRT	105 glioma	Standardized incidence ratio (95% CI) Males: 5.7 (4.3-7.4); Females: 7.6 (5.8-10.0); No p-value reported	SB: low risk AB: low risk DB: unclear CF: low risk
	Taylor 2010	17,980 CCS	17.3 (>5 - …)	51.% (radiotherapy, not further specified)	73 glioma	Standardized incidence ratio (95% CI) Males: 9.0 (6.4-12.5); Females: 13.4 (9.4-18.6); p=0.09	SB: low risk AB: low risk DB: unclear CF: low risk
	Neglia 2006	14,361 CAYA cancer survivors (116 cases matched to 464 controls)	>5-≥15	71.7% (radiotherapy, not further specified)	40 glioma	Standardized incidence ratio (95% CI) Males: 9.64 (6.39-13.8); Females: 7.28 (4.10-11.8); No p-value reported	SB: high risk AB: unclear DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Retrospective cohort studies					
Study limitations:	-1	Some limitations: Selection bias low in 2/4, high in 2/4; Attrition bias low in 2/4, unclear in 2/4; Detection bias unclear in 4/4; Confounding low in 4/4					
Consistency:	0	No important inconsistency, all studies show non-significant effects					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	0	No important imprecision, high total number of patients and events					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	No dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊕⊕⊖ MODERATE					
Conclusion:		No significant effect of gender on the risk of subsequent glioma in CAYA cancer survivors. (4 studies no significant effect; 62,420 participants; 273 events)					

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CRT, cranial radiotherapy; DB, detection bias; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
10.b. Risk subsequent meningioma by gender (n=6 studies)	Kok 2018	5,843 CCS	28.3 (5.0-52.2)	21.9%	96 benign meningioma	Hazard ratio (95% CI) Females vs. males: 1.36 (0.91-2.04)	SB: low risk AB: low risk DB: unclear CF: low risk
	Bowers 2017	4,221 CCS	22.8 (5.5-38.0)	100%	169 meningioma	Hazard ratio (95% CI) Females vs. males: 1.7 (1.2-2.3)	SB: unclear AB: unclear DB: unclear CF: low risk
	Turcotte 2017	23,603 CCS	20.5±7.5	53.1% (any radiotherapy, not further specified)	233 benign meningioma, 7 malignant meningioma	Relative rate (95% CI) Females vs. males: 1.40 (1.00-1.95)	SB: high risk AB: unclear DB: unclear CF: low risk
	Felicetti 2015	90 CCS	24.6 (range 13.2-36.8)	100%	15 meningioma	Odds ratio (95% CI) Gender (reference group unclear): 0.60 (95% CI 0.08-4.81)	SB: unclear AB: low risk DB: unclear CF: low risk
	Patterson 2014	12,098 CAYA cancer survivors	<10-≥20	35.4%	148 meningioma	Rate ratio (95% CI) Females vs. males: 1.8 (1.3-2.6)	SB: high risk AB: unclear DB: unclear CF: low risk
	Friedman 2010	14,359 CAYA cancer survivors	22.7 ± 6.8	59.4% (radiotherapy, not further specified)	170 meningioma	Risk ratio (95% CI) Females vs. males: 1.6 (1.1-2.3)	SB: high risk AB: low risk DB: unclear CF: low risk
	Cardous-Ubbink 2007	1,368 CCS	16.8 (5-≥30)	44.5% (radiotherapy, not further specified)	12 meningioma	Hazard ratio (95% CI) Females vs. males: 0.37 (0.10-1.37)	SB: low risk AB: low risk DB: unclear CF: low risk

GRADE assessment:

Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 2/7, high in 3/7, unclear in 2/7; Attrition bias low in 4/7, unclear in 3/7; Detection bias unclear in 7/7; Confounding low in 7/7
Consistency:	0	No important inconsistency, 4 studies show significant increased risk in females, 3 studies show non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of patients and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect

Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		Increased risk of subsequent meningioma in female CAYA cancer survivors. (4 studies significant effect, 3 studies no significant effect; 16,5892 participants; 850 events)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
10.c. Risk subsequent CNS neoplasms (all different types*) by gender (n=3 studies)	Patterson 2014	12,098 CAYA cancer survivors	<10-≥20	35.4%	219: 55 glioma, 148 meningioma, 16 other	Rate ratio (95% CI) Females vs. males: 1.6 (1.2-2.2)	SB: high risk AB: unclear DB: unclear CF: low risk
	Bhatia 2002	8,831 CAYA ALL survivors	5.5 (0-16.1)	38%	19: 9 glioblastoma multiforme, 4 anaplastic astrocytoma, 3 PNET, 1 medulloblastoma, 2 meningioma	Relative risk (95% CI) Males vs. females: 2.54 (0.9-6.4)	SB: unclear AB: low risk DB: unclear CF: low risk
	Rosso 1994	3,196 CCS	5.8 (0.0-25.1)	75.5% (radiotherapy, not further specified)	9: 4 glioblastoma, 3 astrocytoma, 1 oligodendroglioma, 1 brain lymphoma	Gender was not significantly associated with the risk of subsequent CNS tumors (no effect measure reported)	SB: unclear AB: low risk DB: unclear CF: unclear
GRADE assessment:							
Study design:	+4	Retrospective cohort studies					
Study limitations:	-1	Some limitations: Selection bias high in 1/3, unclear in 2/3; Attrition bias low in 2/3, unclear in 1/3; Detection bias unclear in 3/3; Confounding low in 2/3, unclear in 1/3					
Consistency:	-1	Some inconsistency, 1 study shows significant increased risk in females, 2 studies show non-significant effects					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	0	No important imprecision, high total number of patients and events					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	No dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊕⊖⊖ LOW					
Conclusion:		Increased risk of subsequent CNS neoplasms (different types* of whom the majority diagnosed with a subsequent meningioma) in female CAYA cancer survivors. (1 study significant effect, 3 studies no significant effect; 24,125 participants; 247 events)					

Abbreviations: AB, attrition bias; ALL, acute lymphoblastic leukemia; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; PNET, primitive neuroectodermal tumor; SB, selection bias; yr, year.

* Studies including different types of subsequent CNS neoplasms, not making a distinction between glioma, meningioma and other types.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
11.a. Risk subsequent glioma after hormonal replacement therapy (n=1 study)	Patterson 2014	12,098 CAYA cancer survivors	<10-≥20	35.4%	55 glioma	Rate ratio (95% CI) Growth hormone treatment yes vs. no: 1.9 (0.7-4.8) Self-reported estrogen and/or progesterone treatment yes vs. no: 0.7 (0.5-1.2)	SB: high risk AB: unclear DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Retrospective cohort studies					
Study limitations:	-1	Some limitations: Selection bias high in 1/1; Attrition bias unclear in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1					
Consistency:	0	Not applicable (1 study)					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-1	Some imprecision, only 1 study, but high total number of patients and narrow confidence intervals					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	No dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⨁⨁⨀⨀ LOW					
Conclusion:		No significant effect of hormonal replacement therapy (growth hormone, estrogen/progesterone) on the risk of subsequent glioma in CAYA cancer survivors. (1 study no significant effect; 12,098 participants; 55 events; 1 multivariable analysis)					

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CF, confounding; DB, detection bias; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
11.b. Risk subsequent meningioma after hormonal replacement therapy (n=2 studies)	Swerdlow 2019	1,830 CCS treated with GH	Total 154.795 person years at risk, mean 14.9 yr per patient	63.7%	37 meningioma	Standardized incidence ratio (95% CI) in CCS treated with GH *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* for 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);	SB: high risk AB: low risk DB: unclear CF: low risk

						≥40 mg/kg/d: 1297.5 (95% CI 182.8-9210.9); *P* for 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* for trend = 0.13	
	Patterson 2014	12,098 CAYA cancer survivors	<10-≥20	35.4%	148 meningioma	Rate ratio (95% CI) GH treatment yes vs. no: 0.8 (0.4-1.7) Self-reported estrogen and/or progesterone treatment yes vs. no: 0.7 (0.5-1.2)	SB: high risk AB: unclear DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias high in 2/2; Attrition bias low in 1/2, unclear in 1/2; Detection bias unclear in 2/2; Confounding low in 2/2
Consistency:	0	No important inconsistency
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, very broad confidence intervals in 1 study
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨀⨀ LOW
Conclusion:		No significant effect of GH replacement therapy on the risk of subsequent meningioma in CAYA cancer survivors. (2 studies no significant effect; 13,928 participants; 185 events)

Abbreviations: AB, attrition bias; ALL, acute lymphoblastic leukemia; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CNS, central nervous system; CRT, cranial radiotherapy; DB, detection bias; fup, follow-up; GH, growth hormone; HSCT, hematopoietic stem cell transplant; PNET, primitive neuroectodermal tumor; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
11.c. Risk subsequent CNS neoplasms (all different types*) after hormonal replacement therapy (n=1 study)	Patterson 2014	12,098 CAYA cancer survivors	<10-≥20	35.4%	219: 55 glioma, 148 meningioma, 16 other	Rate ratio (95% CI) Growth hormone treatment yes vs. no: 1.0 (0.6-1.8) Self-reported estrogen and/or progesterone treatment yes vs. no: 0.7 (0.5-1.2)	SB: high risk AB: unclear DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias high in 1/1; Attrition bias unclear in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1
Consistency:	0	Not applicable (1 study)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, only 1 study, but high total number of patients and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		No significant effect of hormonal replacement therapy (growth hormone, estrogen/progesterone) on the risk of subsequent CNS neoplasms (different types)* in CAYA cancer survivors. (1 study no significant effect; 12,098 participants; 219 events)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CF, confounding; CNS, central nervous system; DB, detection bias; SB, selection bias; yr, year.
* Studies including different types of subsequent CNS neoplasms, not making a distinction between glioma, meningioma and other types.

PICO 12.a and 12.b: No studies identified

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
12.c. Risk subsequent CNS neoplasms (all different types*) in patients with neurofibromatosis (n=1 study)	Little 1998	4,199 CCS (22 cases matched to 282 controls)	15.1 (2.2-45.8)	NM	22: 12 malignant brain neoplasm, 10 benign/unspecified brain neoplasm	*Malignant brain neoplasms* Relative risk (95% CI) Neurofibromatosis yes vs. no: >1000 (6.53->1000) (after adjusting for the effects of first CNS tumor, the risk remained statistically significant) *Benign/unspecified brain neoplasms* Relative risk (95% CI) Neurofibromatosis yes vs. no: 10.25 (0.39-267.62)	SB: unclear AB: unclear DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias unclear in 2/2; Attrition bias unclear in 2/2; Detection bias unclear in 2/2; Confounding low in 1/2, high in 1/2
Consistency:	0	Not applicable (1 study)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, only 1 study with low number of events and wide confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		Increased risk of subsequent malignant CNS neoplasms (different types)* in CAYA cancer survivors with neurofibromatosis. (1 study significant effect; 4,199 participants; 22 events) No significant effect of neurofibromatosis on the risk of subsequent benign CNS neoplasms (different types)* in CAYA cancer survivors. (1 study no significant effect; 4,199 participants; 22 events)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CNS, central nervous system; DB, detection bias; SB, selection bias; yr, year.

* Studies including different types of subsequent CNS neoplasms, not making a distinction between glioma, meningioma and other types.

PICO 13.a and 13.b: No studies identified

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
13.c. Risk subsequent CNS neoplasms (all different types*) in patients with	Little 1998	4,199 CCS (22 cases matched to 282 controls)	15.1 (2.2-45.8)	NM	22: 12 malignant brain neoplasm, 10 benign/unspecified brain neoplasm	*Malignant brain neoplasms* Relative risk (95% CI) Genetic syndromes other than neurofibromatosis: 0.00 (0.00-10.09)	SB: unclear AB: unclear DB: unclear CF: low risk

genetic syndromes other than neurofibromatosis (n=1 study)			*Benign/unspecified brain neoplasms* Relative risk (95% CI) Genetic syndromes other than neurofibromatosis: 0.00 (0.00-40.79)
GRADE assessment:			
Study design:	+4	Retrospective cohort studies	
Study limitations:	-1	Some limitations: Selection bias unclear in 1/1; Attrition bias unclear in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1	
Consistency:	0	Not applicable (1 study)	
Directness:	0	Results are direct, population and outcomes broadly generalizable	
Precision:	-2	Important imprecision, only 1 study and broad confidence intervals	
Publication bias:	0	Unlikely	
Effect size:	0	No large magnitude of effect	
Dose-response:	0	No dose response relationship	
Plausible confounding:	0	No plausible confounding	
Quality of evidence:		⨁⊖⊖⊖ VERY LOW	
Conclusion:		No significant effect of genetic syndromes other than neurofibromatosis on the risk of subsequent CNS neoplasms (different types)* in CAYA cancer survivors. (1 study no significant effect; 4,199 participants; 22 events)	

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CNS, central nervous system; DB, detection bias; SB, selection bias; yr, year.

* Studies including different types of subsequent CNS neoplasms, not making a distinction between glioma, meningioma and other types.

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

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
1.a. Latency time subsequent glioma (n=9 studies)	Lee 2018	681 CNS tumor survivors	21.0	100%	6 high-grade glioma	Time interval from primary cancer diagnosis: Mean 10.8 (range 4.1-20.3) yr	SB: unclear AB: unclear DB: unclear
	Bilginer 2015	6 CCS with secondary CNS neoplasms	>2 yr	100%	2 high-grade glioma	Time interval from radiotherapy: 6 yr and 11 yr	SB: unclear AB: unclear DB: unclear
	Tsui 2015	2,779 childhood brain tumor patients	4.5 (0.1-28.2)	75.6%	23 glioma	Time interval from primary cancer diagnosis: Median 7.2 yr	SB: unclear AB: unclear DB: unclear
	Galloway 2012	370 CCS	4.7 (0.1-45.4)	100%	4 glioma	Time interval from primary cancer diagnosis: Median 15 yr	SB: unclear AB: low risk DB: unclear
	Friedman 2010	14,359 CAYA cancer survivors	22.7 ± 6.8	59.4% (radiotherapy, not further specified)	53 glioma	Time interval from primary cancer diagnosis: Median 11.7 (range 6.0-25.5) yr	SB: high risk AB: low risk DB: unclear
	Taylor 2010	17,980 CCS	17.3 (>5 - …)	51.% (radiotherapy, not further specified)	73 glioma (31 low-grade, 42 high-grade)	Time interval from primary cancer diagnosis: Glioma: Mean 17.4 yr; Low-grade glioma: Mean 15.5 yr; High-grade glioma: Mean 18.7 yr	SB: low risk AB: low risk DB: unclear
	Armstrong 2009	1,877 CAYA primary CNS tumor survivors	19.6 (5.1-34.6)	57.8%	15 glioma/astrocytoma	Time interval from primary cancer diagnosis: Median 14.0 yr	SB: high risk AB: low risk DB: unclear
	Neglia 2006	14,361 CAYA cancer survivors	>5-≥15	71.7% (radiotherapy, not further specified)	40 glioma	Time interval from primary cancer diagnosis: Median 9 yr	SB: high risk AB: unclear DB: unclear
	Walter 1998	1,612 childhood ALL patients	15.9 (5.5-29.9)	77.6%	10 high-grade glioma	Time interval from primary cancer diagnosis: Median 9.1 yr	SB: unclear AB: low risk DB: unclear

GRADE assessment:

Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 1/9, high in 3/9, unclear in 5/9; Attrition bias low in 5/9, unclear in 4/9; Detection bias unclear in 9/9
Consistency:	0	No important inconsistency, although the latency times vary among the studies
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of events

Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		The latency time of developing subsequent glioma in CAYA cancer survivors ranges from median 7 to 17 years after primary cancer diagnosis, ranging from minimal 4 years to at least 25.5 years. (9 studies; 54,025 participants; 226 events)

Abbreviations: AB, attrition bias; ALL, acute lymphoblastic leukemia; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CNS, central nervous system; DB, detection bias; NM, not mentioned; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
1.b. Latency time subsequent meningioma (n=18 studies)	Remes 2019	642 childhood brain tumor survivors	19.9	100%	6 meningioma	Time interval from primary cancer diagnosis: Mean 23 ± 4.3 yr	SB: high risk AB: low risk DB: unclear
	Ueda 2019	275 CCS	7 (...-33)	NM	4 meningioma	Time interval from primary cancer diagnosis: Median 26.5 (range 20-29) yr	SB: low risk AB: low risk DB: unclear
	Lee 2018	681 CNS tumor survivors	21.0	100%	13 meningioma	Time interval from primary cancer diagnosis: Mean 19.7 (range 12.2-33) yr	SB: unclear AB: unclear DB: unclear
	Kok 2018	5,843 CCS	28.3 (5.0-52.2)	21.9%	96 benign meningioma	Time interval from primary cancer diagnosis: Median 24.9 (range 8.5-44.5) yr	SB: low risk AB: low risk DB: unclear
	Bowers 2017	4,221 CCS	22.8 (5.5-38.0)	100%	169 meningioma	Time interval from primary cancer diagnosis: Median 22 (range 5-37) yr	SB: unclear AB: unclear DB: unclear
	Felicetti 2015	90 CCS	24.6 (range 13.2-36.8)	100%	15 meningioma	Time interval from primary cancer diagnosis: Median 22.5 (range 12.2-34.3) yr	SB: unclear AB: low risk DB: unclear
	Tsui 2015	2,779 childhood brain tumor patients	4.5 (0.1-28.2)	75.6%	13 non-malignant meningioma	Time interval from primary cancer diagnosis: Median 11.1 yr	SB: unclear AB: unclear DB: unclear
	Hudson 2013	1,713 CCS	25.1 (10.9-47.9)	64.7% (radiotherapy, not further specified)	63 meningioma	Time interval from primary cancer diagnosis: Median 26.6 (interquartile range 20.3-33.5) yr	SB: high risk AB: low risk DB: unclear
	Schmiegelow 2013	642 CAYA ALL survivors	NM	At least 35.8%	22 meningioma	Time interval from primary cancer diagnosis: Median 16.2 (50% range 12.3-18.3) yr	SB: unclear AB: unclear DB: unclear

	Galloway 2012	370 CCS	4.7 (0.1-45.4)	100%	10 meningioma	Time interval from primary cancer diagnosis: Median 22 yr	SB: unclear AB: low risk DB: unclear
	Friedman 2010	14,359 CAYA cancer survivors	22.7 ± 6.8	59.4% (radiotherapy, not further specified)	11 malignant meningioma	Time interval from primary cancer diagnosis: Median 22.9 (range 15.8-32.7) yr	SB: high risk AB: low risk DB: unclear
	Taylor 2010	17,980 CCS	17.3 (>5 - …)	51.% (radiotherapy, not further specified)	137 meningioma	Time interval from primary cancer diagnosis: Mean 23.1 yr	SB: low risk AB: low risk DB: unclear
	Armstrong 2009	1,877 CAYA primary CNS tumor survivors	19.6 (5.1-34.6)	57.8%	4 malignant meningioma	Time interval from primary cancer diagnosis: Median 23.7 yr	SB: high risk AB: low risk DB: unclear
	Banerjee 2009	60 childhood ALL survivors	>10	100%	11 meningioma	Time interval from primary cancer diagnosis: Range 14-34 yr	SB: unclear AB: low risk DB: unclear
	Goshen 2007	210 childhood ALL and non-Hodgkin lymphoma survivors	≥5	41.9%	16 meningioma	Time interval from primary cancer diagnosis: Median 21 (range 10-29) yr	SB: low risk AB: low risk DB: unclear
	Hijiya 2007	1,290 CAYA ALL survivors	18.7 (2.4-41.3)	NM	16 meningioma	Time interval from primary cancer diagnosis in survivors in first complete remission: Median 20.6 (range 12.6-31.7) yr	SB: low risk AB: low risk DB: unclear
	Neglia 2006	14,361 CAYA cancer survivors	>5-≥15	71.7% (radiotherapy, not further specified)	66 meningioma	Time interval from primary cancer diagnosis: Median 17 yr	SB: high risk AB: unclear DB: unclear
	Walter 1998	1,612 childhood ALL patients	15.9 (5.5-29.9)	77.6%	11 meningioma	Time interval from primary cancer diagnosis: Median 19 yr	SB: unclear AB: low risk DB: unclear

GRADE assessment:

Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 5/18, high in 5/18, unclear in 9/18; Attrition bias low in 8/18, unclear in 9/18; Detection bias unclear in 18/18
Consistency:	0	No important inconsistency, although the latency times vary among the studies
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding

Quality of evidence: ⊕⊕⊕⊖ MODERATE

Conclusion: The latency time of developing subsequent meningioma in CAYA cancer survivors ranges from median 11 to 27 years after primary cancer diagnosis, ranging from minimal 5 years to at least 44.5 years. (18 studies; 69,005 participants; 683 events)

Abbreviations: AB, attrition bias; ALL, acute lymphoblastic leukemia; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CNS, central nervous system; DB, detection bias; NM, not mentioned; SB, selection bias; yr, year.

Outcome	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
1.c. Latency time subsequent CNS neoplasms (all different types*) (n=16 studies)	Felice 2017	3.321 childhood acute leukemia or lymphoma patients	Not reported	Not reported (4 patients with a subsequent neoplasm had radiotherapy, not further specified)	5: 1 meningioma, 3 glioblastoma multiforme, 1 PNET	Time interval from primary cancer diagnosis: Median 9.3 (range 3.1-19.7) yr	SB: unclear AB: unclear DB: unclear
	Turcotte 2017	23,603 CCS	20.5±7.5	53.1% (any radiotherapy, not further specified)	340: 233 benign meningioma, 7 malignant meningioma, 82 glial tumors, 7 medulloblastoma/PNET, 11 other CNS neoplasms	Time interval from primary cancer diagnosis: Any: 10.9 (7.8-15.2); Glial tumors: Median 9.4 (interquartile range 7.4-13.2) yr; Medulloblastoma/PNET: Median 9.2 (interquartile range 8.8-13.8) yr	SB: high risk AB: unclear DB: unclear
	Bilginer 2015	6 CCS with secondary CNS neoplasms	>2 yr	100%	6: 1 meningeal sarcoma, 2 high-grade glial tumor, 1 high-grade malignant mesenchymal tumor, 2 high-grade medulloblastoma	Time interval from radiotherapy: Mean 9.5 (range 5-18) yr	SB: unclear AB: unclear DB: unclear
	Ning 2015	455 medulloblastoma survivors	16 (5.0-35.7)	100%	9: 3 glioblastoma, 2 anaplastic astrocytoma, 2 low-grade glioma, 2 other	Time interval from primary cancer diagnosis: Mean 14.4 yr	SB: low risk AB: unclear DB: unclear
	Tsui 2015	2,779 childhood brain tumor patients	4.5 (0.1-28.2)	75.6%	28: 23 glioma, 1 malignant meningioma, 1 medulloblastoma, 1 fibrous histiocytoma, 2 dysembryoplastic neuroepithelial tumor	Time interval from primary cancer diagnosis: Median 7.3 yr	SB: unclear AB: unclear DB: unclear
	Hudson 2013	1,713 CCS	25.1 (10.9-47.9)	64.7% (radiotherapy, not further specified)	73: 63 meningioma, 10 other	Time interval from primary cancer diagnosis: Median 25.1 (interquartile range 19.0-33.1) yr	SB: high risk AB: low risk DB: unclear
	Schmiegelow 2013	642 CAYA ALL survivors	NM	At least 35.8%	116 CNS tumors excluding meningioma (not further specified)	Time interval from primary cancer diagnosis: All CNS neoplasms:	SB: unclear AB: unclear DB: unclear

					Median 8.1 (50% range 6.5-9.8) yr; CNS radiation vs. no radiation: 9.1 vs. 6.6 yr (p=0.01)	
	Strodbeck 2013	1,338 childhood medullobastoma/ PNET patients	(0.2 - >10)	NM	10 brain neoplasms (not further specified)	Time interval from primary cancer diagnosis: Range 1-≥10 yr	SB: unclear AB: unclear DB: unclear
	Friedman 2010	14,359 CAYA cancer survivors	22.7 ± 6.8	59.4% (radiotherapy, not further specified)	77: 53 glial neoplasms, 6 medulloblastoma/PNET, 170 meningioma, 16 other	Time interval from primary cancer diagnosis: Median 13.2 (range 6.0-32.7) yr	SB: high risk AB: low risk DB: unclear
	Armstrong 2009	1,877 CAYA primary CNS tumor survivors	19.6 (5.1-34.6)	57.8%	20: 15 astrocytoma/glial tumor, 4 malignant meningioma, 1 medulloblastoma/PNET	Time interval from primary cancer diagnosis: Median 14.0 yr	SB: high risk AB: low risk DB: unclear
	Hijiya 2007	1,290 CAYA ALL survivors	18.7 (2.4-41.3)	NM	38: 10 glioblastoma multiforme, 9 astrocytoma, 2 oligodendroglioma, 1 other, 16 meningioma	Time interval from primary cancer diagnosis in survivors in first complete remission: All CNS neoplasms: Median 11.9 (range 1.7-31.7) yr; Excluding meningioma (n=22): Median 8.8 (range 1.7-14.1) yr	SB: low risk AB: low risk DB: unclear
	Neglia 2006	14,361 CAYA cancer survivors	>5-≥15	71.7% (radiotherapy, not further specified)	116: 40 glioma, 66 meningioma, 6 PNET, 1 CNS lymphoma, 3 other	Time interval from primary cancer diagnosis: Median 14 (range 5-28) yr	SB: high risk AB: unclear DB: unclear
	Bhatia 2002	8,831 CAYA ALL survivors	5.5 (0-16.1)	38%	19: 9 glioblastoma multiforme, 4 anaplastic astrocytoma, 3 PNET, 1 medulloblastoma, 2 meningioma	Time interval from primary cancer diagnosis: Median 7.1 (range 3.9-13.0) yr	SB: unclear AB: low risk DB: unclear
	Löning 2000	5,006 CAYA ALL patients	5.7 (1.5-18)	77.2%	13: 4 glioblastoma, 4 astrocytoma, 3 PNET, 2 meningioma	Time interval from primary cancer diagnosis: Median 7.9 (range 4-13) yr	SB: unclear AB: unclear DB: unclear
	Walter 1998	1,612 childhood ALL patients	15.9 (5.5-29.9)	77.6%	22: 4 glioblastoma multiforme, 2 anaplastic astrocytoma, 4 other high-grade glioma, 1 low-grade oligodendroglioma, 11 meningioma	Time interval from primary cancer diagnosis: Mean 12.6 (range 5.9-29) yr	SB: unclear AB: low risk DB: unclear
	Rosso 1994	3,196 CCS	5.8 (0.0-25.1)	75.5% (radiotherapy,	9: 4 glioblastoma, 3	Time interval from primary cancer diagnosis:	SB: unclear AB: low risk

				not further specified)	astrocytoma, 1 oligodendroglioma, 1 brain lymphoma	Range 1.1-8.8 yr	DB: unclear
GRADE assessment:							
Study design:	+4	Retrospective cohort studies					
Study limitations:	-1	Some limitations: Selection bias low in 2/16, high in 5/16, unclear in 9/16; Attrition bias low in 7/16, unclear in 9/16; Detection bias unclear in 16/16					
Consistency:	0	No important inconsistency, although the latency times vary among the studies					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	0	No important imprecision, high total number of events					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	No dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊕⊕⊖ MODERATE					
Conclusion:		The latency time of developing subsequent CNS neoplasms (different types)* in CAYA cancer survivors ranges from median 7 to 25 years after primary cancer diagnosis, ranging from minimal 1 year to at least 33 years. (16 studies; 84389 participants; 901 events)					

Abbreviations: AB, attrition bias; ALL, acute lymphoblastic leukemia; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CNS, central nervous system; DB, detection bias; fup, follow-up; NM, not mentioned; PNET, primitive neuroectodermal tumor; SB, selection bias; yr, year.
* Studies including different types of subsequent CNS neoplasms, not making a distinction between glioma, meningioma and other types.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
2.a. Risk subsequent glioma over time (n=3 studies)	Taylor 2010	17,980 CCS	17.3 (>5 - …)	51.% (radiotherapy, not further specified)	73 glioma	Standardized incidence ratio (95% CI) by time since 5-year survival: 0-4 yr: 20.6 (13.6-30.1); 5-9 yr: 7.5 (3.4-14.3); 10-14 yr: 11.0 (5.5-19.7); 15-19 yr: 12.5 (6.2-22.3); 20-29 yr: 7.2 (3.5-13.3); ≥30 yr: 5.0 (1.6-11.7)	SB: low risk AB: low risk DB: unclear
	Neglia 2006	14,361 CAYA cancer survivors (116 cases matched to 464 controls)	>5-≥15	71.7% (radiotherapy, not further specified)	40 glioma	Standardized incidence ratio (95% CI) by time since primary cancer diagnosis: 5-9 yr: 13.9 (8.79-20.8); 10-14 yr: 11.2 (6.43-17.8); 15-20 yr: 3.04 (0.76-7.88); ≥20 yr: 1.28 (0.07-5.63)	SB: high risk AB: unclear DB: unclear
	Walter 1998	1,612 childhood ALL patients	15.9 (5.5-29.9)	77.6%	10 high-grade glioma	Cumulative incidence increased over a follow-up time of 14 years since diagnosis and remained stable after longer follow-up	SB: unclear AB: low risk DB: unclear
GRADE assessment:		**Cumulative incidence**					
Study design:	+4	Retrospective cohort study					

Study limitations:	-1	Some limitations: Selection bias unclear in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1
Consistency:	0	Not applicable (one study)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, small number of events and only one study
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		The cumulative incidence of subsequent high-grade glioma increased over time and reached a plateau 14 years since primary cancer diagnosis in CAYA cancer survivors. (1 study; 1,621 participants; 10 events)
GRADE assessment:		**Standardized incidence ratio**
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 1/2, high in 1/2; Attrition bias low in 1/2, unclear in 1/2; Detection bias unclear in 2/2
Consistency:	0	No important inconsistency, both studies show decreased incidence over time
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		The standardized incidence ratio of subsequent glioma decreases over time in CAYA cancer survivors. (2 studies; 32,341 participants; 113 events)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; DB, detection bias; NM, not mentioned; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
2.b. Risk subsequent meningioma over time (n=9 studies)	Remes 2019	642 childhood brain tumor survivors	19.9	100%	6 meningioma	Increased cumulative incidence over time (no data reported)	SB: high risk AB: low risk DB: unclear
	Kok 2018	5,843 CCS	28.3 (5.0-52.2)	21.9%	96 benign meningioma	Increased cumulative incidence over time that did not seem to plateau (no data reported)	SB: low risk AB: low risk DB: unclear
	Bowers 2017	4,221 CCS	22.8 (5.5-38.0)	100%	169 meningioma	Increased cumulative incidence over time that did not seem to plateau (no data reported)	SB: unclear AB: unclear DB: unclear
	Patterson 2014	12,098 CAYA cancer survivors	<10-≥20	35.4%	148 meningioma	Increased cumulative incidence over time in patients treated with CRT (no data reported)	SB: high risk AB: unclear DB: unclear
	Armstrong 2009	1,877 CAYA primary CNS tumor survivors	19.6 (5.1-34.6)	57.8%	4 malignant meningioma	Cumulative incidence increased sharply with continued follow-up (no data reported)	SB: high risk AB: low risk DB: unclear

	Cardous-Ubbink 2007	1,368 CCS	16.8 (5-≥30)	44.5% (radiotherapy, not further specified)	12 meningioma	Standardized incidence ratio increased with longer follow-up resulting in a SIR of 212 after ≥25 years of follow-up (no data reported)	SB: low risk AB: low risk DB: unclear
	Goshen 2007	210 childhood ALL and non-Hodgkin lymphoma survivors	≥5	41.9%	16 meningioma	Cumulative incidence: 10-yr: 1.5% ± 1.4; 15-yr: 6.3% ± 3.5; 20-yr: 14.8% ± 5.7; 25-yr: 53.8% ± 11.6	SB: low risk AB: low risk DB: unclear
	Vinchon 2011	552 childhood brain tumor patients	94.3 (0.6-27.1) months	100%	26 meningioma	Cumulative incidence: 5-yr: 0.1%; 10-yr: 1.8%; 20-yr: 28.9%	SB: unclear AB: unclear DB: unclear
	Walter 1998	1,612 childhood ALL patients	15.9 (5.5-29.9)	77.6%	11 meningioma	Increased cumulative incidence over a follow-up time of 30 years since diagnosis	SB: unclear AB: low risk DB: unclear

GRADE assessment:		**Cumulative incidence**
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 2/8, high in 3/8, unclear in 3/8; Attrition bias low 5/8 unclear in 3/8; Detection bias unclear in 8/8
Consistency:	0	No important inconsistency, all studies show increased incidence over time
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		The cumulative incidence of subsequent meningioma increases over time which does not seem to plateau in CAYA cancer survivors. (8 studies; 270,55 participants; 476 events)
GRADE assessment:		**Standardized incidence ratio**
Study design:	+4	Retrospective cohort studies
Study limitations:	0	No important limitations: Selection bias low in 1/1, Attrition bias low in 1/1; Detection bias unclear in 1/1
Consistency:	0	Not applicable (1 study)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, only 1 study including 12 events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		The standardized incidence ratio of subsequent meningioma increases over time which does not seem to plateau in CAYA cancer survivors. (1 study; 1,368 participants; 12 events)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CNS, central nervous system; CRT, cranial radiotherapy; DB, detection bias; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cranial radiotherapy	Events	Effect size	Risk of bias
2.c. Risk subsequent CNS neoplasms (all different types*) over time (n=8 studies)	Strodbeck 2013	1,338 childhood medullobastoma/ PNET patients	(0.2 - >10)	NM	10: 10 brain neoplasms (not further specified)	Standardized incidence ratio (95% CI) by time since primary cancer diagnosis: 1-5 yr: 13.91 (0.35-77.48); 5-10 yr: 54.2 (11.17-158.3); ≥10 yr: 59.59 (21.87-129.7)	SB: unclear AB: unclear DB: unclear
	Galloway 2012	370 CCS	4.7 (0.1-45.4)	100%	14: 10 meningioma, 4 glioma (+ 1 sarcoma and 1 thyroid tumor included)	Cumulative incidence: 10-yr: 3%; 15-yr: 4%; 20-yr: 8%; 25-yr: 19%; 30-yr: 24%	SB: unclear AB: low risk DB: unclear
	Friedman 2010	14,359 CAYA cancer survivors	22.7 ± 6.8	59.4% (radiotherapy, not further specified)	77: 53 glial neoplasms, 6 medulloblastoma/PNET, 170 meningioma, 16 other	Cumulative incidence increased over time (no data reported)	SB: high risk AB: low risk DB: unclear
	Inskip 2007	25,965 CAYA cancer survivors	6.3 (0.16-30.0)	37.1% (radiotherapy, not further specified)	51: Not further specified	Standardized incidence ratio by time since primary cancer diagnosis: 0.16-<1 yr: 6.8; p<0.05; 1-4 yr: 4.6; p<0.05; 5-9 yr: 10.7; p<0.05; 10-14 yr: 9.2; p<0.05; 15-19 yr: 6.9; p<0.05; ≥20 yr: 11.0; p<0.05	SB: unclear AB: low risk DB: unclear
	Hijiya 2007	1,290 CAYA ALL survivors	18.7 (2.4-41.3)	NM	38: 10 glioblastoma multiforme, 9 astrocytoma, 2 oligodendroglioma, 1 other, 16 meningioma	Cumulative incidence in survivors in first complete remission: 5-yr: 0.05% ± 0.05; 10-yr: 0.8% ± 1.24; 15-yr: 1.24% ± 0.26; 20-yr: 1.87% ± 0.35; 30-yr: 3.0% ± 0.59; Cumulative incidence excluding meningioma in survivors in first complete remission: 5-yr: 0.05% ± 0.05; 10-yr: 0.8% ± 0.2;	SB: low risk AB: low risk DB: unclear

						15-yr: 1.17% ± 0.25; 20-yr: 1.17% ± 0.25; 30-yr: 1.17% ± 0.25	
	Bhatia 2002	8,831 CAYA ALL survivors	5.5 (0-16.1)	38%	19: 9 glioblastoma multiforme, 4 anaplastic astrocytoma, 3 PNET, 1 medulloblastoma, 2 meningioma	Cumulative incidence (95% CI): 10-yr: 0.47% (0.2-0.6); 15-yr: 0.90% (0.4-1.4); Standardized incidence ratio (95% CI) by time since primary cancer diagnosis: 0-5 yr: 10.8 (2.8-24.0); 6-10 yr: 17.5 (8.7-29.3); 11-15 yr: 3.2 (0.3-9.1)	SB: unclear AB: low risk DB: unclear
	Löning 2000	5,006 CAYA ALL patients	5.7 (1.5-18)	77.2%	13: 4 glioblastoma, 4 astrocytoma, 3 PNET, 2 meningioma	Cumulative incidence (95% CI) in survivors in first complete remission: 5-yr: 0.1%; 10-yr: 0.4%; 15-yr: 1.0% (0.4-1.8)	SB: unclear AB: unclear DB: unclear
	Rosso 1994	3,196 CCS	5.8 (0.0-25.1)	75.5% (radiotherapy, not further specified)	9: 4 glioblastoma, 3 astrocytoma, 1 oligodendroglioma, 1 brain lymphoma	Cumulative incidence (95% CI) in ALL patients: 5-yr: 0.1% (0.0-0.2); 10-yr: 1.9% (0.5-3.2); Standardized incidence ratio (95% CI) by time since end of therapy: 0-4 yr: 9.3 (0.2-51.9); 5-9 yr: 199.7 (86.0-393.6)	SB: unclear AB: low risk DB: unclear

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 1/6, high in 1/6, unclear in 4/6; Attrition bias low in 5/6, unclear in 1/6; Detection bias unclear in 6/6
Consistency:	0	No important inconsistency, all show increased incidence over time
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		The cumulative incidence of subsequent CNS neoplasms increases over time in CAYA cancer survivors. (6 studies; 33,052 participants; 170 events)
GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias unclear in 4/4; Attrition bias low in 3/4, unclear in 1/4; Detection bias unclear in 4/4
Consistency:	-1	Some inconsistency, 2 studies show increased risks over time (expressed in standardized incidence ratios), 1 study showed decreased risk over time (expressed in standardized incidence ratios) and 1 study shows fluctuating risks over time (expressed in standardized incidence ratios)
Directness:	0	Results are direct, population and outcomes broadly generalizable

Precision:	0	No important imprecision, high total number of events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		The standardized incidence ratio of subsequent CNS neoplasms (different types)* increases over time in CAYA cancer survivors; presence of plateau cannot be assessed. (4 studies; 39,330 participants; 89 events)

Abbreviations: AB, attrition bias; ALL, acute lymphoblastic leukemia; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CNS, central nervous system; CRT, cranial radiotherapy; DB, detection bias; NM, not mentioned; PNET, primitive neuroectodermal tumor; SB, selection bias; yr, year.
* Studies including different types of subsequent CNS neoplasms, not making a distinction between glioma, meningioma and other types.

PICO 3.a-3.c: No studies identified

Key question: What surveillance modality should be used?

PICO 1-4: No studies identified