Summary of findings tables, grading of the evidence and detailed conclusions of evidence HP dysfunction

WG1; Who needs surveillance?

Childhood cancer survivors (CNS tumor)

Question 1. What is the risk to develop HP dysfunction in childhood cancer survivors (CNS tumor) with cranial radiotherapy exposure and is it modified by radiotherapy dose (Gy), dose rate, radiotherapy type (e.g. electron, IMRT, brachytherapy, proton beam therapy) and field?

a. What is the risk of HP dysfunction in childhood cancer survivors (CNS tumor) treated with radiotherapy exposing (parts) of the brain versus no radiotherapy?

i. What is the risk of GHD in childhood cancer survivors (CNS tumor) treated with radiotherapy exposing (parts) of the brain versus no radiotherapy?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
1a. Risk GHD after radiotherapy (n=4 studies)	Armstrong 2011	240 CAYA CNS tumor survivors	10 (5-21.5)	46.3% RT *RT details;* Not reported	15-yr cumulative incidence GHD: 29% Diagnosed by provocative testing, GH peak cut-off value unknown	Hazard ratio (95% CI) GHD: radiotherapy (yes vs. no) 3.9 (1.9-8.2)*	SB: unclear AB: unclear DB: unclear CF: low risk
	Clement 2016	718 CAYA CNS tumor survivors	6.6 (2.0-13.4)	35.9% RT *RT details;* Cranial RT, n=144, RT dose, median 54.0 Gy (range 12.5-60.0) Craniospinal RT, n=114, RT dose, median 24.0 Gy (range 18.0-39.7)	Prevalence at last follow-up GHD: n=90 (12.5%) Diagnosed by provocative testing, GH peak <20-30 mU/L or diagnosis by treating physician	Odds ratio (95% CI) GHD: radiotherapy (yes vs. no) 79.39 (24.21-260.37)*	SB: unclear AB: high risk DB: unclear CF: low risk
	Gan 2015	166 CAYA CNS tumor survivors	8.3 (0.04-26.8)	41.6% RT *RT details;* Focal RT to total dose 48-55 Gy	Prevalence at last follow-up: GHD: n=67 (40.3%) Diagnosed by provocative testing, GH peak <7 ng/mL	Hazard ratio (95% CI) GHD: primary radiotherapy (yes vs. no) 2.48 (1.36-4.52)* GHD: any radiotherapy (yes vs. no) 5.76 (2.93-11.23)*	SB: low risk AB: unclear DB: unclear CF: low risk
	Shalitin 2011	114 CAYA CNS tumor survivors	12.8 (3.7-28.7)	56.1% RT *RT details;* Cranial RT, n=55, RT dose 35-56 Gy	Prevalence at last follow-up GHD: n=40 (35.1%) Diagnosed by	Odds ratio (95% CI) GHD: cranial radiotherapy (yes vs. no) 10.3 (3.48-31.25)*	SB: low risk AB: low risk DB: unclear CF: high risk

				Spinal RT, n=27, RT dose 30-54 Gy	provocative testing, GH peak <10 ng/mL		
GRADE assessment							
Study design:	+4	Observational evidence					
Study limitations:	-1	Some limitations: Selection bias low in 2/4, unclear in 2/4; Attrition bias low in 1/4, high in 1/4, unclear in 2/4; Detection bias unclear in 4/4; Confounding low in 3/4, high in 1/4					
Consistency:	0	No important inconsistency, all studies show effect of cranial radiotherapy					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	0	No important imprecision, large sample size, high total number of events and narrow confidence intervals in two of four studies					
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:	There is an increased risk for GHD after cranial radiotherapy versus no cranial radiotherapy in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (4 studies significant effect; 1238 participants; 197 events (in 3/4), unknown number of events (in 1/4))						

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; GH, growth hormone; GHD, growth hormone deficiency; Gy, Gray; RT, radiotherapy; SB, selection bias; yr, year.
*Statistically significant outcome

ii. What is the risk of TSHD in childhood cancer survivors (CNS tumor) treated with radiotherapy exposing (parts) of the brain versus no radiotherapy?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
1a. Risk TSHD after radiotherapy (n=1 study)	Clement 2016	718 CAYA CNS tumor survivors	6.6 (2.0-13.4)	35.9% RT *RT details;* Cranial RT, n=144, RT dose, median 54.0 Gy (range 12.5-60.0) Craniospinal RT, n=114, RT dose, median 24.0 Gy (range 18.0-39.7)	Prevalence at last follow-up TSHD: n=66 (9.1%) Diagnosed by low FT4 concentrations with low, normal or mildly raised TSH	Odds ratio (95% CI) TSHD: radiotherapy (yes vs. no) 11.48 (5.51-23.92)*	SB: unclear AB: high risk DB: unclear CF: low risk
GRADE assessment							
Study design:	+4	Observational evidence					
Study limitations:	-1	Some limitations: Selection bias unclear in 1/1; Attrition bias high 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:	-2	Important imprecision, only 1 study included and high number of participants and events, but broad confidence intervals					
Publication bias:	0	Unlikely					
Effect size:	+1	Large magnitude of effect					

Dose-response:	0	Unclear if dose-response relationship (dichotomous outcome)
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊖⊖ LOW	
Conclusion:	There is an increased risk for TSHD after cranial radiotherapy versus no cranial radiotherapy in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study significant effect; 718 participants; 66 events)	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; FT4, free thyroxine; RT, radiotherapy; SB, selection bias; TSH, thyroid-stimulating hormone; TSHD, thyroid-stimulating hormone deficiency; yr, year.
*Statistically significant outcome

iii. What is the risk of LH/FSHD in childhood cancer survivors (CNS tumor) treated with radiotherapy exposing (parts) of the brain versus no radiotherapy?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
1a. Risk LH/FSHD after radiotherapy (n=1 study)	Gan 2015	166 CAYA CNS tumor survivors	8.3 (0.04-26.8)	41.6% RT *RT details:* Focal RT to total dose 48-55 Gy	Prevalence at last follow-up: LH/FSHD: n=21/103 (20.4%) Diagnosed by absence of pubertal development or pubertal arrest with undetectable testosterone/estradiol and/or abnormal GnRH testing	Hazard ratio (95% CI) LH/FSHD: primary radiotherapy (yes vs. no) 3.27 (1.35-7.94)*	SB: low risk AB: unclear DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	0	No serious limitations: Selection bias low 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:	-2	Important imprecision, only 1 study included and low number of events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship (dichotomous outcome)
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊖⊖ LOW	
Conclusion:	There is an increased risk for LH/FSHD after cranial radiotherapy versus no cranial radiotherapy in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study significant effect; 166 participants; 21 events)	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; GnRH, Gonadotropin-releasing hormone; Gy, Gray; LH/FSHD, luteinizing hormone and follicle-stimulating hormone deficiency; RT, radiotherapy; SB, selection bias; yr, year.

*Statistically significant outcome

iv. What is the risk of ACTHD in childhood cancer survivors (CNS tumor) treated with radiotherapy exposing (parts) of the brain versus no radiotherapy?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
1a. Risk ACTHD after radiotherapy (n=2 studies)	Armstrong 2011	240 CAYA CNS tumor survivors	10 (5-21.5)	46.3% RT *RT details;* Not reported	15-yr cumulative incidence ACTHD: 25.7% Diagnosed by provocative testing, cut-off value unknown	Hazard ratio (95% CI) ACTHD: radiotherapy (yes vs. no) 4.6 (2.1-10.0)*	SB: unclear AB: unclear DB: unclear CF: low risk
	Gan 2015	166 CAYA CNS tumor survivors	8.3 (0.04-26.8)	41.6% RT *RT details:* Focal RT to total dose 48-55 Gy	Prevalence at last follow-up: ACTHD: n=22 (13.3%) Diagnosed by provocative testing, peak cortisol <500nmol/L	Hazard ratio (95% CI) ACTHD: primary radiotherapy (yes vs. no) 5.16 (2.12-12.57)*	SB: low risk AB: unclear DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias low in 1/2, unclear in 1/2; Attrition bias unclear in 2/2; Detection bias unclear in 2/2; Confounding low in 2/2
Consistency:	0	No important inconsistency, both show effect of cranial radiotherapy
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, large sample size, high total number of events and participants, but broad confidence intervals
Publication bias:	0	Unlikely
Effect size:	+1	Large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship (dichotomous outcomes)
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊕⊖ MODERATE	
Conclusion:	There is an increased risk for ACTHD after cranial radiotherapy versus no cranial radiotherapy in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (2 studies significant effect; 406 participants; 22 events (in 1/2), unknown number of events (in 1/2))	

Abbreviations: AB, attrition bias; ACTHD, adrenocorticotropic hormone deficiency; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; Gy, Gray; RT, radiotherapy; SB, selection bias; yr, year.
*Statistically significant outcome

v. What is the risk of CPP in childhood cancer survivors (CNS tumor) treated with radiotherapy exposing (parts) of the brain versus no radiotherapy?

Outcome	Study	No. of participants	Follow up (median/mean,	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias

			range) yr				
1a. Risk CPP after radiotherapy (n=1 study)	Clement 2016	718 CAYA CNS tumor survivors	6.6 (2.0-13.4)	35.9% RT *RT details;* Cranial RT, n=144, RT dose, median 54.0 Gy (range 12.5-60.0) Craniospinal RT, n=114, RT dose, median 24.0 Gy (range 18.0-39.7)	Prevalence at last follow-up CPP: n=48 (12.2% of evaluable patients) Onset of puberty diagnosed by Tanner B2 in girls <8 years and testes >4mL in boys >9 years.	Odds ratio (95% CI) CPP: radiotherapy (yes vs. no) 2.97 (1.20-7.32)*	SB: unclear AB: high risk DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias unclear in 1/1; Attrition bias high 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 included and high number of participants and events, but narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship (dichotomous outcome)
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊖⊖ LOW	
Conclusion:	There is an increased risk for CPP after cranial radiotherapy versus no cranial radiotherapy in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study significant effect; 718 participants; 48 events)	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; CPP, central precocious puberty; DB, detection bias; Gy, Gray; RT, radiotherapy; SB, selection bias; yr, year.
*Statistically significant outcome

b. What is the risk of HP dysfunction in childhood cancer survivors (CNS tumor) treated with higher versus lower doses radiotherapy?

i. What is the risk of GHD in childhood cancer survivors (CNS tumor) treated with higher versus lower doses radiotherapy?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
1b. Risk GHD after higher vs. lower radiotherapy dose (n=3 studies)	Clayton 1991	82 CAYA survivors (n=66 CAYA CNS tumor survivors)[1]	4.3 (0.2-18.9)	100% RT *RT details;* Cranial RT, n=24 Craniospinal RT, n=58 HP-RT dose Range 27-47.5 Gy <30 Gy, n=46 (56.1%) ≥30 Gy, n=36 (43.9%)	Incidence >5 yrs after RT GHD: incidence 74% Diagnosed by provocative testing (ITT); peak GH ≤15	Relative risk (95% CI) GHD: HP axis dose, RR not reported, p=0.03*	SB: unclear AB: high risk DB: unclear CF: high risk

	Merchant 2011	192 CAYA CNS tumor survivors	Max 60 months	100% RT *RT details;* All received conformal RT or intensity-modulated RT Ependymoma: Cranial RT dose 59.4 Gy, n=73 Cranial RT dose 54.0 Gy, n=15 Low grade glioma: Cranial RT dose 54 Gy, n=51	Prevalence not reported GHD diagnosed by provocative testing (arginine/L-DOPA), GH peak <7 ng/mL	Mixed models analysis Peak GH: interaction between time and radiotherapy dose, p<0.001*	SB: unclear AB: unclear DB: unclear CF: high risk
	Schmiegelow 2000	73 CAYA CNS tumor survivors	15 (2-28)	100% RT *RT details;* Craniospinal RT, n=30 (41.1%) Whole brain RT, n=13 (17.8%) Focal brain RT, n=30 (41.1%) Median BED to HP region 74 Gy (range 0-99)	Prevalence (cross-sectional) GHD: n=58 (80%) Diagnosed by provocative testing, GH peak <9 ng/mL for adults, peak GH <15 mU/L for children	Regression coefficient, p-value Peak GH: BED to HP region, β -0.47, p<0.0001*	SB: low risk AB: low risk DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence, partially for prognostic and diagnostic questions
Study limitations:	-1	Some limitations: Selection bias low in 1/3, unclear in 2/3; Attrition bias low in 1/3, high in 1/3, unclear in 1/3; Detection bias unclear in 3/3; Confounding low in 1/3, high in 2/3
Consistency:	0	No important inconsistency, all show effect of cranial radiotherapy
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size and high total number of events. Confidence intervals not reported.
Publication bias:	0	Unlikely
Effect size:	0	Magnitude of effect cannot be determined
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:	There is an increased risk for GHD after increasing doses of cranial radiotherapy in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (3 studies significant effect; 347 participants; 58 events (in 1/3), unknown number of events (in 2/3))	

Abbreviations: AB, attrition bias; BED, biological effective dose; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; GH, growth hormone; GHD, growth hormone deficiency; Gy, Gray; HP, hypothalamic-pituitary; ITT, insulin tolerance test; RT, radiotherapy; SB, selection bias; yr, year.
*Statistically significant outcome
[1] Study comprises ≥75% CAYA CNS tumor survivors

ii. What is the risk of TSHD in childhood cancer survivors (CNS tumor) treated with higher versus lower doses radiotherapy?

No studies included

iii. What is the risk of LH/FSHD in childhood cancer survivors (CNS tumor) treated with higher versus lower doses radiotherapy?
No studies included

iv. What is the risk of ACTHD in childhood cancer survivors (CNS tumor) treated with higher versus lower doses radiotherapy?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
1b. Risk ACTHD after higher vs. lower radiotherapy dose (n=1 study)	Schmiegelow 2003	73 CAYA CNS tumor survivors (17 controls)	15 (2-29)	100% RT *RT details;* Craniospinal RT, n=30 Whole brain RT, n=14 Focal brain RT, n=29 Median BED to HP region 73 Gy (range 0-94)	Prevalence (cross-sectional) ACTHD: n=14 (19%) Diagnosed by basal cortisol levels <500 nmol/L and peak cortisol <500 nmol/L to ACTH test or ITT	Regression coefficient, p-value Peak cortisol: BED to HP region, β -0.53, p=0.04*	SB: low risk AB: high risk DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence, partially for prognostic and diagnostic questions
Study limitations:	-1	Some limitations: Selection bias low in 1/1; Attrition bias high 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:	-2	Important imprecision, only 1 study included and low number of participants and events
Publication bias:	0	Unlikely
Effect size:	0	Magnitude of effect cannot be determined
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	⊕⊕⊖⊖ LOW	
Conclusion:	There is an increased risk for ACTHD after increasing doses of cranial radiotherapy in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study significant effect; 73 participants; 14 events)	

Abbreviations: AB, attrition bias; ACTHD, adrenocorticotropic hormone deficiency; BED, biological effective dose; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; Gy, Gray; HP, hypothalamic-pituitary; ITT, insulin tolerance test; RT, radiotherapy; SB, selection bias; yr, year.
*Statistically significant outcome

v. What is the risk of CPP in childhood cancer survivors (CNS tumor) treated with higher versus lower doses radiotherapy?
No studies included

c. What is the risk of HP dysfunction in childhood cancer survivors (CNS tumor) treated with different dose rates?
No studies included for all five types of HP dysfunction

d. What is the risk of HP dysfunction in childhood cancer survivors (CNS tumor) treated with different types of radiotherapy (e.g. electron, IMRT, brachytherapy, proton beam therapy)?

i. What is the risk of GHD in childhood cancer survivors (CNS tumor) treated with <u>different types of</u> radiotherapy (e.g. electron, IMRT, brachytherapy, proton beam therapy)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
1d. Risk GHD by different types of radiotherapy (n=1 study)	Eaton 2016	77 CAYA CNS tumor survivors	7.0 (3.5-13.5) for photon RT 5.8 (3.3-21.9) for proton RT	100% RT *RT details;* All received craniospinal RT Photon RT, n=37, dose 54-55.8 Gy (n=36), >55.8 Gy (n=1) Proton RT, n=40, dose 54-55.8 Gy	Prevalence at last follow-up GHD: n=42 (54.5%) Diagnosed by provocative testing, GH peak cut-off not reported	Odds ratio (95% CI) <u>GHD:</u> radiotherapy (proton RT vs. photon RT) 0.81 (0.26-2.59)	SB: low risk AB: high risk DB: unclear CF: low risk

GRADE assessment		
<u>Study design:</u>	+4	Observational evidence
<u>Study limitations:</u>	-1	Some limitations: Selection bias low in 1/1; Attrition bias high in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1
<u>Consistency:</u>	0	N/A (1 study)
<u>Directness:</u>	0	Results are direct, population and outcomes broadly generalizable
<u>Precision:</u>	-2	Important imprecision, only 1 study included and low number of participants
<u>Publication bias:</u>	0	Unlikely
<u>Effect size:</u>	0	No large magnitude of effect
<u>Dose-response:</u>	0	Unclear if dose-response relationship
<u>Plausible confounding</u>	0	No plausible confounding
Quality of evidence	⊕⊖⊖⊖ VERY LOW	
Conclusion:	There is no significant effect of proton radiotherapy versus photon radiotherapy on the risk for GHD in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study non-significant effect; 77 participants; 42 events)	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; GH, growth hormone; GHD, growth hormone deficiency; Gy, Gray; RT, radiotherapy; SB, selection bias; yr, year.

ii. What is the risk of TSHD in childhood cancer survivors (CNS tumor) treated with <u>different types of</u> radiotherapy (e.g. electron, IMRT, brachytherapy, proton beam therapy)?

No studies included

iii. What is the risk of LH/FSHD in childhood cancer survivors (CNS tumor) treated with <u>different types of</u> radiotherapy (e.g. electron, IMRT, brachytherapy, proton beam therapy)?

No studies included

iv. What is the risk of ACTHD in childhood cancer survivors (CNS tumor) treated with <u>different types of</u> radiotherapy (e.g. electron, IMRT, brachytherapy, proton beam therapy)?

No studies included

v. What is the risk of CPP in childhood cancer survivors (CNS tumor) treated with <u>different types of</u> radiotherapy (e.g. electron, IMRT, brachytherapy, proton beam therapy)?
No studies included

e. What is the risk of HP dysfunction in childhood cancer survivors (CNS tumor) treated with radiotherapy at <u>different fields (other than cranial RT)</u>?

i. What is the risk GHD in childhood cancer survivors (CNS tumor) treated with radiotherapy at <u>different fields (other than cranial RT)</u>?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
1e. Risk GHD after different radiotherapy fields (n=1 study)	Shalitin 2011	114 CAYA CNS tumor survivors	12.8 (3.7-28.7)	56.1% RT *RT details;* Cranial RT, n=55, RT dose 35-56 Gy Spinal RT, n=27, RT dose 30-54 Gy	Prevalence at last follow-up GHD: n=40 (35.1%) Diagnosed by provocative testing, GH peak <10 ng/mL	Odds ratio (95% CI) <u>GHD:</u> spinal radiotherapy, 3.49 (0.83-14.9)	SB: low risk AB: low risk DB: unclear CF: high risk

GRADE assessment		
<u>Study design:</u>	+4	Observational evidence
<u>Study limitations:</u>	-1	Some limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding high in 1/1
<u>Consistency:</u>	0	N/A (1 study)
<u>Directness:</u>	0	Results are direct, population and outcomes broadly generalizable
<u>Precision:</u>	-2	Important imprecision, only 1 study included, low number of events and broad confidence intervals
<u>Publication bias:</u>	0	Unlikely
<u>Effect size:</u>	0	No large magnitude of effect
<u>Dose-response:</u>	0	Unclear if dose-response relationship
<u>Plausible confounding</u>	0	No plausible confounding
Quality of evidence	⊕⊖⊖⊖ VERY LOW	
Conclusion:	There is no significant effect of spinal radiotherapy versus no spinal radiotherapy on the risk for GHD in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study non-significant effect, 114 participants; 40 events)	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; GH, growth hormone; GHD, growth hormone deficiency; Gy, Gray; HP, RT, radiotherapy; SB, selection bias; yr, year.

ii. What is the risk TSHD in childhood cancer survivors (CNS tumor) treated with radiotherapy at <u>different fields (other than cranial RT)</u>?
No studies included

iii. What is the risk LH/FSHD in childhood cancer survivors (CNS tumor) treated with radiotherapy at <u>different fields (other than cranial RT)</u>?

No studies included

vi. What is the risk ACTHD in childhood cancer survivors (CNS tumor) treated with radiotherapy at <u>different fields (other than cranial RT)</u>?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
1e. Risk ACTHD after different radiotherapy fields (n=1 study)	Schmiegelow 2003	73 CAYA CNS tumor survivors (17 controls)	15 (2-29)	100% RT *RT details;* Craniospinal RT, n=30 Whole brain RT, n=14 Focal brain RT, n=29 Median BED to HP region 73 Gy (range 0-94)	Prevalence (cross-sectional) ACTHD: n=14 (19%) Diagnosed by basal cortisol levels <500 nmol/L and peak cortisol <500 nmol/L to ACTH test or ITT	Regression coefficient, p-value <u>Peak cortisol:</u> BED to the spine, β 0.32, p=0.21	SB: low risk AB: high risk DB: unclear CF: low risk

GRADE assessment		
<u>Study design:</u>	+4	Observational evidence
<u>Study limitations:</u>	-1	Some limitations: Selection bias low in 1/1; Attrition bias high in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1
<u>Consistency:</u>	0	N/A (1 study)
<u>Directness:</u>	0	Results are direct, population and outcomes broadly generalizable
<u>Precision:</u>	-2	Important imprecision, only 1 study included and low number of events
<u>Publication bias:</u>	0	Unlikely
<u>Effect size:</u>	0	Magnitude of effect cannot be determined
<u>Dose-response:</u>	0	Unclear if dose-response relationship
<u>Plausible confounding</u>	0	No plausible confounding
Quality of evidence	⊕⊖⊖⊖ VERY LOW	
Conclusion:	There is no significant effect of spinal radiotherapy on the risk for ACTHD in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study non-significant effect, 73 participants; 14 events)	

Abbreviations: AB, attrition bias; ACTHD, adrenocorticotropic hormone deficiency; BED, biological effective dose; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; Gy, Gray; HP, hypothalamic-pituitary; ITT, insulin tolerance test; RT, radiotherapy; SB, selection bias; yr, year.

v. What is the risk CPP in childhood cancer survivors (CNS tumor) treated with radiotherapy at <u>different fields (other than cranial RT)</u>?
No studies included

Question 2. What is the risk to develop HP dysfunction in childhood cancer survivors (CNS tumor) who received chemotherapy (with or without neurosurgery but no cranial radiation) and is it modified by the type of chemotherapeutic agent (e.g. alkylating), administration route (intravenous or intrathecal), duration of chemotherapy, gender, age at start treatment, ethnicity, race, histology/type of cancer, genetic profile of the patient, time after diagnosis or time after exposure?

a. What is the risk of HP dysfunction in childhood cancer survivors (CNS tumor) treated with both chemotherapy and radiotherapy?

i. What is the risk for GHD in childhood cancer survivors (CNS tumor) treated with chemotherapy and radiotherapy?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
2a. Risk GHD after chemotherapy and radiotherapy (n=2 studies)	Armstrong 2011	240 CAYA CNS tumor survivors	10 (5-21.5)	46.3% RT *RT details;* Not reported	15-yr cumulative incidence GHD: 29% Diagnosed by provocative testing, GH peak cut-off value unknown	Hazard ratio (95% CI) GHD: chemotherapy (yes vs. no) 0.8 (0.4-1.4)	SB: unclear AB: unclear DB: unclear CF: low risk
	Schmiegelow 2000	73 CAYA CNS tumor survivors	15 (2-28)	100% RT *RT details;* Craniospinal RT, n=30 (41.1%) Whole brain RT, n=13 (17.8%) Focal brain RT, n=30 (41.1%) Median BED to HP region 74 Gy (range 0-99)	Prevalence (cross-sectional) GHD: n=58 (80%) Diagnosed by provocative testing, GH peak <9 ng/mL for adults, peak GH <15 mU/L for children	Regression coefficient, p-value Peak GH: chemotherapy, β 0.02, p=0.86	SB: low risk AB: low risk DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence, partially for prognostic and diagnostic questions
Study limitations:	0	No serious limitations: Selection bias low 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, both studies show no effect of chemotherapy
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding	0	No plausible confounding
Quality of evidence	⨁⨁⨁⨁ HIGH	
Conclusion:	There is no significant effect of chemotherapy versus no chemotherapy on the risk for GHD in childhood cancer survivors (CNS tumor) exposed to cranial radiotherapy and diagnosed before the age of 25 years. (2 studies non-significant effect; 313 participants; 58 events (in 1/2), unknown number of events (in 1/2))	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; GH, growth hormone; GHD, growth hormone deficiency; Gy, Gray; HP, hypothalamic-pituitary; RT, radiotherapy; SB, selection bias; yr, year.
*Statistically significant outcome

ii. What is the risk for TSHD in childhood cancer survivors (CNS tumor) treated with chemotherapy and radiotherapy?

No studies included

iii. What is the risk for LH/FSHD in childhood cancer survivors (CNS tumor) treated with chemotherapy and radiotherapy?
No studies included

iv. What is the risk for ACTHD in childhood cancer survivors (CNS tumor) treated with chemotherapy and radiotherapy?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
2a. Risk ACTHD after chemotherapy and radiotherapy (n=3 studies)	Armstrong 2011	240 CAYA CNS tumor survivors	10 (5-21.5)	46.3% RT *RT details;* Not reported	15-yr cumulative incidence ACTHD: 25.7% Diagnosed by provocative testing, cut-off value unknown	Hazard ratio (95% CI) ACTHD: chemotherapy (yes vs. no) 0.8 (0.4-1.5)	SB: unclear AB: unclear DB: unclear CF: low risk
	Gan 2015	166 CAYA CNS tumor survivors	8.3 (0.04-26.8)	41.6% RT *RT details:* Focal RT to total dose 48-55 Gy	Prevalence at last follow-up: ACTHD: n=22 (13.3%) Diagnosed by provocative testing, peak cortisol <500nmol/L	Hazard ratio (95% CI) ACTHD: any chemotherapy (yes vs. no) 0.30 (0.10-0.92)*	SB: low risk AB: unclear DB: unclear CF: low risk
	Schmiegelow 2003	73 CAYA CNS tumor survivors (17 controls)	15 (2-29)	100% RT *RT details;* Craniospinal RT, n=30 Whole brain RT, n=14 Focal brain RT, n=29 Median BED to HP region 73 Gy (range 0-94)	Prevalence (cross-sectional) ACTHD: n=14 (19%) Diagnosed by basal cortisol levels <500 nmol/L and peak cortisol <500 nmol/L to ACTH test or ITT	Regression coefficient, p-value Peak cortisol: chemotherapy, β 0.31, p=0.21	SB: low risk AB: high risk DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence, partially for prognostic and diagnostic questions
Study limitations:	0	No serious limitations: Selection bias low in 2/3, unclear in 1/3; Attrition bias high in 1/3, unclear in 2/3; Detection bias unclear in 3/3; Confounding low in 3/3
Consistency:	-1	Some inconsistency, one study significant effect of chemotherapy and two studies non-significant effect
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊕⊖ MODERATE	
Conclusion:	There is no significant effect of chemotherapy versus no chemotherapy on the risk for ACTHD in childhood cancer survivors (CNS tumor) exposed to cranial radiotherapy and diagnosed before the age of 25 years. (1 study significant effect, 2 studies non-significant effect; 479 participants; 36 events (in 2/3), unknown number of events (in 1/3))	

Abbreviations: AB, attrition bias; adrenocorticotropic hormone deficiency (ACTHD); BED, biological effective dose; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; Gy, Gray; HP, hypothalamic-pituitary; ITT, insulin tolerance test; RT, radiotherapy; SB, selection bias; yr, year.
*Statistically significant outcome

v. What is the risk for CPP in childhood cancer survivors (CNS tumor) treated with chemotherapy and radiotherapy?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
2a. Risk CPP after chemotherapy and radiotherapy (n=1 study)	Gan 2015	166 CAYA CNS tumor survivors	8.3 (0.04-26.8)	41.6% RT *RT details:* Focal RT to total dose 48-55 Gy	Prevalence at last follow-up: CPP: n=32/123 (26.0%) Diagnosed by Tanner staging, pubertal concentrations of testosterone/estradiol and/or pubertal response to provocative testing	Hazard ratio (95% CI) CPP: any chemotherapy (yes vs. no), 0.42 (0.20-0.90)*	SB: low risk AB: unclear DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence, partially for prognostic and diagnostic questions
Study limitations:	-1	Some limitations: Selection bias low 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, large sample size, but small total number of events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊖⊖ LOW	
Conclusion:	There is no increased risk for CPP after chemotherapy versus no chemotherapy in childhood cancer survivors (CNS tumor) exposed to cranial radiotherapy and diagnosed before the age of 25 years (1 study significant effect; 166 participants; 32 events)	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CPP, central precocious puberty; CNS, central nervous system; DB, detection bias; Gy, Gray; RT, radiotherapy; SB, selection bias; yr, year.
*Statistically significant outcome

b. What is the risk of HP dysfunction in childhood cancer survivors (CNS tumor) treated with chemotherapy, but no radiotherapy?

No studies included for all five types of HP dysfunction

Question 3. What is the risk to develop HP dysfunction in childhood cancer survivors (CNS tumor) who received neurosurgery (with or without cranial radiotherapy or chemotherapy) and is it modified by gender, ethnicity, race, the tumor site, hydrocephalus at diagnosis,

histology/type of cancer, genetic profile of the patient, radiotherapy & chemotherapy, conditioning for stem cell transplantation, molecular targeted therapy), time after diagnosis or time after exposure?

a. What is the risk of HP dysfunction in childhood cancer survivors (CNS tumor) treated with neurosurgery?

i. What is the risk for GHD in childhood cancer survivors (CNS tumor) treated with neurosurgery?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
3a. Risk GHD after neurosurgery (n=2 studies)	Armstrong 2011	240 CAYA CNS tumor survivors	10 (5-21.5)	46.3% RT *RT details;* Not reported	15-yr cumulative incidence GHD: 29% Diagnosed by provocative testing, GH peak cut-off value unknown	Hazard ratio (95% CI) GHD: surgery (GTR vs. no GTR) 0.2 (0.1-0.6)*	SB: unclear AB: unclear DB: unclear CF: low risk
	Clement 2016	718 CAYA CNS tumor survivors	6.6 (2.0-13.4)	35.9% RT *RT details;* Cranial RT, n=144, RT dose, median 54.0 Gy (range 12.5-60.0) Craniospinal RT, n=114, RT dose, median 24.0 Gy (range 18.0-39.7)	Prevalence at last follow-up GHD: n=90 (12.5%) Diagnosed by provocative testing, GH peak <20-30 mU/L or diagnosis by treating physician	Odds ratio (95% CI) GHD: neurosurgery (yes vs. no) 8.52 (0.84-86.35)	SB: unclear AB: high risk DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias unclear in 2/2; Attrition bias high in 1/2, unclear in 1/2; Detection bias unclear in 2/2; Confounding low in 2/2
Consistency:	0	No important inconsistency, both studies do not show an increased risk after neurosurgery
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, large sample size, but broad confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊖⊖ LOW	
Conclusion:	There is no increased risk for GHD after neurosurgery versus no neurosurgery in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study significant effect, 1 study non-significant effect; 958 participants; 90 events (in 1/2), unknown number of events (in 1/2))	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; GH, growth hormone; GHD, growth hormone deficiency; Gy, Gray; GTR, gross total resection; RT, radiotherapy; SB, selection bias; yr, year.
*Statistically significant outcome

ii. What is the risk for TSHD in childhood cancer survivors (CNS tumor) treated with neurosurgery?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
3a. Risk TSHD after neurosurgery (n=1 study)	Clement 2016	718 CAYA CNS tumor survivors	6.6 (2.0-13.4)	35.9% RT *RT details;* Cranial RT, n=144, RT dose, median 54.0 Gy (range 12.5-60.0) Craniospinal RT, n=114, RT dose, median 24.0 Gy (range 18.0-39.7)	Prevalence at last follow-up TSHD: n=66 (9.1%) Diagnosed by low FT4 concentrations with low, normal or mildly raised TSH	Odds ratio (95% CI) TSHD: neurosurgery (yes vs. no) 2.39 (0.59-9.75)	SB: unclear AB: high risk DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias unclear in 1/1; Attrition bias high 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 included and high number of participants and events.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship (dichotomous outcome)
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊖⊖ LOW	
Conclusion:	There is no significant effect of neurosurgery versus no neurosurgery on the risk for TSHD in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study non-significant effect; 718 participants; 66 events)	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; FT4, free thyroxine; RT, radiotherapy; SB, selection bias; TSH, thyroid-stimulating hormone; TSHD, thyroid-stimulating hormone deficiency; yr, year.

iii. What is the risk for LH/FSHD in childhood cancer survivors (CNS tumor) treated with neurosurgery?

No studies included

iv. What is the risk for ACTHD in childhood cancer survivors (CNS tumor) treated with neurosurgery?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
3a. Risk ACTHD after neurosurgery (n=1 study)	Armstrong 2011	240 CAYA CNS tumor survivors	10 (5-21.5)	46.3% RT *RT details;* Not reported	15-yr cumulative incidence ACTHD: 25.7% Diagnosed by provocative testing, cut-off value unknown	Hazard ratio (95% CI) ACTHD: surgery (GTR vs. no GTR) 0.4 (0.2-1.2)	SB: unclear AB: unclear DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence
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	N/A (1 study)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, only 1 study included. Number of events unknown, but narrow confidence intervals and high number of participants.
Publication bias:	0	Unlikely
Effect size:	0	Magnitude of effect cannot be determined
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding	0	No plausible confounding
Quality of evidence	⨁⨁⨀⨀ LOW	
Conclusion:	There is no significant effect of neurosurgery versus no neurosurgery on the risk for ACTHD in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study non-significant effect; 240 participants; unknown number of events)	

Abbreviations: AB, attrition bias; adrenocorticotropic hormone deficiency (ACTHD); CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; Gy, Gray; GTR, gross total resection; RT, radiotherapy; SB, selection bias; yr, year.
*Statistically significant outcome

v. What is the risk for CPP in childhood cancer survivors (CNS tumor) treated with neurosurgery?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
3a. Risk CPP after neurosurgery (n=1 study)	Clement 2016	718 CAYA CNS tumor survivors	6.6 (2.0-13.4)	35.9% RT *RT details;* Cranial RT, n=144, RT dose, median 54.0 Gy (range 12.5-60.0) Craniospinal RT, n=114, RT dose, median 24.0 Gy (range 18.0-39.7)	Prevalence at last follow-up CPP: n=48 (12.2% of evaluable patients) Onset of puberty diagnosed by Tanner B2 in girls <8 years and testes >4mL in boys >9 years.	Odds ratio (95% CI) CPP: neurosurgery (yes vs. no) 1.68 (0.61-4.63)	SB: unclear AB: high risk DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias unclear in 1/1; Attrition bias high 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 included and high number of participants and events.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship (dichotomous outcome)
Plausible confounding	0	No plausible confounding
Quality of evidence	⨁⨁⨀⨀ LOW	
Conclusion:	There is no significant effect of neurosurgery versus no neurosurgery on the risk for CPP in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study non-significant effect; 718 participants; 48 events)	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; CPP, central precocious puberty; DB, detection bias; Gy, Gray; RT, radiotherapy; SB, selection bias; yr, year.

b. What is the risk of HP dysfunction in childhood cancer survivors (CNS tumor) treated with higher versus lower numbers of neurosurgeries?

i. What is the risk for GHD in childhood cancer survivors (CNS tumor) treated with higher versus lower numbers of neurosurgeries?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
3b. Risk GHD after number of neurosurgeries (n=1 study)	Gan 2015	166 CAYA CNS tumor survivors	8.3 (0.04-26.8)	41.6% RT *RT details:* Focal RT to total dose 48-55 Gy	Prevalence at last follow-up: GHD: n=67 (40.3%) Diagnosed by provocative testing, GH peak <7 ng/mL	Hazard ratio (95% CI) GHD: number of surgeries, 1.09 (1.04-1.14)*	SB: low risk AB: unclear DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence, partially for prognostic and diagnostic questions
Study limitations:	-1	Some limitations: Selection bias low in 1/1; Attrition bias unclear in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1
Consistency:	0	No important inconsistency, both studies show effect of surgery
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, only 1 study included. Number of events unknown, but narrow confidence intervals.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Although it seems that a higher number of surgeries are associated with an increased risk as compared to lower numbers of surgery, we are not 100% confident
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊖⊖ LOW	
Conclusion:	There is an increased risk for GHD after higher number versus lower numbers of neurosurgeries in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study significant effect; 166 participants; 67 events	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; GH, growth hormone; GHD, growth hormone deficiency; Gy, Gray; RT, radiotherapy; SB, selection bias; yr, year.
*Statistically significant outcome

ii. What is the risk for TSHD in childhood cancer survivors (CNS tumor) treated with higher versus lower numbers of neurosurgeries?

No studies included

iii. What is the risk for LH/FSHD in childhood cancer survivors (CNS tumor) treated with higher versus lower numbers of neurosurgeries?

No studies included

iv. What is the risk for ACTHD in childhood cancer survivors (CNS tumor) treated with higher versus lower numbers of neurosurgeries?

No studies included

v. **What is the risk for CPP in childhood cancer survivors (CNS tumor) treated with higher versus lower numbers of neurosurgeries?**
No studies included

Question 4. Are there other etiological factors associated with the risk of HP dysfunction in childhood cancer survivors (CNS tumor)? (i.e. gender, ethnicity/race, neurofibromatosis, hydrocephalus at diagnosis, tumor location, histology/type of cancer, genetic profile of the patient, type and duration of treatment (i.e. no treatment, neurosurgery, radiotherapy, chemotherapy, radiotherapy & chemotherapy, conditioning for stem cell transplantation, molecular targeted therapy), age at diagnosis/treatment, time since diagnosis/treatment, treatment era)?

a. What is the influence of gender on the risk of HP dysfunction in childhood cancer survivors (CNS tumor)?

i. What is the influence of gender on the risk of GHD in childhood cancer survivors (CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
4a. Risk GHD by gender (n=3 studies)	Clement 2016	718 CAYA CNS tumor survivors	6.6 (2.0-13.4)	35.9% RT *RT details;* Cranial RT, n=144, RT dose, median 54.0 Gy (range 12.5-60.0) Craniospinal RT, n=114, RT dose, median 24.0 Gy (range 18.0-39.7)	Prevalence at last follow-up GHD: n=90 (12.5%) Diagnosed by provocative testing, GH peak <20-30 mU/L or diagnosis by treating physician	Odds ratio (95% CI) GHD: gender (male vs. female) 1.66 (0.93-2.98)	SB: unclear AB: high risk DB: unclear CF: low risk
	Eaton 2016	77 CAYA CNS tumor survivors	7.0 (3.5-13.5) for photon RT 5.8 (3.3-21.9) for proton RT	100% RT *RT details;* All received craniospinal RT Photon RT, n=37, dose 54-55.8 Gy (n=36), >55.8 Gy (n=1) Proton RT, n=40, dose 54-55.8 Gy	Prevalence at last follow-up GHD: n=42 (54.5%) Diagnosed by provocative testing, GH peak cut-off not reported	Odds ratio (95% CI) GHD: gender (male vs. female) 3.80 (1.29-11.17)*	SB: low risk AB: high risk DB: unclear CF: low risk
	Schmiegelow 2000	73 CAYA CNS tumor survivors	15 (2-28)	100% RT *RT details;* Craniospinal RT, n=30 (41.1%) Whole brain RT, n=13 (17.8%) Focal brain RT, n=30 (41.1%)	Prevalence (cross-sectional) GHD: n=58 (80%) Diagnosed by provocative testing, GH peak <9 ng/mL for adults, peak GH <15 mU/L for children	Regression coefficient, p-value Peak GH: gender, β -0.07, p=0.52	SB: low risk AB: low risk DB: unclear CF: low risk

		Median BED to HP region 74 Gy (range 0-99)
GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias low in 2/3, unclear in 1/3; Attrition bias low in 1/3, high in 2/3; Detection bias unclear in 3/3; Confounding low in 3/3
Consistency:	-1	Some inconsistency, one study significant effect of gender and two studies non-significant effect
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size and high total number of events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊖⊖ LOW	
Conclusion:	There is an increased risk for GHD in male childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study significant effect, 2 studies non-significant effect; 868 participants; 190 events)	

Abbreviations: AB, attrition bias; BED, biological effective dose; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; GH, growth hormone; GHD, growth hormone deficiency; Gy, Gray; HP, hypothalamic-pituitary; RT, radiotherapy; SB, selection bias; yr, year.
*Statistically significant outcome

ii. What is the influence of gender on the risk of TSHD in childhood cancer survivors (CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
4a. Risk TSHD by gender (n=1 study)	Clement 2016	718 CAYA CNS tumor survivors	6.6 (2.0-13.4)	35.9% RT *RT details;* Cranial RT, n=144, RT dose, median 54.0 Gy (range 12.5-60.0) Craniospinal RT, n=114, RT dose, median 24.0 Gy (range 18.0-39.7)	Prevalence at last follow-up TSHD: n=66 (9.1%) Diagnosed by low FT4 concentrations with low, normal or mildly raised TSH	Odds ratio (95% CI) TSHD: gender (male vs. female) 2.02 (1.10-3.70)*	SB: unclear AB: high risk DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias unclear in 1/1; Attrition bias high 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 included and high number of participants and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊖⊖ LOW	

Conclusion:	There is an increased risk for TSHD in male childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study significant effect; 718 participants; 66 events)

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; FT4, free thyroxine; RT, radiotherapy; SB, selection bias; TSH, thyroid-stimulating hormone; TSHD, thyroid-stimulating hormone deficiency; yr, year.
*Statistically significant outcome

iii. What is the influence of gender on the risk of LH/FSHD in childhood cancer survivors (CNS tumor)?

No studies included

iv. What is the influence of gender on the risk of ACTHD in childhood cancer survivors (CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
4a. Risk ACTHD by gender (n=3 studies)	Armstrong 2011	240 CAYA CNS tumor survivors	10 (5-21.5)	46.3% RT *RT details;* Not reported	15-yr cumulative incidence ACTHD: 25.7% Diagnosed by provocative testing, cut-off value unknown	Hazard ratio (95% CI) ACTHD: gender (male vs. female) 1.6 (0.9-3.0)	SB: unclear AB: unclear DB: unclear CF: low risk
	Gan 2015	166 CAYA CNS tumor survivors	8.3 (0.04-26.8)	41.6% RT *RT details:* Focal RT to total dose 48-55 Gy	Prevalence at last follow-up: ACTHD: n=22 (13.3%) Diagnosed by provocative testing, peak cortisol <500nmol/L	Hazard ratio (95% CI) ACTHD: gender (female vs. male) 0.30 (0.12-0.74)*	SB: low risk AB: unclear DB: unclear CF: low risk
	Schmiegelow 2003	73 CAYA CNS tumor survivors (17 controls)	15 (2-29)	100% RT *RT details;* Craniospinal RT, n=30 Whole brain RT, n=14 Focal brain RT, n=29 Median BED to HP region 73 Gy (range 0-94)	Prevalence (cross-sectional) ACTHD: n=14 (19%) Diagnosed by basal cortisol levels <500 nmol/L and peak cortisol <500 nmol/L to ACTH test or ITT	Regression coefficient, p-value Peak cortisol: gender, β 0.00, p=1.00	SB: low risk AB: high risk DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence, partially for prognostic and diagnostic questions
Study limitations:	0	No serious limitations: Selection bias low in 2/3, unclear in 1/3; Attrition bias high in 1/3, unclear in 2/3; Detection bias unclear in 3/3; Confounding low in 3/3
Consistency:	-1	Some inconsistency, one study significant effect of gender and two studies non-significant effect
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship

Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊕⊖ MODERATE	
Conclusion:	There is an increased risk for ACTHD in male childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (2 studies non-significant effect, 1 study significant effect; 479 participants; 36 events (in 2/3), unknown number of events (in 1/3))	

Abbreviations: AB, attrition bias; ACTHD, adrenocorticotropic hormone deficiency; BED, biological effective dose; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; Gy, Gray; HP, hypothalamic-pituitary; ITT, insulin tolerance test; RT, radiotherapy; SB, selection bias; yr, year.
*Statistically significant outcome

v. What is the influence of gender on the risk of CPP in childhood cancer survivors (CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
4a. Risk CPP by gender (n=2 studies)	Clement 2016	718 CAYA CNS tumor survivors	6.6 (2.0-13.4)	35.9% RT *RT details;* Cranial RT, n=144, RT dose, median 54.0 Gy (range 12.5-60.0) Craniospinal RT, n=114, RT dose, median 24.0 Gy (range 18.0-39.7)	Prevalence at last follow-up CPP: n=48 (12.2% of evaluable patients) Onset of puberty diagnosed by Tanner B2 in girls <8 years and testes >4mL in boys >9 years.	Odds ratio (95% CI) CPP: gender (male vs. female) 0.88 (0.41-1.87)	SB: unclear AB: high risk DB: unclear CF: low risk
	Gan 2015	166 CAYA CNS tumor survivors	8.3 (0.04-26.8)	41.6% RT *RT details:* Focal RT to total dose 48-55 Gy	Prevalence at last follow-up: CPP: n=32/123 (26.0%) Diagnosed by Tanner staging, pubertal concentrations of testosterone/estradiol and/or pubertal response to provocative testing	Hazard ratio (95% CI) CPP: gender (female vs. male) 0.43 (0.21-0.90)*	SB: low risk AB: unclear DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias low in 1/2, unclear in 1/2; Attrition bias high in 1/2, unclear in 1/2; Detection bias unclear in 2/2; Confounding low in 2/2
Consistency:	-1	Some inconsistency, one study significant effect of gender and one study non-significant effect of gender
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊖⊖ LOW	
Conclusion:	There is an increased risk for CPP in male childhood cancer survivors (CNS tumor), diagnosed before the age of 25 years. (1 study significant effect, 1 study non-significant effect; 884 participants; 80 events)	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; CPP, central precocious puberty; DB, detection bias; Gy, Gray; RT, radiotherapy; SB, selection bias; yr, year.
*Statistically significant outcome

b. What is the influence of ethnicity/race on the risk of HP dysfunction in childhood cancer survivors (CNS tumor)?

No studies included for all five types of HP dysfunction

c. What is the influence of neurofibromatosis on the risk of HP dysfunction in childhood cancer survivors (CNS tumor)?

i. What is the influence of neurofibromatosis on the risk of GHD in childhood cancer survivors (CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
4c. Risk GHD by neurofibromatosis (n=1 study)	Armstrong 2011	240 CAYA CNS tumor survivors	10 (5-21.5)	46.3% RT *RT details;* Not reported	15-yr cumulative incidence GHD: 29% Diagnosed by provocative testing, GH peak cut-off value unknown	Hazard ratio (95% CI) GHD: neurofibromatosis (yes vs. no) 1.1 (0.5-2.1)	SB: unclear AB: unclear DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence
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	N/A (1 study)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, only 1 study included. Number of events unknown, but narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊖⊖ LOW	
Conclusion:	There is no significant effect of neurofibromatosis on the risk for GHD in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study non-significant effect; 240 participants; unknown number of events)	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; GH, growth hormone; GHD, growth hormone deficiency; RT, radiotherapy; SB, selection bias; yr, year.

ii. What is the influence of neurofibromatosis on the risk of TSHD in childhood cancer survivors (CNS tumor)?

No studies included

iii. What is the influence of neurofibromatosis on the risk of LH/FSHD in childhood cancer survivors (CNS tumor)?

No studies included

iv. What is the influence of neurofibromatosis on the risk of ACTHD in childhood cancer survivors (CNS tumor)?
No studies included

v. What is the influence of neurofibromatosis on the risk of CPP in childhood cancer survivors (CNS tumor)?
No studies included

d. What is the influence of hydrocephalus/shunt on the risk of HP dysfunction in childhood cancer survivors (CNS tumor)?

i. What is the influence of hydrocephalus/shunt on the risk of GHD in childhood cancer survivors (CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
4d. Risk GHD by hydrocephalus/shunt (n=2 studies)	Clement 2016	718 CAYA CNS tumor survivors	6.6 (2.0-13.4)	35.9% RT *RT details;* Cranial RT, n=144, RT dose, median 54.0 Gy (range 12.5-60.0) Craniospinal RT, n=114, RT dose, median 24.0 Gy (range 18.0-39.7)	Prevalence at last follow-up GHD: n=90 (12.5%) Diagnosed by provocative testing, GH peak <20-30 mU/L or diagnosis by treating physician	Odds ratio (95% CI) GHD: hydrocephalus (yes vs. no) 1.33 (0.71-2.49)	SB: unclear AB: high risk DB: unclear CF: low risk
	Merchant 2011	192 CAYA CNS tumor survivors	Max 60 months	100% RT *RT details;* All received conformal RT or intensity-modulated RT Ependymoma: Cranial RT dose 59.4 Gy, n=73 Cranial RT dose 54.0 Gy, n=15 Low grade glioma: Cranial RT dose 54 Gy, n=51	Prevalence not reported GHD diagnosed by provocative testing (arginine/L-DOPA), GH peak <7 ng/mL	Mixed models analysis Peak GH: interaction between time and CSF shunt, p<0.0350*	SB: unclear AB: unclear DB: unclear CF: high risk

GRADE assessment		
Study design:	+4	Observational evidence, partially for prognostic and diagnostic questions
Study limitations:	-1	Some limitations: Selection bias unclear in 2/2; Attrition bias high in 1/2, unclear in 1/2; Detection bias unclear in 2/2; Confounding low in 1/2, high in 1/2
Consistency:	-1	Some inconsistency, one study significant effect of hydrocephalus and one study non-significant effect
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship

Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊖⊖ LOW	
Conclusion:	There is an increased risk for GHD after CSF shunting/hydrocephalus versus no CSF shunting/hydrocephalus in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study significant effect, 1 study non-significant effect; 910 participants; 90 events (in 1/2), unknown number of events (in 1/2))	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; CSF shunt, cerebrospinal fluid shunt; DB, detection bias; GH, growth hormone; GHD, growth hormone deficiency; Gy, Gray; HP, hypothalamic-pituitary; ITT, insulin tolerance test; RT, radiotherapy; SB, selection bias; yr, year.
*Statistically significant outcome

ii. What is the influence of hydrocephalus/shunt on the risk of TSHD in childhood cancer survivors (CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
4d. Risk TSHD by hydrocephalus/shunt (n=1 study)	Clement 2016	718 CAYA CNS tumor survivors	6.6 (2.0-13.4)	35.9% RT *RT details;* Cranial RT, n=144, RT dose, median 54.0 Gy (range 12.5-60.0) Craniospinal RT, n=114, RT dose, median 24.0 Gy (range 18.0-39.7)	Prevalence at last follow-up TSHD: n=66 (9.1%) Diagnosed by low FT4 concentrations with low, normal or mildly raised TSH	Odds ratio (95% CI) TSHD: hydrocephalus (yes vs. no) 1.59 (0.86-2.92)	SB: unclear AB: high risk DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias unclear in 1/1; Attrition bias high 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 included and high number of participants and events, but narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship (dichotomous outcome)
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊖⊖ LOW	
Conclusion:	There is no significant effect of hydrocephalus versus no hydrocephalus on the risk for THSD in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study non-significant effect; 718 participants; 66 events)	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; FT4, free thyroxine; RT, radiotherapy; SB, selection bias; TSH, thyroid-stimulating hormone; TSHD, thyroid-stimulating hormone deficiency; yr, year.

iii. What is the influence of hydrocephalus/shunt on the risk of LH/FSHD in childhood cancer survivors (CNS tumor)?

No studies included

iv. What is the influence of hydrocephalus/shunt on the risk of ACTHD in childhood cancer survivors (CNS tumor)?

No studies included

v. What is the influence of hydrocephalus/shunt on the risk of CPP in childhood cancer survivors (CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
4d. Risk CPP by hydrocephalus/shunt (n=1 study)	Clement 2016	718 CAYA CNS tumor survivors	6.6 (2.0-13.4)	35.9% RT *RT details;* Cranial RT, n=144, RT dose, median 54.0 Gy (range 12.5-60.0) Craniospinal RT, n=114, RT dose, median 24.0 Gy (range 18.0-39.7)	Prevalence at last follow-up CPP: n=48 (12.2% of evaluable patients) Onset of puberty diagnosed by Tanner B2 in girls <8 years and testes >4mL in boys >9 years.	Odds ratio (95% CI) CPP: hydrocephalus (yes vs. no) 3.73 (1.56-8.89)*	SB: unclear AB: high risk DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias unclear in 1/1; Attrition bias high 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 included and high number of participants and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship (dichotomous outcome)
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊖⊖ LOW	
Conclusion:	There is an increased risk for CPP after hydrocephalus versus no hydrocephalus in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study significant effect; 718 participants; 48 events)	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; CPP, central precocious puberty; DB, detection bias; Gy, Gray; RT, radiotherapy; SB, selection bias; yr, year.
*Statistically significant outcome

e. What is the influence of tumor location on the risk of HP dysfunction in childhood cancer survivors (CNS tumor)?

i. What is the influence of tumor location on the risk of GHD in childhood cancer survivors (CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias

4e. Risk GHD by tumor location (n=2 studies)	Armstrong 2011	240 CAYA CNS tumor survivors	10 (5-21.5)	46.3% RT *RT details;* Not reported	15-yr cumulative incidence GHD: 29% Diagnosed by provocative testing, GH peak cut-off value unknown	Hazard ratio (95% CI) GHD: tumor location (diencephalon vs. other) 3.5 (1.6-7.7)*	SB: unclear AB: unclear DB: unclear CF: low risk
	Clement 2016	718 CAYA CNS tumor survivors	6.6 (2.0-13.4)	35.9% RT *RT details;* Cranial RT, n=144, RT dose, median 54.0 Gy (range 12.5-60.0) Craniospinal RT, n=114, RT dose, median 24.0 Gy (range 18.0-39.7)	Prevalence at last follow-up GHD: n=90 (12.5%) Diagnosed by provocative testing, GH peak <20-30 mU/L or diagnosis by treating physician	Odds ratio (95% CI) GHD: tumor location (suprasellar vs. supratentorial) 10.15 (3.48-29.56)* GHD: tumor location (infratentorial vs. supratentorial) 5.64 (2.66-11.94)*	SB: unclear AB: high risk DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias unclear in 2/2; Attrition bias high in 1/2, unclear in 1/2; Detection bias unclear in 2/2; Confounding low in 2/2
Consistency:	0	No important inconsistency, both studies show an increased risk for suprasellar/diencephalic tumor location
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, large sample size, but broad confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊖⊖ LOW	
Conclusion:	There is an increased risk for GHD in patients with suprasellar/diencephalic tumor location versus supratentorial or other tumor location in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (2 studies significant effect; 958 participants; 90 events (in 1/2), unknown number of events (in 1/2)) There is an increased risk for GHD in patients with infratentorial tumor location versus supratentorial tumor location in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study significant effect; 718 participants; 90 events		

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; GH, growth hormone; GHD, growth hormone deficiency; RT, radiotherapy; SB, selection bias; yr, year.
*Statistically significant outcome

ii. What is the influence of tumor location on the risk of TSHD in childhood cancer survivors (CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
4e. Risk TSHD by tumor location (n=2 studies)	Clement 2016	718 CAYA CNS tumor survivors	6.6 (2.0-13.4)	35.9% RT *RT details;* Cranial RT, n=144, RT dose, median 54.0 Gy (range	Prevalence at last follow-up TSHD: n=66 (9.1%) Diagnosed by low FT4	Odds ratio (95% CI) TSHD: tumor location (suprasellar vs. supratentorial) 13.04 (5.04-33.76)*	SB: unclear AB: high risk DB: unclear CF: low risk

				12.5-60.0) Craniospinal RT, n=114, RT dose, median 24.0 Gy (range 18.0-39.7)	concentrations with low, normal or mildly raised TSH	TSHD: tumor location (infratentorial vs. supratentorial) 2.46 (1.17-5.19)*	
	Gan 2015	166 CAYA CNS tumor survivors	8.3 (0.04-26.8)	41.6% RT *RT details:* Focal RT to total dose 48-55 Gy	Prevalence at last follow-up: TSHD: n=22 (13.3%) Diagnosed by low FT4 concentrations with inappropriately normal/ low TSH	Hazard ratio (95% CI) TSHD: hypothalamic involvement (yes vs. no) 7.18 (2.41-21.38)*	SB: low risk AB: unclear DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias low in 1/2, unclear in 1/2; Attrition bias high in 1/2, unclear in 1/2; Detection bias unclear in 2/2; Confounding low in 2/2
Consistency:	0	No important inconsistency, both studies show an increased risk for suprasellar/hypothalamic tumor location
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, large sample size, but broad confidence intervals
Publication bias:	0	Unlikely
Effect size:	+1	Large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊕⊖ MODERATE	
Conclusion:	There is an increased risk for TSHD in patients with suprasellar/hypothalamic tumor location/involvement versus supratentorial tumor location/no hypothalamic involvement in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (2 studies significant effect; 884 participants; 88 events) There is an increased risk for TSHD in patients with infratentorial tumor location versus supratentorial location in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study significant effect; 718 participants; 66 events)	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; FT4, free thyroxine; RT, radiotherapy; SB, selection bias; TSH, thyroid-stimulating hormone; TSHD, thyroid-stimulating hormone deficiency; yr, year.
*Statistically significant outcome

iii. What is the influence of tumor location on the risk of LH/FSHD in childhood cancer survivors (CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias

4e. Risk LH/FSHD by tumor location (n=1 study)	Gan 2015	166 CAYA CNS tumor survivors	8.3 (0.04-26.8)	41.6% RT *RT details:* Focal RT to total dose 48-55 Gy	Prevalence at last follow-up: LH/FSHD: n=21/103 (20.4%) Diagnosed by absence of pubertal development or pubertal arrest with undetectable testosterone/estradiol and/or abnormal GnRH testing	Hazard ratio (95% CI) LH/FSHD: hypothalamic involvement (yes vs. no) 5.09 (1.95-13.31)*	SB: low risk AB: unclear DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	0	No serious limitations: Selection bias low 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:	-2	Important imprecision, only 1 study included and low number of events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding	0	No plausible confounding
Quality of evidence	⨁⨁⨀⨀ LOW	
Conclusion:	There is an increased risk for LH/FSHD in patients with hypothalamic tumor involvement versus no hypothalamic tumor involvement in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study significant effect; 166 participants; 21 events)	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; GnRH, Gonadotropin-releasing hormone; Gy, Gray; LH/FSHD, luteinizing hormone and follicle-stimulating hormone deficiency; RT, radiotherapy; SB, selection bias; yr, year.
*Statistically significant outcome

iv. What is the influence of tumor location on the risk of ACTHD in childhood cancer survivors (CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
4e. Risk ACTHD by tumor location (n=1 study)	Armstrong 2011	240 CAYA CNS tumor survivors	10 (5-21.5)	46.3% RT *RT details;* Not reported	15-yr cumulative incidence ACTHD: 25.7% Diagnosed by provocative testing, cut-off value unknown	Hazard ratio (95% CI) ACTHD: tumor location (diencephalon vs. other) 3.4 (1.6-7.3)*	SB: unclear AB: unclear DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence

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	N/A (1 study)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, only 1 study included, but large sample size.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊖⊖ LOW	
Conclusion:	There is an increased risk for ACTHD in patients with diencephalic tumor location versus other tumor location in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study significant effect; 240 participants; unknown number of events)	

Abbreviations: AB, attrition bias; ACTHD, adrenocorticotropic hormone deficiency; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; Gy, Gray; RT, radiotherapy; SB, selection bias; yr, year.
*Statistically significant outcome

v. What is the influence of tumor location on the risk of CPP in childhood cancer survivors (CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
4e. Risk CPP by tumor location (n=2 studies)	Clement 2016	718 CAYA CNS tumor survivors	6.6 (2.0-13.4)	35.9% RT *RT details;* Cranial RT, n=144, RT dose, median 54.0 Gy (range 12.5-60.0) Craniospinal RT, n=114, RT dose, median 24.0 Gy (range 18.0-39.7)	Prevalence at last follow-up CPP: n=48 (12.2% of evaluable patients) Onset of puberty diagnosed by Tanner B2 in girls <8 years and testes >4mL in boys >9 years.	Odds ratio (95% CI) CPP: tumor location (suprasellar vs. supratentorial) 110.45 (23.90-510.35)* CPP: tumor location (infratentorial vs. supratentorial) 1.96 (0.52-7.46)	SB: unclear AB: high risk DB: unclear CF: low risk
	Gan 2015	166 CAYA CNS tumor survivors	8.3 (0.04-26.8)	41.6% RT *RT details:* Focal RT to total dose 48-55 Gy	Prevalence at last follow-up: CPP: n=32/123 (26.0%) Diagnosed by Tanner staging, pubertal concentrations of testosterone/estradiol and/or pubertal response to provocative testing	Hazard ratio (95% CI) CPP: hypothalamic involvement (yes vs. no) 4.42 (1.97-9.92)*	SB: low risk AB: unclear DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias low in 1/2, unclear in 1/2; Attrition bias high in 1/2, unclear in 1/2; Detection bias unclear in 2/2; Confounding low in 2/2
Consistency:	0	No important inconsistency, both studies show an increased risk for suprasellar/hypothalamic tumor location
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, large sample size, but broad confidence intervals

Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊖⊖ LOW	
Conclusion:	There is an increased risk for CPP in patients with suprasellar/hypothalamic tumor location/involvement versus supratentorial tumor location/no hypothalamic involvement in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (2 studies significant effect; 884 participants; 80 events) There is no significant effect of infratentorial versus supratentorial tumor location on the risk for CPP in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study significant effect; 718 participants; 48 events)	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; CPP, central precocious puberty; DB, detection bias; Gy, Gray; RT, radiotherapy; SB, selection bias; yr, year.
*Statistically significant outcome

f. What is the influence of tumor histology/type on the risk of HP dysfunction in childhood cancer survivors (CNS tumor)?

i. What is the influence of tumor histology/type on the risk of GHD in childhood cancer survivors (CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
4f. Risk GHD by tumor histology/type (n=1 study)	Eaton 2016	77 CAYA CNS tumor survivors	7.0 (3.5-13.5) for photon RT 5.8 (3.3-21.9) for proton RT	100% RT *RT details;* All received craniospinal RT Photon RT, n=37, dose 54-55.8 Gy (n=36), >55.8 Gy (n=1) Proton RT, n=40, dose 54-55.8 Gy	Prevalence at last follow-up GHD: n=42 (54.5%) Diagnosed by provocative testing, GH peak cut-off not reported	Odds ratio (95% CI) GHD: histology (classic medulloblastoma vs. other medulloblastoma histology) 7.07 (1.66-30.19)*	SB: low risk AB: high risk DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias low in 1/1; Attrition bias high 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:	-2	Important imprecision, only 1 study included and low number of participants
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊖⊖⊖ VERY LOW	
Conclusion:	There is an increased risk for GHD in patients with classic medulloblastoma histology vs. other medulloblastoma histologies in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study significant effect; 77 participants; 42 events)	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; GH, growth hormone; GHD, growth hormone deficiency; Gy, Gray; RT, radiotherapy; SB, selection bias; yr, year.
*Statistically significant outcome

ii. What is the influence of tumor histology/type on the risk of TSHD in childhood cancer survivors (CNS tumor)?
No studies included

iii. What is the influence of tumor histology/type on the risk of LH/FSHD in childhood cancer survivors (CNS tumor)?
No studies included

iv. What is the influence of tumor histology/type on the risk of ACTHD in childhood cancer survivors (CNS tumor)?
No studies included

v. What is the influence of tumor histology/type on the risk of CPP in childhood cancer survivors (CNS tumor)?
No studies included

g. What is the influence of the genetic profile on the risk of HP dysfunction in childhood cancer survivors (CNS tumor)?

No studies included for all five types of HP dysfunction

h. What is the influence of the age at diagnosis/treatment on the risk of HP dysfunction in childhood cancer survivors (CNS tumor)?

i. What is the influence of the age at diagnosis/treatment on the risk of GHD in childhood cancer survivors (CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
4h. Risk GHD by age at diagnosis/treatment (n=5 studies)	Clayton 1991	82 CAYA survivors (n=66 CAYA CNS tumor survivors)[1]	4.3 (0.2-18.9)	100% RT *RT details;* Cranial RT, n=24 Craniospinal RT, n=58 HP-RT dose Range 27-47.5 Gy <30 Gy, n=46 (56.1%) ≥30 Gy, n=36 (43.9%)	Incidence >5 yrs after RT GHD: incidence 74% Diagnosed by provocative testing (ITT); peak GH ≤15	Relative risk (95% CI) GHD: age at radiotherapy, RR not reported, p=NS	SB: unclear AB: high risk DB: unclear CF: high risk
	Clement 2016	718 CAYA CNS tumor survivors	6.6 (2.0-13.4)	35.9% RT *RT details;* Cranial RT, n=144, RT dose, median 54.0 Gy (range 12.5-60.0) Craniospinal RT, n=114, RT	Prevalence at last follow-up GHD: n=90 (12.5%) Diagnosed by provocative testing, GH peak <20-30 mU/L or diagnosis by	Odds ratio (95% CI) GHD: younger age at diagnosis (years) 1.06 (1.00-1.13)	SB: unclear AB: high risk DB: unclear CF: low risk

				dose, median 24.0 Gy (range 18.0-39.7)	treating physician		
	Eaton 2016	77 CAYA CNS tumor survivors	7.0 (3.5-13.5) for photon RT 5.8 (3.3-21.9) for proton RT	100% RT *RT details;* All received craniospinal RT Photon RT, n=37, dose 54-55.8 Gy (n=36), >55.8 Gy (n=1) Proton RT, n=40, dose 54-55.8 Gy	Prevalence at last follow-up GHD: n=42 (54.5%) Diagnosed by provocative testing, GH peak cut-off not reported	Odds ratio (95% CI) GHD: age at diagnosis, 0.83 (0.71-0.97)*	SB: low risk AB: high risk DB: unclear CF: low risk
	Shalitin 2011	114 CAYA CNS tumor survivors	12.8 (3.7-28.7)	56.1% RT *RT details;* Cranial RT, n=55, RT dose 35-56 Gy Spinal RT, n=27, RT dose 30-54 Gy	Prevalence at last follow-up GHD: n=40 (35.1%) Diagnosed by provocative testing, GH peak <10 ng/mL	Odds ratio (95% CI) GHD: age at tumor diagnosis, 0.88 (0.79-0.97)*	SB: low risk AB: low risk DB: unclear CF: high risk
	Schmiegelow 2000	73 CAYA CNS tumor survivors	15 (2-28)	100% RT *RT details;* Craniospinal RT, n=30 (41.1%) Whole brain RT, n=13 (17.8%) Focal brain RT, n=30 (41.1%) Median BED to HP region 74 Gy (range 0-99)	Prevalence (cross-sectional) GHD: n=58 (80%) Diagnosed by provocative testing, GH peak <9 ng/mL for adults, peak GH <15 mU/L for children	Regression coefficient, p-value Peak GH: age at radiotherapy, β 0.06, p=0.60	SB: low risk AB: low risk DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence, partially for prognostic and diagnostic questions
Study limitations:	-1	Some limitations: Selection bias low in 3/5, unclear in 2/5; Attrition bias low in 2/5, high in 3/5; Detection bias unclear in 5/5; Confounding low in 3/5, high in 2/5
Consistency:	-1	Some inconsistency, two studies shows significant effect of age at tumor diagnosis, 3 studies show non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Although it seems that younger ages are associated with an increased risk as compared to older ages, we are not 100% confident
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊖⊖ LOW	
Conclusion:	There is a significant effect of younger age at tumor diagnosis/treatment versus older age on the risk for GHD in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (2 studies significant effect, 3 studies non-significant effect, 1064 participants; 230 events (in 4/5), unknown number of events (in 1/5))	

Abbreviations: AB, attrition bias; BED, biological effective dose; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; GH, growth hormone; GHD, growth hormone deficiency; Gy, Gray; HP, hypothalamic-pituitary; ITT, insulin tolerance test; NS, not significant; RT, radiotherapy; SB, selection bias; yr, year.
*Statistically significant outcome
[1] Study comprises ≥75% CAYA CNS tumor survivors

ii. What is the influence of the age at diagnosis/treatment on the risk of TSHD in childhood cancer survivors (CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
4h. Risk TSHD by age at diagnosis/treatment (n=1 study)	Clement 2016	718 CAYA CNS tumor survivors	6.6 (2.0-13.4)	35.9% RT *RT details;* Cranial RT, n=144, RT dose, median 54.0 Gy (range 12.5-60.0) Craniospinal RT, n=114, RT dose, median 24.0 Gy (range 18.0-39.7)	Prevalence at last follow-up TSHD: n=66 (9.1%) Diagnosed by low FT4 concentrations with low, normal or mildly raised TSH	Odds ratio (95% CI) TSHD: younger age at diagnosis (years) 1.00 (0.93-1.06)	SB: unclear AB: high risk DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias unclear in 1/1; Attrition bias high 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 included and high number of participants and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊖⊖ LOW	
Conclusion:	There is no significant effect of younger age at tumor diagnosis/treatment versus older age on the risk for TSHD in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study non-significant effect, 718 participants; 66 events)	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; FT4, free thyroxine; RT, radiotherapy; SB, selection bias; TSH, thyroid-stimulating hormone; TSHD, thyroid-stimulating hormone deficiency; yr, year.

iii. What is the influence of the age at diagnosis/treatment on the risk of LH/FSHD in childhood cancer survivors (CNS tumor)?

No studies included

iv. What is the influence of the age at diagnosis/treatment on the risk of ACTHD in childhood cancer survivors (CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
4h. Risk ACTHD by age at diagnosis/treatment	Schmiegelow 2003	73 CAYA CNS tumor survivors (17 controls)	15 (2-29)	100% RT *RT details;* Craniospinal RT, n=30 Whole brain RT, n=14	Prevalence (cross-sectional) ACTHD: n=14 (19%) Diagnosed by basal	Regression coefficient, p-value Peak cortisol: age at radiotherapy, β 0.01, p=0.40	SB: low risk AB: high risk DB: unclear CF: low risk

(n=1 study)			Focal brain RT, n=29 Median BED to HP region 73 Gy (range 0-94)	cortisol levels <500 nmol/L and peak cortisol <500 nmol/L to ACTH test or ITT

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias low in 1/1; Attrition bias high 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:	-2	Important imprecision, only 1 study included and low number of participants and events.
Publication bias:	0	Unlikely
Effect size:	0	Magnitude of effect cannot be determined
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊖⊖⊖ VERY LOW	
Conclusion:	There is no significant effect of younger age at tumor diagnosis/treatment versus older age on the risk for ACTHD in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study non-significant effect, 73 participants; 14 events)	

Abbreviations: AB, attrition bias; ACTHD, adrenocorticotropic hormone deficiency; BED, biological effective dose; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; Gy, Gray; HP, hypothalamic-pituitary; ITT, insulin tolerance test; RT, radiotherapy; SB, selection bias; yr, year.
*Statistically significant outcome

v. What is the influence of the age at diagnosis/treatment on the risk of CPP in childhood cancer survivors (CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
4h. Risk CPP by age at diagnosis/treatment (n=1 study)	Clement 2016	718 CAYA CNS tumor survivors	6.6 (2.0-13.4)	35.9% RT *RT details;* Cranial RT, n=144, RT dose, median 54.0 Gy (range 12.5-60.0) Craniospinal RT, n=114, RT dose, median 24.0 Gy (range 18.0-39.7)	Prevalence at last follow-up CPP: n=48 (12.2% of evaluable patients) Onset of puberty diagnosed by Tanner B2 in girls <8 years and testes >4mL in boys >9 years.	Odds ratio (95% CI) CPP: younger age at diagnosis (years) 0.86 (0.77-1.03)	SB: unclear AB: high risk DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias unclear in 1/1; Attrition bias high 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 included and high number of participants and events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect

Dose-response:	0	Unclear if dose-response relationship
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊖⊖ LOW	
Conclusion:	There is no significant effect of younger age at tumor diagnosis/treatment versus older age on the risk for CPP in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study non-significant effect, 718 participants; 48 events)	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; CPP, central precocious puberty; DB, detection bias; Gy, Gray; RT, radiotherapy; SB, selection bias; yr, year.

i. What is the influence of age at follow-up on the risk of HP dysfunction in childhood cancer survivors (CNS tumor)?

No studies included for all five types of HP dysfunction

j. What is the influence of time since diagnosis/treatment on the risk of HP dysfunction in childhood cancer survivors (CNS tumor)?

i. What is the influence of time since diagnosis/treatment on the risk of GHD in childhood cancer survivors (CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
4j. Risk GHD by time since diagnosis/treatment (n=4 studies)	Clayton 1991	82 CAYA survivors (n=66 CAYA CNS tumor survivors)[1]	4.3 (0.2-18.9)	100% RT *RT details;* Cranial RT, n=24 Craniospinal RT, n=58 HP-RT dose Range 27-47.5 Gy <30 Gy, n=46 (56.1%) ≥30 Gy, n=36 (43.9%)	Incidence >5 yrs after RT GHD: incidence 74% Diagnosed by provocative testing (ITT); peak GH ≤15	Relative risk (95% CI) GHD: time since radiotherapy, RR not reported, p=0.0007*	SB: unclear AB: high risk DB: unclear CF: high risk
	Clement 2016	718 CAYA CNS tumor survivors	6.6 (2.0-13.4)	35.9% RT *RT details;* Cranial RT, n=144, RT dose, median 54.0 Gy (range 12.5-60.0) Craniospinal RT, n=114, RT dose, median 24.0 Gy (range 18.0-39.7)	Prevalence at last follow-up GHD: n=90 (12.5%) Diagnosed by provocative testing, GH peak <20-30 mU/L or diagnosis by treating physician	Odds ratio (95% CI) GHD: follow-up time (years) 1.17 (1.07-1.28)*	SB: unclear AB: high risk DB: unclear CF: low risk
	Schmiegelow 2000	73 CAYA CNS tumor survivors	15 (2-28)	100% RT *RT details;* Craniospinal RT, n=30 (41.1%) Whole brain RT, n=13 (17.8%) Focal brain RT, n=30	Prevalence (cross-sectional) GHD: n=58 (80%) Diagnosed by provocative testing, GH peak <9 ng/mL for adults, peak GH <15 mU/L for children	Regression coefficient, p-value Peak GH: length of follow-up, β -0.20, p=0.05	SB: low risk AB: low risk DB: unclear CF: low risk

				(41.1%) Median BED to HP region 74 Gy (range 0-99)			
	Merchant 2011	192 CAYA CNS tumor survivors	Max 60 months	100% RT *RT details;* All received conformal RT or intensity-modulated RT Ependymoma: Cranial RT dose 59.4 Gy, n=73 Cranial RT dose 54.0 Gy, n=15 Low grade glioma: Cranial RT dose 54 Gy, n=51	Prevalence not reported GHD diagnosed by provocative testing (arginine/L-DOPA), GH peak <7 ng/mL	Mixed models analysis Peak GH: Interaction between time and baseline GH, p=0.0029*	SB: unclear AB: unclear DB: unclear CF: high risk

GRADE assessment		
Study design:	+4	Observational evidence, partially for prognostic and diagnostic questions
Study limitations:	-1	Some limitations: Selection bias low in 1/4, unclear in 3/4; Attrition bias low in 1/4, high in 2/4, unclear in 1/4; Detection bias unclear in 4/4; Confounding low in 2/4, high in 2/4
Consistency:	-1	Some inconsistency, three studies show significant effect of follow-up, 1 study shows non-significant effects, but trends towards effect of follow-up duration.
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size and high total number of events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Although it seems that longer follow-up time is associated with an increased risk, we are not 100% confident.
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊖⊖ LOW	
Conclusion:	There is an increased risk for GHD after longer follow-up duration versus shorter follow-up duration in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (3 studies significant effect, 1 study non-significant effect; 1065 participants; 148 events (in 2/4), unknown number of events (in 2/4))	

Abbreviations: AB, attrition bias; BED, biological effective dose; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; GH, growth hormone; GHD, growth hormone deficiency; Gy, Gray; HP, hypothalamic-pituitary; ITT, insulin tolerance test; RT, radiotherapy; SB, selection bias; yr, year.
*Statistically significant outcome
[1] Study comprises ≥75% CAYA CNS tumor survivors

ii. What is the influence of time since diagnosis/treatment on the risk of TSHD in childhood cancer survivors (CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
4j. Risk TSHD by time since diagnosis/treatment	Clement 2016	718 CAYA CNS tumor survivors	6.6 (2.0-13.4)	35.9% RT *RT details;* Cranial RT, n=144, RT dose,	Prevalence at last follow-up TSHD: n=66 (9.1%)	Odds ratio (95% CI) TSHD: follow-up time (years) 1.08 (0.99-1.18)	SB: unclear AB: high risk DB: unclear

(n=1 study)			median 54.0 Gy (range 12.5-60.0) Craniospinal RT, n=114, RT dose, median 24.0 Gy (range 18.0-39.7)	Diagnosed by low FT4 concentrations with low, normal or mildly raised TSH		CF: low risk
GRADE assessment						
Study design:	+4	Observational evidence				
Study limitations:	-1	Some limitations: Selection bias unclear in 1/1; Attrition bias high 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 included and high number of participants and events				
Publication bias:	0	Unlikely				
Effect size:	0	No large magnitude of effect				
Dose-response:	0	Unclear if dose-response relationship				
Plausible confounding	0	No plausible confounding				
Quality of evidence	⨁⨁⨀⨀ LOW					
Conclusion:	There is no significant effect after longer follow-up duration versus shorter follow-up duration on the risk for TSHD in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study non-significant effect; 718 participants; 66 events)					

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; FT4, free thyroxine; RT, radiotherapy; SB, selection bias; TSH, thyroid-stimulating hormone; TSHD, thyroid-stimulating hormone deficiency; yr, year.

iii. What is the influence of time since diagnosis/treatment on the risk of LH/FSHD in childhood cancer survivors (CNS tumor)?

No studies included

iv. What is the influence of time since diagnosis/treatment on the risk of ACTHD in childhood cancer survivors (CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
4j. Risk ACTHD by time since diagnosis/treatment (n=1 study)	Schmiegelow 2003	73 CAYA CNS tumor survivors (17 controls)	15 (2-29)	100% RT *RT details;* Craniospinal RT, n=30 Whole brain RT, n=14 Focal brain RT, n=29 Median BED to HP region 73 Gy (range 0-94)	Prevalence (cross-sectional) ACTHD: n=14 (19%) Diagnosed by basal cortisol levels <500 nmol/L and peak cortisol <500 nmol/L to ACTH test or ITT	Regression coefficient, p-value Peak cortisol: length of follow up, β -0.49, p=0.06	SB: low risk AB: high risk DB: unclear CF: low risk
GRADE assessment							
Study design:	+4	Observational evidence for prognostic and diagnostic questions					
Study limitations:	-1	Some limitations: Selection bias low in 1/1; Attrition bias high 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:	-2	Important imprecision, only 1 study included and low number of events
Publication bias:	0	Unlikely
Effect size:	0	Magnitude of effect cannot be determined
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊖⊖⊖ VERY LOW	
Conclusion:	There is no significant effect after longer follow-up duration versus shorter follow-up duration on the risk for ACTHD in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study non-significant effect; 73 participants; 14 events)	

Abbreviations: AB, attrition bias; ACTHD, adrenocorticotropic hormone deficiency; BED, biological effective dose; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; Gy, Gray; HP, hypothalamic-pituitary; ITT, insulin tolerance test; RT, radiotherapy; SB, selection bias; yr, year.

v. What is the influence of time since diagnosis/treatment on the risk of CPP in childhood cancer survivors (CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
4j. Risk CPP by time since diagnosis/treatment (n=1 study)	Clement 2016	718 CAYA CNS tumor survivors	6.6 (2.0-13.4)	35.9% RT *RT details;* Cranial RT, n=144, RT dose, median 54.0 Gy (range 12.5-60.0) Craniospinal RT, n=114, RT dose, median 24.0 Gy (range 18.0-39.7)	Prevalence at last follow-up CPP: n=48 (12.2% of evaluable patients) Onset of puberty diagnosed by Tanner B2 in girls <8 years and testes >4mL in boys >9 years.	Odds ratio (95% CI) CPP: follow-up time (years) 1.03 (0.92-1.17)	SB: unclear AB: high risk DB: unclear CF: low risk
GRADE assessment							
Study design:	+4	Observational evidence					
Study limitations:	-1	Some limitations: Selection bias unclear in 1/1; Attrition bias high 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 included and high number of participants and events					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	Unclear if dose-response relationship					
Plausible confounding	0	No plausible confounding					
Quality of evidence	⊕⊕⊖⊖ LOW						
Conclusion:	There is no significant effect after longer follow-up duration versus shorter follow-up duration on the risk for CPP in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study non-significant effect; 718 participants; 48 events)						

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; CPP, central precocious puberty; DB, detection bias; Gy, Gray; RT, radiotherapy; SB, selection bias; yr, year.

k. What is the influence of treatment era on the risk of HP dysfunction in childhood cancer survivors (CNS tumor)?

i. What is the influence of treatment era on the risk of GHD in childhood cancer survivors (CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
4k. Risk GHD by treatment era (n=1 study)	Gan 2015	166 CAYA CNS tumor survivors	8.3 (0.04-26.8)	41.6% RT *RT details:* Focal RT to total dose 48-55 Gy	Prevalence at last follow-up: GHD: n=67 (40.3%) Diagnosed by provocative testing, GH peak <7 ng/mL	Hazard ratio (95% CI) GHD: treatment era (1997-2004 vs. 1980-1996), 0.89 (CI 0.50-1.58) GHD: treatment era (2005-2010 vs. 1980-1996), 2.48 (95% CI 1.29-4.79)*	SB: low risk AB: unclear DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	0	No serious limitations: Selection bias low 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 included, large sample size and high number of events, and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊕⊖ MODERATE	
Conclusion:	There is an increased risk for GHD in later treatment eras versus earlier treatment eras in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study significant effect; 166 participants; 67 events)	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; GH, growth hormone; GHD, growth hormone deficiency; Gy, Gray; RT, radiotherapy; SB, selection bias; yr, year.
*Statistically significant outcome

ii. What is the influence of treatment era on the risk of TSHD in childhood cancer survivors (CNS tumor)?

No studies included

iii. What is the influence of treatment era on the risk of LH/FSHD in childhood cancer survivors (CNS tumor)?

No studies included

iv. What is the influence of treatment era on the risk of ACTHD in childhood cancer survivors (CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
4k. Risk ACTHD by treatment era	Armstrong 2011	240 CAYA CNS tumor survivors	10 (5-21.5)	46.3% RT *RT details;*	15-yr cumulative incidence	Hazard ratio (95% CI) ACTHD: treatment era (1985-	SB: unclear AB: unclear

(n=1 study)			Not reported	ACTHD: 25.7% Diagnosed by provocative testing, cut-off value unknown	1996 vs. 1997-2007) 0.5 (0.3-0.9)*	DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence
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	N/A (1 study)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, only 1 study included, but large sample size.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊖⊖ LOW	
Conclusion:	There is an increased risk for ACTHD in later treatment eras versus earlier treatment eras in childhood cancer survivors (CNS tumor) diagnosed before the age of 25 years. (1 study significant effect; 240 participants; unknown number of events)	

Abbreviations: AB, attrition bias; ACTHD, adrenocorticotropic hormone deficiency; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; Gy, Gray; RT, radiotherapy; SB, selection bias; yr, year.
*Statistically significant outcome

v. What is the influence of treatment era on the risk of CPP in childhood cancer survivors (CNS tumor)?
No studies included

Childhood cancer survivors (non-CNS tumor)

Question 5. What is the risk to develop HP dysfunction in childhood cancer survivors (non-CNS tumor) who received radiotherapy to the neck and head region and is it modified by gender, ethnicity, race, histology/type of cancer, genetic profile of the patient, type and duration of treatment (radiotherapy, chemotherapy, radiotherapy & chemotherapy, conditioning for stem cell transplantation, TBI, molecular targeted therapy), time after diagnosis or time after exposure?

a. What is the risk of HP dysfunction in childhood cancer survivors (non-CNS tumor) who received radiotherapy to the neck and head region versus no radiotherapy?

i. What is the risk of GHD in childhood cancer survivors (non-CNS tumor) who received radiotherapy to the neck and head region versus no radiotherapy?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias

5a. Risk GHD after radiotherapy (n=3 studies)	Gurney 2006	75 ALL CAYA survivors	24.6 ± 4.8	Percentage RT not reported *RT details;* Cranial RT dose: <24 Gy, n=25 >24 Gy, n=25 RT field: Brain, n=50 Spine, n=17 Pelvis or testes, n=11 TBI, n=5	Prevalence (cross-sectional) GHD: n=33/72 (46%) GH insufficient: n=13/72 (18.1%) Diagnosed by provocative testing (GHRH/arginine). GHD; peak GH <9 µg/L, GH insufficiency; peak GH 9-16.5 µg/L	Relative risk (95% CI) Peak GH: cranial radiotherapy (yes vs. no) RR unknown, -31.5 to -64.8*	SB: high risk AB: low risk DB: unclear CF: low risk
	Shalitin 2006	91 BMT CAYA survivors	6.2 ± 3.5	Percentage RT not reported *RT details;* Pre-conditioning: -Cranial RT, n=5 (5.5%) -Neck/mediastinal RT, n=5 (5.5%) Conditioning: -TBI (12 Gy), n=14 (15.4%) -Cranial RT (7 Gy) + TBI, n=1 (1.1%) -Thoraco-abdominal RT (4-5 Gy), n=3 (3.3%)	Prevalence at last follow-up GHD: n=10 (11%) Diagnosed by provocative testing, GH peak <10 ng/mL	Odds ratio (95% CI) GHD: conditioning with TBI 37 (5.94-231)*	SB: low risk AB: high risk DB: unclear CF: high risk
	Davis 2015	22 BMT CAYA survivors	8.8 (1.4-19.2)	100% RT *RT details;* TBI 14.4 Gy, n=20 TBI 10 Gy, n=2 Additional CNS boost (6Gy), n=2 Additional CNS prophylactic RT (12-18 Gy), n=2	Prevalence (cross-sectional) GHD: n=18 (81.8%) Diagnosed by provocative testing (ITT), peak GH <3µg/l for adults, <7µg/l for children	Relative risk (95% CI) GH AUC: BMT/TBI (yes vs. no) RR not reported, p<0.001*	SB: high risk AB: low risk DB: unclear CF: high risk

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias low in 1/3, high in 2/3; Attrition bias low in 2/3, high in 1/3; Detection bias unclear in 3/3; Confounding low in 1/3, high in 2/3
Consistency:	0	No important inconsistency, all studies show effect of cranial radiotherapy
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size and high total number of 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:	There is an increased risk for GHD after radiotherapy to the head and neck region versus no radiotherapy in childhood cancer survivors (non-CNS tumor) diagnosed before the age of 25 years. (3 studies significant effect; 188 participants; 61 events)	

Abbreviations: AB, attrition bias; ALL, acute lymphoblastic leukemia; AUC, area under the curve; BMT, bone marrow transplantation; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; GH, growth hormone; GHD, growth hormone deficiency; GHRH, growth hormone-releasing hormone; Gy, Gray; ITT, insulin tolerance test; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; yr, year.
*Statistically significant outcome

ii. What is the risk of TSHD in childhood cancer survivors (non-CNS tumor) who received radiotherapy to the neck and head region versus no radiotherapy?
No studies included

iii. What is the risk of LH/FSHD in childhood cancer survivors (non-CNS tumor) who received radiotherapy to the neck and head region versus no radiotherapy?
No studies included

iv. What is the risk of ACTHD in childhood cancer survivors (non-CNS tumor) who received radiotherapy to the neck and head region versus no radiotherapy?
No studies included

v. What is the risk of CPP in childhood cancer survivors (non-CNS tumor) who received radiotherapy to the neck and head region versus no radiotherapy?
No studies included

b. What is the risk of HP dysfunction in childhood cancer survivors (non-CNS tumor) treated with higher versus lower doses radiotherapy?

i. What is the risk of GHD in childhood cancer survivors (non-CNS tumor) treated with higher versus lower doses radiotherapy?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
5b. Risk GHD after higher vs. lower radiotherapy dose (n=3 studies)	Brennan 1998	32 ALL CAYA survivors (35 controls)	Not reported	100% RT *RT details;* 18 Gy, n=11 19-25 Gy, n=21 Additional spinal RT (24 Gy) in n=4	Prevalence at last follow-up GHD: n= 9 (28.1%) GH insufficient: n=12 (37.5%) Diagnosed by provocative testing. GHD; peak GH <9 mU/L to two provocative tests, GH insufficiency; peak GH <20 mU/L and in one or both >9mU/L	Relative risk (95% CI) Peak GH: radiotherapy dose (18 Gy vs. 24/25 Gy), RR not reported, p=0.11	SB: unclear AB: low risk DB: unclear CF: high risk

	Chemaitilly 2015	748 CAYA survivors (n=658 CAYA non-CNS tumor survivors)[1]	27.3 (10.8-47.7)	100% RT *RT details;* Cranial RT dose 1-14.9 Gy, n=40 15-21.9 Gy, n=208 22-29.9 Gy, n=316 30-39.9 Gy, n=31 ≥40 Gy, n=153	Prevalence at last follow-up: GHD: n=348 (46.5%) Established by a previous diagnosis or IGF-1 z-scores <-2	Odds ratio (95% CI) GHD: cranial radiotherapy dose (22-29.9 Gy vs. ≤21.9 Gy) 1.99 (1.4-2.9)* GHD: cranial radiotherapy dose (≥30 Gy vs. ≤21.9 Gy) 0.91 (0.6-1.4)	SB: high risk AB: low risk DB: unclear CF: low risk
	Leung 2007	155 HSCT CAYA survivors	9 (3.1-15.9)	79.4% RT *RT details;* Dose of TBI: 14.4 Gy, n=59 8-12 Gy, n=64	Prevalence at last follow-up GHD: n=39 (25%) Diagnosed by provocative testing; peak GH <10ng/mL	Hazard ratio (95% CI) GHD: radiotherapy dose (per Gy) 1.54 (1.13-2.09)*	SB: low risk AB: low risk DB: unclear CF: unclear

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias low in 1/3, high in 1/3, unclear in 1/3; Attrition bias low in 3/3; Detection bias unclear in 3/3; Confounding low in 1/3, high in 1/3, unclear in 1/3
Consistency:	-1	Some inconsistency, two studies show significant effect of radiotherapy dose and one study non-significant effect, but compares radiotherapy dosages that are relatively close together, which may explain non-significant effect
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No 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	⊕⊕⊕⊖ MODERATE	
Conclusion:	There is an increased risk for GHD after increasing doses radiotherapy to the head and neck region versus lower doses in childhood cancer survivors (non-CNS tumor) diagnosed before the age of 25 years. (2 studies significant effect, 1 study non-significant effect; 935 participants; 396 events)	

Abbreviations: AB, attrition bias; ALL, acute lymphoblastic leukemia; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; GH, growth hormone; GHD, growth hormone deficiency; Gy, Gray; HSCT, hematopoietic stem cell transplantation; IGF-1, insulin-like growth factor-1; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; yr, year.
*Statistically significant outcome; [1] Study comprises ≥75% CAYA non-CNS tumor survivors

ii. What is the risk of TSHD in childhood cancer survivors (non-CNS tumor) treated with higher versus lower doses radiotherapy?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
5b. Risk TSHD after higher vs. lower	Chemaitilly 2015	748 CAYA survivors (n=658 CAYA non-CNS tumor	27.3 (10.8-47.7)	100% RT *RT details;* Cranial RT dose	Prevalence at last follow-up: TSHD: n=56 (7.5%)	Odds ratio (95% CI) TSHD: cranial radiotherapy dose (22-29.9 Gy vs. ≤21.9 Gy) 1.57	SB: high risk AB: low risk DB: unclear

radiotherapy dose (n=1 study)		survivors)[1]	1-14.9 Gy, n=40 15-21.9 Gy, n=208 22-29.9 Gy, n=316 30-39.9 Gy, n=31 ≥40 Gy, n=153	Established by a previous diagnosis or FT4 <0.9 ng/dL with TSH<4 mIU/L	(0.7-3.7) TSHD: cranial radiotherapy (≥30 Gy vs. ≤21.9 Gy) 4.46 (2.1-9.7)*	CF: low risk
GRADE assessment						
Study design:	+4	Observational evidence				
Study limitations:	-1	Some limitations: Selection bias high in 1/1; Attrition bias low 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 included. Large sample size, high total number of events and narrow confidence intervals				
Publication bias:	0	Unlikely				
Effect size:	0	No 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	⊕⊕⊕⊖ MODERATE					
Conclusion:	There is an increased risk for TSHD after increasing doses radiotherapy to the head and neck region versus lower doses in childhood cancer survivors (non-CNS tumor) diagnosed before the age of 25 years. (1 study significant effect; 748 participants; 56 events)					

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; FT4, free thyroxine; RT, radiotherapy; SB, selection bias; TSH, thyroid-stimulating hormone; TSHD, thyroid-stimulating hormone deficiency; yr, year.
*Statistically significant outcome; [1] Study comprises ≥75% CAYA non-CNS tumor survivors

iii. What is the risk of LH/FSHD in childhood cancer survivors (non-CNS tumor) treated with higher versus lower doses radiotherapy?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
5b. Risk LH/FSHD after higher vs. lower radiotherapy dose (n=1 study)	Chemaitilly 2015	748 CAYA survivors (n=658 CAYA non-CNS tumor survivors)[1]	27.3 (10.8-47.7)	100% RT *RT details;* Cranial RT dose 1-14.9 Gy, n=40 15-21.9 Gy, n=208 22-29.9 Gy, n=316 30-39.9 Gy, n=31 ≥40 Gy, n=153	Prevalence at last follow-up: LH/FSHD: n=79 (10.8%) Established by a previous diagnosis or total testosterone <200ng/dL coincided with LH<7 IU/L and FSH <9.2 IU/L in males. In amenorrheic women <40 yrs old, estradiol <17 pg/mL and FSH <11.2 IU/L	Odds ratio (95% CI) LH/FSHD: cranial radiotherapy dose (22-29.9 Gy vs. ≤21.9 Gy) 3.02 (1.3-7.0)* LH/FSHD: cranial radiotherapy dose (≥30 Gy vs. ≤21.9 Gy) 9.71 (4.2-22.3)*	SB: high risk AB: low risk DB: unclear CF: low risk
GRADE assessment							
Study design:	+4	Observational evidence					
Study limitations:	-1	Some limitations: Selection bias high in 1/1; Attrition bias low 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 included. Large sample size and high total number of events
Publication bias:	0	Unlikely
Effect size:	0	No 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	⊕⊕⊕⊖ MODERATE	
Conclusion:	There is an increased risk for LH/FSHD after increasing doses radiotherapy to the head and neck region versus lower doses in childhood cancer survivors (non-CNS tumor) diagnosed before the age of 25 years. (1 study significant effect; 748 participants; 79 events)	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; FSH, follicle-stimulating hormone; Gy, Gray; LH, luteinizing hormone; LH/FSHD, luteinizing hormone and follicle-stimulating hormone deficiency; RT, radiotherapy; SB, selection bias; yr, year.
*Statistically significant outcome; [1] Study comprises ≥75% CAYA non-CNS tumor survivors

iv. What is the risk of ACTHD in childhood cancer survivors (non-CNS tumor) treated with higher versus lower doses radiotherapy?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
5b. Risk ACTHD after higher vs. lower radiotherapy dose (n=1 study)	Chemaitilly 2015	748 CAYA survivors (n=658 CAYA non-CNS tumor survivors)[1]	27.3 (10.8-47.7)	100% RT *RT details;* Cranial RT dose 1-14.9 Gy, n=40 15-21.9 Gy, n=208 22-29.9 Gy, n=316 30-39.9 Gy, n=31 ≥40 Gy, n=153	Prevalence at last follow-up: ACTHD: n=30 (4.0%) Established by a previous diagnosis or 08.00 AM cortisol <5µg/dL	Odds ratio (95% CI) ACTHD: cranial radiotherapy dose (22-29.9 Gy vs ≤ 21.9 Gy) 2.93 (0.7-12.5) ACTHD: cranial radiotherapy (≥30 Gy vs ≤ 21.9 Gy) 8.81 (2.5-30.9)*	SB: high risk AB: low risk DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias high in 1/1; Attrition bias low 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:	-2	Some imprecision, only 1 study included. Large sample size, but broad confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No 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	⊕⊕⊖⊖ LOW	
Conclusion:	There is an increased risk for ACTHD after increasing doses radiotherapy to the head and neck region versus lower doses in childhood cancer survivors (non-CNS tumor) diagnosed before the age of 25 years. (1 study significant effect; 748 participants; 30 events)	

Abbreviations: AB, attrition bias; ACTHD, adrenocorticotropic hormone deficiency; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; Gy, Gray; RT, radiotherapy; SB, selection bias; yr, year.
*Statistically significant outcome; [1] Study comprises ≥75% CAYA non-CNS tumor survivors

v. What is the risk of CPP in childhood cancer survivors (non-CNS tumor) treated with <u>higher versus lower doses</u> radiotherapy?
No studies included

c. What is the risk of HP dysfunction in childhood cancer survivors (non-CNS tumor) treated with <u>TBI versus no TBI</u>?

i. What is the risk of GHD in childhood cancer survivors (non-CNS tumor) who have been treated with TBI versus no TBI?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
5c. Risk GHD after TBI (n=2 studies)	Shalitin 2006	91 BMT CAYA survivors	6.2 ± 3.5	Percentage RT not reported *RT details;* Pre-conditioning: -Cranial RT, n=5 (5.5%) -Neck/mediastinal RT, n=5 (5.5%) Conditioning: -TBI (12 Gy), n=14 (15.4%) -Cranial RT (7 Gy) + TBI, n=1 (1.1%) -Thoraco-abdominal RT (4-5 Gy), n=3 (3.3%)	Prevalence at last follow-up GHD: n=10 (11%) Diagnosed by provocative testing, GH peak <10 ng/mL	Odds ratio (95% CI) <u>GHD:</u> conditioning with TBI 37 (5.94-231)*	SB: low risk AB: high risk DB: unclear CF: high risk
	Davis 2015	22 BMT CAYA survivors	8.8 (1.4-19.2)	100% RT *RT details;* TBI 14.4 Gy, n=20 TBI 10 Gy, n=2 Additional CNS boost (6Gy), n=2 Additional CNS prophylactic RT (12-18 Gy), n=2	Prevalence (cross-sectional) GHD: n=18 (81.8%) Diagnosed by provocative testing (ITT), peak GH <3μg/l for adults, <7μg/l for children	Relative risk (95% CI) <u>GH AUC:</u> BMT/TBI (yes vs. no) RR not reported, p<0.001*	SB: high risk AB: low risk DB: unclear CF: high risk

GRADE assessment		
<u>Study design:</u>	+4	Observational evidence
<u>Study limitations:</u>	-1	Some limitations: Selection bias low in 1/2, high in 1/2; Attrition bias low in 1/2, high in 1/2; Detection bias unclear in 2/2; Confounding high in 2/2
<u>Consistency:</u>	0	No important inconsistency, both studies show effect of TBI
<u>Directness:</u>	0	Results are direct, population and outcomes broadly generalizable
<u>Precision:</u>	-2	Important imprecision, low number of events and broad confidence intervals
<u>Publication bias:</u>	0	Unlikely
<u>Effect size:</u>	0	No large magnitude of effect
<u>Dose-response:</u>	0	Unclear if dose-response relationship (dichotomous outcomes)

Plausible confounding	0 No plausible confounding
Quality of evidence	⊕⊖⊖⊖ VERY LOW
Conclusion:	There is an increased risk for GHD after TBI versus no TBI in childhood cancer survivors (non-CNS tumor) diagnosed before the age of 25 years. (2 studies significant effect; 113 participants; 28 events)

Abbreviations: AB, attrition bias; AUC, area under the curve; BMT, bone marrow transplantation; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; GH, growth hormone; GHD, growth hormone deficiency; GHRH, growth hormone-releasing hormone; Gy, Gray; ITT, insulin tolerance test; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; yr, year.
*Statistically significant outcome

ii. **What is the risk of TSHD in childhood cancer survivors (non-CNS tumor) who have been treated with TBI versus no TBI?**
No studies included

iii. **What is the risk of LH/FSHD in childhood cancer survivors (non-CNS tumor) who have been treated with TBI versus no TBI?**
No studies included

iv. **What is the risk of ACTHD in childhood cancer survivors (non-CNS tumor) who have been treated with TBI versus no TBI?**
No studies included

v. **What is the risk of CPP in childhood cancer survivors (non-CNS tumor) who have been treated with TBI versus no TBI?**
No studies included

d. **What is the risk of HP dysfunction in childhood cancer survivors (non-CNS tumor) treated with different dose rates?**
No studies included for all five types of HP dysfunction

e. **What is the risk of HP dysfunction in childhood cancer survivors (non-CNS tumor) treated with different types (e.g. electron, IMRT, brachytherapy, proton beam therapy) of radiotherapy?**
No studies included for all five types of HP dysfunction

Question 6. What is the risk to develop HP dysfunction in childhood cancer survivors (non-CNS tumor) who received chemotherapy (including those with a surgery in history) and is it modified by the type of chemotherapeutic agent (e.g. alkylating), administration route (intravenous or intrathecal), duration of chemotherapy? gender, age at start treatment, ethnicity, race, histology/type of cancer, genetic profile of the patient, time after diagnosis or time after exposure?

a. **What is the risk of HP dysfunction in childhood cancer survivors (non-CNS tumor) treated with both chemotherapy and radiotherapy?**
No studies included for all five types of HP dysfunction

Question 7. What is the risk to develop HP dysfunction in childhood cancer survivors (non-CNS tumor) who received chemotherapy (with or without neurosurgery but no cranial radiotherapy) and is it modified by the type of chemotherapeutic agent (e.g. alkylating), administration

route (intravenous or intrathecal), duration of chemotherapy, gender, age at start treatment, ethnicity, race, histology/type of cancer, genetic profile of the patient, time after diagnosis or time after exposure?

a. **What is the risk of HP dysfunction in childhood cancer survivors (non-CNS tumor) treated with chemotherapy, but no radiotherapy?**

No studies included for all five types of HP dysfunction

Question 8. What is the risk in brain injured childhood cancer survivors (non-CNS tumor) to develop HP dysfunction? Brain injury is defined as: increased intracranial pressure, meningitis, cerebral thrombosis, cerebral bleeding, cerebral leukemia, abscesses, drug/chemo induced encephalopathy or other cerebral inflammation (encephalitis, fungal infections, vasculitis or graft versus host diseases).

a. **What is the risk of HP dysfunction in brain injured childhood cancer survivors (non-CNS tumor)?**

No studies included for all five types of HP dysfunction

Question 9. Are there other etiological risk factors associated with the risk of HP dysfunction in childhood cancer survivors (non-CNS tumor)?

a. **What is the influence of gender on the risk of HP dysfunction in childhood cancer survivors (non-CNS tumor)?**

i. **What is the influence of gender on the risk of GHD in childhood cancer survivors (non-CNS tumor)?**
No studies included

ii. **What is the influence of gender on the risk of TSHD in childhood cancer survivors (non-CNS tumor)?**
No studies included

iii. **What is the influence of gender on the risk of LH/FSHD in childhood cancer survivors (non-CNS tumor)?**

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
9a. Risk LH/FSHD by gender (n=1 study)	Chemaitilly 2015	748 CAYA survivors (n=658 CAYA non-CNS tumor survivors)[1]	27.3 (10.8-47.7)	100% RT *RT details;* Cranial RT dose 1-14.9 Gy, n=40 15-21.9 Gy, n=208 22-29.9 Gy, n=316 30-39.9 Gy, n=31 ≥40 Gy, n=153	Prevalence at last follow-up: LH/FSHD: n=79 (10.8%) Established by a previous diagnosis or or total testosterone <200ng/dL coincided with LH<7 IU/L and FSH <9.2 IU/L in males. In amenorrheic	Odds ratio (95% CI) LH/FSHD: gender (female vs. male) 0.58 (0.3-0.97)*	SB: high risk AB: low risk DB: unclear CF: low risk

					women <40 yrs old, estradiol <17 pg/mL and FSH <11.2 IU/L		
GRADE assessment							
Study design:	+4	Observational evidence					
Study limitations:	-1	Some limitations: Selection bias high in 1/1; Attrition bias low 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 included. Large sample size, high total number of events and narrow confidence intervals					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	Unclear if dose-response relationship					
Plausible confounding	0	No plausible confounding					
Quality of evidence	⊕⊕⊖⊖ LOW						
Conclusion:	There is an increased risk for LH/FSHD in male childhood cancer survivors (non-CNS tumor) diagnosed before the age of 25 years. (1 study significant effect; 748 participants; 79 events)						

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; FSH, follicle-stimulating hormone; Gy, Gray; LH, luteinizing hormone; LH/FSHD, luteinizing hormone and follicle-stimulating hormone deficiency; RT, radiotherapy; SB, selection bias; yr, year.
*Statistically significant outcome; [1] Study comprises ≥75% CAYA non-CNS tumor survivors

iv. What is the influence of gender on the risk of ACTHD in childhood cancer survivors (non-CNS tumor)?
No studies included

v. What is the influence of gender on the risk of CPP in childhood cancer survivors (non-CNS tumor)?
No studies included

b. What is the influence of ethnicity/race on the risk of HP dysfunction in childhood cancer survivors (non-CNS tumor)?

i. What is the influence of ethnicity/race on the risk of GHD in childhood cancer survivors (non-CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
9b. Risk GHD by ethnicity/race (n=1 study)	Chemaitilly 2015	748 CAYA survivors (n=658 CAYA non-CNS tumor survivors)[1]	27.3 (10.8-47.7)	100% RT *RT details;* Cranial RT dose 1-14.9 Gy, n=40 15-21.9 Gy, n=208 22-29.9 Gy, n=316 30-39.9 Gy, n=31 ≥40 Gy, n=153	Prevalence at last follow-up: GHD: n=348 (46.5%) Established by a previous diagnosis or IGF-1 z-scores <-2	Odds ratio (95% CI) GHD: ethnicity (nonwhite vs. white) 0.66 (0.4-1.1)	SB: high risk AB: low risk DB: unclear CF: low risk
GRADE assessment							

Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias high in 1/1; Attrition bias low 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 included. Large sample size, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding	0	No plausible confounding
Quality of evidence	⨁⨁⨀⨀ LOW	
Conclusion:	There is no significant effect of ethnicity on the risk for GHD in childhood cancer survivors (non-CNS tumor) diagnosed before the age of 25 years. (1 study non-significant effect; 748 participants; 348 events)	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; GHD, growth hormone deficiency; Gy, Gray; IGF-1, insulin-like growth factor-1; RT, radiotherapy; SB, selection bias; yr, year.

[1] Study comprises ≥75% CAYA non-CNS tumor survivors

ii. What is the influence of ethnicity/race on the risk of TSHD in childhood cancer survivors (non-CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
9b. Risk TSHD by ethnicity/race (n=1 study)	Chemaitilly 2015	748 CAYA survivors (n=658 CAYA non-CNS tumor survivors)[1]	27.3 (10.8-47.7)	100% RT *RT details;* Cranial RT dose 1-14.9 Gy, n=40 15-21.9 Gy, n=208 22-29.9 Gy, n=316 30-39.9 Gy, n=31 ≥40 Gy, n=153	Prevalence at last follow-up: TSHD: n=56 (7.5%) Established by a previous diagnosis or FT4 <0.9 ng/dL with TSH<4 mIU/L	Odds ratio (95% CI) TSHD: ethnicity (nonwhite vs. white) 0.16 (0.04-0.7)*	SB: high risk AB: low risk DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias high in 1/1; Attrition bias low 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 included. Large sample size, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding	0	No plausible confounding
Quality of evidence	⨁⨁⨀⨀ LOW	
Conclusion:	There is an increased risk for TSHD in patients with white ethnicity versus nonwhite ethnicity in childhood cancer survivors (non-CNS tumor) diagnosed before the age of 25 years. (1 study significant effect; 748 participants; 56 events)	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; FT4, free thyroxine; RT, radiotherapy; SB, selection bias; TSH, thyroid-stimulating hormone; TSHD, thyroid-stimulating hormone deficiency; yr, year.
*Statistically significant outcome; [1] Study comprises ≥75% CAYA non-CNS tumor survivors

iii. What is the influence of ethnicity/race on the risk of LH/FSHD in childhood cancer survivors (non-CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
9b. Risk LH/FSHD by ethnicity/race (n=1 study)	Chemaitilly 2015	748 CAYA survivors (n=658 CAYA non-CNS tumor survivors)[1]	27.3 (10.8-47.7)	100% RT *RT details;* Cranial RT dose 1-14.9 Gy, n=40 15-21.9 Gy, n=208 22-29.9 Gy, n=316 30-39.9 Gy, n=31 ≥40 Gy, n=153	Prevalence at last follow-up: LH/FSHD: n=79 (10.8%) Established by a previous diagnosis or or total testosterone <200ng/dL coincided with LH<7 IU/L and FSH <9.2 IU/L in males. In amenorrheic women <40 yrs old, estradiol <17 pg/mL and FSH <11.2 IU/L	Odds ratio (95% CI) LH/FSHD: ethnicity (nonwhite vs. white) 0.28 (0.1-0.8)*	SB: high risk AB: low risk DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias high in 1/1; Attrition bias low 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 included. Large sample size, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊖⊖ LOW	
Conclusion:	There is an increased risk for LH/FSHD in patients with white ethnicity versus nonwhite ethnicity in childhood cancer survivors (non-CNS tumor) diagnosed before the age of 25 years. (1 study significant effect; 748 participants; 79 events)	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; FSH, follicle-stimulating hormone; Gy, Gray; LH, luteinizing hormone; LH/FSHD, luteinizing hormone and follicle-stimulating hormone deficiency; RT, radiotherapy; SB, selection bias; yr, year.
*Statistically significant outcome; [1] Study comprises ≥75% CAYA non-CNS tumor survivors

iv. What is the influence of ethnicity/race on the risk of ACTHD in childhood cancer survivors (non-CNS tumor)?

v. What is the influence of ethnicity/race on the risk of CPP in childhood cancer survivors (non-CNS tumor)?

c. What is the influence of tumor location on the risk of HP dysfunction in childhood cancer survivors (non-CNS tumor)?

No studies included for all five types of HP dysfunction

d. What is the influence of tumor histology/type on the risk of HP dysfunction in childhood cancer survivors (non-CNS tumor)?

No studies included for all five types of HP dysfunction

e. What is the influence of the genetic profile on the risk of HP dysfunction in childhood cancer survivors (non-CNS tumor)?

No studies included for all five types of HP dysfunction

f. What is the influence of the age at diagnosis/treatment on the risk of HP dysfunction in childhood cancer survivors (non-CNS tumor)?

i. What is the influence of the age at diagnosis/treatment on the risk of GHD in childhood cancer survivors (non-CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
9f. Risk GHD by age at diagnosis/treatment (n=3 studies)	Chemaitilly 2015	748 CAYA survivors (n=658 CAYA non-CNS tumor survivors)[1]	27.3 (10.8-47.7)	100% RT *RT details;* Cranial RT dose 1-14.9 Gy, n=40 15-21.9 Gy, n=208 22-29.9 Gy, n=316 30-39.9 Gy, n=31 ≥40 Gy, n=153	Prevalence at last follow-up: GHD: n=348 (46.5%) Established by a previous diagnosis or IGF-1 z-scores <-2	Odds ratio (95% CI) GHD: age at cranial radiotherapy (5-9 yrs vs. <5 yrs) 0.73 (0.5-1.0) GHD: age at cranial radiotherapy (10-14 yrs vs. <5 yrs) 0.63 (0.4-0.9)* GHD: age at cranial radiotherapy (≥15 yrs vs. <5 yrs) 0.43 (0.2-0.7)*	SB: high risk AB: low risk DB: unclear CF: low risk
	Brennan 1998	32 ALL CAYA survivors (35 controls)	Not reported	100% RT *RT details;* 18 Gy, n=11 19-25 Gy, n=21 Additional spinal RT (24 Gy) in n=4	Prevalence at last follow-up GHD: n= 9 (28.1%) GH insufficient: n=12 (37.5%) Diagnosed by provocative testing. GHD; peak GH <9 mU/L to two provocative tests, GH insufficiency; peak GH <20 mU/L and in one or both >9mU/L	Relative risk (95% CI) Peak GH: age at radiotherapy, RR not reported, p=0.41	SB: unclear AB: low risk DB: unclear CF: high risk
	Leung 2007	155 HSCT CAYA survivors	9 (3.1-15.9)	79.4% RT *RT details;*	Prevalence at last follow-up	Hazard ratio (95% CI) GHD: age at HSCT (per yr), HR	SB: low risk AB: low risk

		Dose of TBI: 14.4 Gy, n=59 8-12 Gy, n=64	GHD: n=39 (25%) Diagnosed by provocative testing; peak GH <10ng/mL	0.83 (95% CI 0.76-0.89)*	DB: unclear CF: unclear

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias high in 1/3, low in 1/3, unclear in 1/3; Attrition bias low in 3/3; Detection bias unclear in 3/3; Confounding low in 1/3, high in 1/3, unclear in 1/3
Consistency:	-1	Some inconsistency, two studies show significant effect of age at tumor diagnosis/treatment, 1 study shows non-significant effect
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Although it seems that younger ages are associated with an increased risk as compared to older ages, we are not 100% confident
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊖⊖ LOW	
Conclusion:	There is an increased risk for GHD after a younger age at tumor diagnosis/treatment versus older age in childhood cancer survivors (non-CNS tumor) diagnosed before the age of 25 years. (2 studies significant effect, 1 study non-significant effect; 935 participants; 396 events)	

Abbreviations: AB, attrition bias; ALL, acute lymphoblastic leukemia; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; GH, growth hormone; GHD, growth hormone deficiency; Gy, Gray; HSCT, hematopoietic stem cell transplantation; IGF-1, insulin-like growth factor-1; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; yr, year.
*Statistically significant outcome; [1] Study comprises ≥75% CAYA non-CNS tumor survivors

ii. What is the influence of the age at diagnosis/treatment on the risk of TSHD in childhood cancer survivors (non-CNS tumor)?
No studies included

iii. What is the influence of the age at diagnosis/treatment on the risk of LH/FSHD in childhood cancer survivors (non-CNS tumor)?
No studies included

iv. What is the influence of the age at diagnosis/treatment on the risk of ACTHD in childhood cancer survivors (non-CNS tumor)?
No studies included

v. What is the influence of the age at diagnosis/treatment on the risk of CPP in childhood cancer survivors (non-CNS tumor)?
No studies included

g. What is the influence of the age at follow-up on the risk of HP dysfunction in childhood cancer survivors (non-CNS tumor)?

i. What is the influence of the age at follow-up on the risk of GHD in childhood cancer survivors (non-CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
9g. Risk GHD by age at follow-up (n=2 studies)	Chemaitilly 2015	748 CAYA survivors (n=658 CAYA non-CNS tumor survivors)[1]	27.3 (10.8-47.7)	100% RT *RT details;* Cranial RT dose 1-14.9 Gy, n=40 15-21.9 Gy, n=208 22-29.9 Gy, n=316 30-39.9 Gy, n=31 ≥40 Gy, n=153	Prevalence at last follow-up: GHD: n=348 (46.5%) Established by a previous diagnosis or IGF-1 z-scores <-2	Odds ratio (95% CI) GHD: age at study (≥26-35 yrs vs. <26 yrs) 0.51 (0.6-13) GHD: age at study (≥36 yrs vs. <26 yrs) 0.51 (0.3-0.9)*	SB: high risk AB: low risk DB: unclear CF: low risk
	Davis 2015	22 BMT CAYA survivors	8.8 (1.4-19.2)	100% RT *RT details;* TBI 14.4 Gy, n=20 TBI 10 Gy, n=2 Additional CNS boost (6Gy), n=2 Additional CNS prophylactic RT (12-18 Gy), n=2	Prevalence (cross-sectional) GHD: n=18 (81.8%) Diagnosed by provocative testing (ITT), peak GH <3μg/l for adults, <7μg/l for children	Relative risk (95% CI) GH AUC: age at study, RR not reported, NS	SB: high risk AB: low risk DB: unclear CF: high risk

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias high 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:	-1	Some inconsistency, one study shows significant effect, one study shows non-significant effect
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Although it seems that younger age at follow-up is associated with an increased risk, we are not 100% confident
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊖⊖ LOW	
Conclusion:	There is an increased risk for GHD after a younger age at follow-up versus older age at follow-up in childhood cancer survivors (non-CNS tumor) diagnosed before the age of 25 years. (1 study significant effect, 1 study non-significant effect; 766 participants; 366 events)	

Abbreviations: AB, attrition bias; AUC, area under the curve; BMT, bone marrow transplantation; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; GH, growth hormone; GHD, growth hormone deficiency; Gy, Gray; IGF-1, insulin-like growth factor-1; ITT, insulin tolerance test; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; yr, year.
*Statistically significant outcome; [1] Study comprises ≥75% CAYA non-CNS tumor survivors

ii. What is the influence of the age at follow-up on the risk of TSHD in childhood cancer survivors (non-CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias

9g. Risk TSHD by age at follow-up (n=1 study)	Chemaitilly 2015	748 CAYA survivors (n=658 CAYA non-CNS tumor survivors)[1]	27.3 (10.8-47.7)	100% RT *RT details;* Cranial RT dose 1-14.9 Gy, n=40 15-21.9 Gy, n=208 22-29.9 Gy, n=316 30-39.9 Gy, n=31 ≥40 Gy, n=153	Prevalence at last follow-up: TSHD: n=56 (7.5%) Established by a previous diagnosis or FT4 <0.9 ng/dL with TSH<4 mIU/L	Odds ratio (95% CI) TSHD: age at study (26-35 yrs vs. <26 yrs) 0.37 (0.2-0.8)* TSHD: age at study (≥36 yrs vs. <26 yrs) 0.20 (0.1-0.6)*	SB: high risk AB: low risk DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias high in 1/1; Attrition bias low 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 included. Large sample size, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Although it seems that younger age at follow-up is associated with an increased risk, we are not 100% confident
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊖⊖ LOW	
Conclusion:	There is an increased risk for TSHD after a younger age at follow-up versus older age at follow-up in childhood cancer survivors (non-CNS tumor) diagnosed before the age of 25 years. (1 study significant effect; 748 participants; 56 events)	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; FT4, free thyroxine; RT, radiotherapy; SB, selection bias; TSH, thyroid-stimulating hormone; TSHD, thyroid-stimulating hormone deficiency; yr, year.
*Statistically significant outcome; [1] Study comprises ≥75% CAYA non-CNS tumor survivors

iii. What is the influence of the age at follow-up on the risk of LH/FSHD in childhood cancer survivors (non-CNS tumor)?
No studies included

iv. What is the influence of the age at follow-up on the risk of ACTHD in childhood cancer survivors (non-CNS tumor)?
No studies included

v. What is the influence of the age at follow-up on the risk of CPP in childhood cancer survivors (non-CNS tumor)?
No studies included

h. What is the influence of the time since diagnosis/treatment on the risk of HP dysfunction in childhood cancer survivors (non-CNS tumor)?

i. What is the influence of the time since diagnosis/treatment on the risk of GHD in childhood cancer survivors (non-CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
9h. Risk GHD by time since diagnosis/treatment (n=2 studies)	Brennan 1998	32 ALL CAYA survivors (35 controls)	Not reported	100% RT *RT details;* 18 Gy, n=11 19-25 Gy, n=21 Additional spinal RT (24 Gy) in n=4	Prevalence at last follow-up GHD: n= 9 (28.1%) GH insufficient: n=12 (37.5%) Diagnosed by provocative testing. GHD; peak GH <9 mU/L to two provocative tests, GH insufficiency; peak GH <20 mU/L and in one or both >9mU/L	Relative risk (95% CI) Peak GH: time since radiotherapy, RR not reported, p=<0.01*	SB: unclear AB: low risk DB: unclear CF: high risk
	Davis 2015	22 BMT CAYA survivors	8.8 (1.4-19.2)	100% RT *RT details;* TBI 14.4 Gy, n=20 TBI 10 Gy, n=2 Additional CNS boost (6Gy), n=2 Additional CNS prophylactic RT (12-18 Gy), n=2	Prevalence (cross-sectional) GHD: n=18 (81.8%) Diagnosed by provocative testing (ITT), peak GH <3μg/l for adults, <7μg/l for children	Relative risk (95% CI) GH AUC: time since BMT, RR not reported, NS	SB: high risk AB: low risk DB: unclear CF: high risk

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias high in 1/2, unclear in 1/2; Attrition bias low in 2/2; Detection bias unclear in 2/2; Confounding high in 2/2
Consistency:	-1	Some inconsistency, one study shows significant effect, one study shows non-significant effect
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, only two studies included with small sample sizes and low number of events
Publication bias:	0	Unlikely
Effect size:	0	Magnitude of effect cannot be determined
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊖⊖⊖ VERY LOW	
Conclusion:	There is an increased risk for GHD after longer follow-up duration versus shorter follow-up duration in childhood cancer survivors (non-CNS tumor) diagnosed before the age of 25 years. (1 study significant effect, 1 study non-significant effect; 54 participants; 27 events)	

Abbreviations: AB, attrition bias; ALL, acute lymphoblastic leukemia; AUC, area under the curve; BMT, bone marrow transplantation; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; GH, growth hormone; GHD, growth hormone deficiency; Gy, Gray; ITT, insulin tolerance test; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; yr, year.
*Statistically significant outcome

ii. What is the influence of the time since diagnosis/treatment on the risk of TSHD in childhood cancer survivors (non-CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
9h. Risk TSHD by time since diagnosis/treatment (n=1 study)	Chemaitilly 2015	748 CAYA survivors (n=658 CAYA non-CNS tumor survivors)[1]	27.3 (10.8-47.7)	100% RT *RT details;* Cranial RT dose 1-14.9 Gy, n=40 15-21.9 Gy, n=208 22-29.9 Gy, n=316 30-39.9 Gy, n=31 ≥40 Gy, n=153	Prevalence at last follow-up: TSHD: n=56 (7.5%) Established by a previous diagnosis or FT4 <0.9 ng/dL with TSH<4 mIU/L	Odds ratio (95% CI) TSHD: time since cranial radiotherapy (15-19 yrs vs. <15 yrs) 0.70 (0.2-2.0) TSHD: time since cranial radiotherapy (20-24 yrs vs. <15 yrs) 0.94 (0.3-2.7) TSHD: time since cranial radiotherapy (≥25 yrs vs. <15 yrs) 0.88 (0.3-2.9)	SB: high risk AB: low risk DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias high in 1/1; Attrition bias low 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 included. Large sample size, high total 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	⊕⊕⊖⊖ LOW	
Conclusion:	There is no significant effect of longer follow-up duration versus shorter follow-up duration on the risk for TSHD in childhood cancer survivors (non-CNS tumor) diagnosed before the age of 25 years. (1 study non-significant effect; 748 participants; 56 events)	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; FT4, free thyroxine; RT, radiotherapy; SB, selection bias; TSH, thyroid-stimulating hormone; TSHD, thyroid-stimulating hormone deficiency; yr, year.

[1] Study comprises ≥75% CAYA non-CNS tumor survivors

iii. What is the influence of the time since diagnosis/treatment on the risk of LH/FSHD in childhood cancer survivors (non-CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
9h. Risk LH/FSHD by time since diagnosis/treatment (n=1 study)	Chemaitilly 2015	748 CAYA survivors (n=658 CAYA non-CNS tumor survivors)[1]	27.3 (10.8-47.7)	100% RT *RT details;* Cranial RT dose 1-14.9 Gy, n=40 15-21.9 Gy, n=208 22-29.9 Gy, n=316	Prevalence at last follow-up: LH/FSHD: n=79 (10.8%) Established by a previous diagnosis or or total testosterone <200ng/dL	Odds ratio (95% CI) LH/FSHD: time since cranial radiotherapy (15-19 yrs vs. <15 yrs) 0.38 (0.1-1.1) LH/FSHD: time since cranial radiotherapy (20-24 yrs vs. <15	SB: high risk AB: low risk DB: unclear CF: low risk

			30-39.9 Gy, n=31 ≥40 Gy, n=153	coincided with LH<7 IU/L and FSH <9.2 IU/L in males. In amenorrheic women <40yrs old, estradiol <17 pg/mL and FSH <11.2 IU/L	yrs) 0.77 (0.3-2.0) LH/FSHD: time since cranial radiotherapy (≥25 yrs vs. <15 yrs) 0.67 (0.3-1.7)	
GRADE assessment						
Study design:	+4	Observational evidence				
Study limitations:	-1	Some limitations: Selection bias high in 1/1; Attrition bias low 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 included. Large sample size, high total 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	⊕⊕⊖⊖ LOW					
Conclusion:	There is no significant effect of longer follow-up duration versus shorter follow-up duration for LH/FSHD in childhood cancer survivors (non-CNS tumor) diagnosed before the age of 25 years. (1 study non-significant effect, 748 participants; 79 events)					

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; FSH, follicle-stimulating hormone; Gy, Gray; LH, luteinizing hormone; LH/FSHD, luteinizing hormone and follicle-stimulating hormone deficiency; RT, radiotherapy; SB, selection bias; yr, year.

[1] Study comprises ≥75% CAYA non-CNS tumor survivors

iv. What is the influence of the time since diagnosis/treatment on the risk of ACTHD in childhood cancer survivors (non-CNS tumor)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
9h. Risk ACTHD by time since diagnosis/treatment (n=1 study)	Chemaitilly 2015	748 CAYA survivors (n=658 CAYA non-CNS tumor survivors)[1]	27.3 (10.8-47.7)	100% RT *RT details;* Cranial RT dose 1-14.9 Gy, n=40 15-21.9 Gy, n=208 22-29.9 Gy, n=316 30-39.9 Gy, n=31 ≥40 Gy, n=153	Prevalence at last follow-up: ACTHD: n=30 (4.0%) Established by a previous diagnosis or 08.00 AM cortisol <5µg/dL	Odds ratio (95% CI) ACTHD: time since cranial radiotherapy (15-19 yrs vs. <15 yrs) 0.53 (0.2-1.5) ACTHD: time since cranial radiotherapy (20-24 yrs vs. <15 yrs) 0.41 (0.1-1.2) ACTHD: time since cranial radiotherapy (≥25 yrs vs. <15 yrs) 0.11 (0.03-0.4)*	SB: high risk AB: low risk DB: unclear CF: low risk
GRADE assessment							
Study design:	+4	Observational evidence					
Study limitations:	-1	Some limitations: Selection bias high in 1/1; Attrition bias low 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 included. Large sample size, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Although it seems that longer time since cranial radiotherapy is associated with an increased risk, we are not 100% confident
Plausible confounding	0	No plausible confounding
Quality of evidence	⨁⨁⨀⨀ LOW	
Conclusion:	There is an increased risk for ACTHD after shorter follow-up duration versus longer follow-up duration in childhood cancer survivors (non-CNS tumor) diagnosed before the age of 25 years. (1 study significant effect; 748 participants; 30 events)	

Abbreviations: AB, attrition bias; ACTHD, adrenocorticotropic hormone deficiency; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; Gy, Gray; RT, radiotherapy; SB, selection bias; yr, year.
*Statistically significant outcome; [1] Study compris es ≥75% CAYA non-CNS tumor survivors

v. What is the influence of the time since diagnosis/treatment on the risk of CPP in childhood cancer survivors (non-CNS tumor)?
No studies included

WG2; When should surveillance be initiated? At what frequency and for how long should surveillance be performed?

Question 1. When should screening for HP dysfunction in childhood cancer survivors (CNS tumor and non-CNS tumor) be initiated?

a. What is the latency time to develop HP dysfunction in childhood cancer survivors (CNS tumor and non-CNS tumor) treated with radiotherapy?

i. What is the latency time to develop GHD in childhood cancer survivors (CNS tumor and non-CNS tumor) treated with radiotherapy?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Latency time	Risk of bias
1a. Latency time GHD after radiotherapy (n=11 studies)	Brauner 1990	21 CAYA CNS tumor survivors	5.1 (1-14.3)	100% RT *RT details;* Cranial RT dose 45-55 Gy	Prevalence at last follow-up: GHD: n=21 (100%) Diagnosed by provocative testing (arginine-insulin); peak GH <8µg/L	Latency time from RT: GHD: mean 1.5 ± 0.2 yrs (range 1-2.3)	SB: unclear AB: high risk DB: unclear
	Clayton 1991	82 CAYA CNS and non-CNS tumor survivors	4.3 (0.2-18.9)	100% RT *RT details;* Cranial RT, n=24	Incidence >5 yrs after RT GHD: incidence 74% Diagnosed by provocative	Latency time from RT: 55% became GHD within one year	SB: unclear AB: high risk DB: unclear

				Craniospinal RT, n=58 RT dose to HP region Range 27-47.5 Gy <30 Gy, n=46 (56.1%) ≥30 Gy, n=36 (43.9%)	testing (ITT); peak GH ≤15		
	Clement 2016	718 CAYA CNS tumor survivors	6.6 (2.0-13.4)	35.9% RT *RT details;* Cranial RT, n=144, RT dose, median 54.0 Gy (range 12.5-60.0) Craniospinal RT, n=114, RT dose, median 24.0 Gy (range 18.0-39.7)	Prevalence at last follow-up GHD: n=90 (12.5%) Diagnosed by provocative testing, GH peak <20-30 mU/L or diagnosis by treating physician	Latency time from tumor diagnosis GHD: median 2.5 yrs (range 0.05-8.4)	SB: unclear AB: high risk DB: unclear
	Clement 2016	80 CAYA head and neck rhabdomyosarcoma survivors	11.8 (2.4-22.9)	92.5% RT *RT details;* AMORE, n=25 EBRT, n=38 Proton, n=2 Initial local RT dose median 45.0 Gy (range 36.0-57.8)	Prevalence at last follow-up: GHD: n=22 (28%) Diagnosed by provocative testing; GH peak cut-off value unknown	Latency time from cancer diagnosis: GHD: median 3.2 yrs (range 2.0-11.1)	SB: high risk AB: low risk DB: unclear
	Kanev 1991	65 CAYA CNS tumor survivors	Not reported	100% RT *RT details;* Not reported (only reported for original cohort)	Prevalence at last follow-up: GHD: n=26 (40%) Diagnosed by provocative testing; peak GH <10ng/mL	Latency time from cancer diagnosis: GHD: mean 26 months in boys, 17 months in girls (range 6-42 months)	SB: unclear AB: high risk DB: unclear
	Laughton 2008	88 CAYA CNS tumor survivors	Median 4.7 to 5.1 (2.1-9.6) depending on risk category	100% RT *RT details;* Average-risk patients (n=53): -Hypothalamus dose: median 38.6 Gy -Craniospinal dose: 23.4 Gy High-risk patients (n=35) hypothalamus: -Hypothalamus dose: median 50.5 Gy -Craniospinal dose: 39.6 Gy	Prevalence at last follow-up: GHD (assessed in n=70): n=66 (94%) Diagnosed by provocative testing; peak GH <10 µg/ml	Latency time from RT: GHD: median 1.8 yrs (range 0.9-4.3)	SB: low risk AB: low risk DB: unclear
	Leung 2007	155 CAYA survivors after HCT	9 (3.1-15.9)	79.4% RT *RT details;* Dose of TBI: 14.4 Gy, n=59 8-12 Gy, n=64	Prevalence at last follow-up GHD, n=39 (25%) Diagnosed by provocative testing; peak GH <10ng/mL	Latency time from HCT: GHD: median 36 months (25^{th} percentile: 24 months and 75^{th} percentile 58 months)	SB: low risk AB: low risk DB: unclear
	Merchant 2011	192 CAYA CNS tumor survivors	60 months	100% RT *RT details;* All received conformal RT or intensity-modulated RT	Not reported GHD diagnosed by provocative testing (arginine/L-DOPA), GH	Average patient would develop GHD with the following combinations of time after cranial RT and dose	SB: unclear AB: unclear DB: unclear

				Ependymoma: Cranial RT dose 59.4 Gy, n=73 Cranial RT dose 54.0 Gy, n=15 Low grade glioma: Cranial RT dose 54 Gy, n=unknown	peak <7 ng/mL	to hypothalamus: 12 months and >60Gy; 36 months and 25-30Gy; 60 months and 15-20Gy.	
	Sanders 2005	90 CAYA survivors after HCT	11.0 (2.7-23)	100% RT *RT details;* TBI, n=90 Preceding CNS RT (9-24 Gy), n=32 TBI regimen 12 Gy, n=17 TBI regimen 14-15.75Gy, n=73 All received Cobalt-60 RT	Prevalence at last follow-up GHD: 90 of 107 patients tested (of original cohort) (84%) Diagnosed by having both abnormal spontaneous GH production and GH peak <8.6 ng/dL after GH stimulation test	Latency time from HCT: GHD: median 1.3 years (range, 0.8-9.5)	SB: high risk AB: low risk DB: unclear
	Shalitin 2011	114 CAYA CNS tumor survivors	12.8 ± 6.25 (3.7-28.7)	56.1% RT *RT details;* Cranial RT, n=55, RT dose 35-56 Gy Spinal RT, n=27, RT dose 30-54 Gy	Prevalence at last follow-up GHD: n=40 (35%) Diagnosed by provocative testing, GH peak <10 ng/mL	Latency time from cancer diagnosis: GHD: mean 4.43 ± 0.48 Latency time from chemotherapy GHD: mean 4.16 ± 0.58 Latency time from radiotherapy GHD: mean 3.96 ± 0.55	SB: low risk AB: low risk DB: unclear
	Uday 2015	35 CAYA medulloblastoma survivors	18 (10-28)	100% RT *RT details;* Craniospinal RT: n=32, median dose 35 Gy and posterior fossa boost with median dose 55 Gy (range 54-55.8) Gy One patient received 35 Gy Craniospinal RT + 12 Gy posterior fossa boost One patient received 35 Gy Craniospinal RT + 28 Gy posterior fossa boost	Prevalence at last follow-up -Complete GHD: 28/35 (80%) -Partial GHD: 6/35 (17%) Complete GHD: peak GH level <3 µg/L in adults, and <7 µg/L in children Partial GHD: peak GH level between 3 and 7 µg/L in adults	Latency time from end of treatment: GHD: median 1.7 yrs (range 0.7-15)	SB: high risk AB: low risk DB: unclear

GRADE assessment		
Study design:	+4	Observational evidence, partially for prognostic and diagnostic questions
Study limitations:	-1	Some limitations: Selection bias low in 3/11, high in 3/11, unclear in 5/11; Attrition bias low in 6/11, high in 4/11, unclear in 1/11; Detection bias unclear in 11/11
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
Quality of evidence	⊕⊕⊕⊖ MODERATE	
Conclusion:	The *overall* average latency time of GHD in childhood cancer survivors (CNS tumor and non-CNS tumor) diagnosed before the age of 25 years ranges from <1 to 4.4 years ranging from minimal 0.05 years to at least 15 years. The average latency time of GHD *after tumor diagnosis* in childhood cancer survivors (CNS tumor and non-CNS tumor) diagnosed before the age of 25 years ranges from 1.4 to 4.4 years ranging from minimal 0.05 to at least 11.1 years. The average latency time of GHD *after start of RT* in childhood cancer survivors (CNS tumor and non-CNS tumor) diagnosed before the age of 25 years ranges from <1 to 3.96 years ranging from minimal 0.9 to at least 4.3 years. (11 studies; 1640 participants; 422 events (in 9/11 studies), unknown number of events (in 2/11))	

Abbreviations: AB, attrition bias; AMORE, Ablative surgery, Mould brachytherapy and surgical Reconstruction; CAYA, childhood, adult and young adult; CI, confidence interval; CNS, central nervous system; DB, detection bias; EBRT: external beam (conventional) radiotherapy; GH, growth hormone; GHD, growth hormone deficiency; Gy, Gray; HCT, hematopoietic cell transplantation; HP, hypothalamic-pituitary; ITT, insulin tolerance test; n.a., not applicable; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; yr, year.

ii. What is the latency time to develop TSHD in childhood cancer survivors (CNS tumor and non-CNS tumor) treated with radiotherapy?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Latency time	Risk of bias
1a. Latency time TSHD after radiotherapy (n=4 studies)	Clement 2016	718 CAYA CNS tumor survivors	6.6 (2.0-13.4)	35.9% RT *RT details;* Cranial RT, n=144, RT dose, median 54.0 Gy (range 12.5-60.0) Craniospinal RT, n=114, RT dose, median 24.0 Gy (range 18.0-39.7)	Prevalence at last follow-up TSHD: n=66 (9.1%) Diagnosed by low FT4 concentrations with low, normal or mildly raised TSH	Latency time from tumor diagnosis TSHD: median 2.8 yrs (range 0.02-10.3)	SB: unclear AB: high risk DB: unclear
	Clement 2016	80 CAYA head and neck rhabdomyosarcoma survivors	11.8 (2.4-22.9)	92.5% RT *RT details;* AMORE, n=25 EBRT, n=38 Proton, n=2 Initial local RT dose median 45.0 Gy (range 36.0-57.8)	Prevalence at last follow-up: TSHD: n=7 (9%) Diagnosed by a FT4 below the reference range, an inadequate low, normal or mildly raised TSH level.	Latency time from cancer diagnosis: TSHD: median 4.5 yrs (range 0.3-11.9)	SB: high risk AB: low risk DB: unclear
	Laughton 2008	88 CAYA CNS tumor survivors	Median 4.7 to 5.1 (2.1-9.6) depending on risk category	100% RT *RT details;* Average-risk patients (n=53): -Hypothalamus dose: median 38.6 Gy -Craniospinal dose: 23.4 Gy High-risk patients (n=35)	Prevalence at last follow-up: TSHD (assessed in n=87): n=9 (10%) Diagnosed by a FT4 below the normal range, with a normal or low TSH level.	Latency time from RT: TSHD: median 1.8 yrs (range 1.1-3.7)	SB: low risk AB: low risk DB: unclear

				hypothalamus: -Hypothalamus dose: median 50.5 Gy -Craniospinal dose: 39.6 Gy			
	Ramanauskienė 2014	51 CAYA CNS tumor survivors	21 months (0.25-10.6 yrs)	56.9% RT *RT details;* Cranial RT, n=13 (25.5%) Craniospinal RT, n=16 (31.4%) Mean cumulative dose, 54.2 Gy (range 45.0–60.0)	Prevalence at last follow-up TSHD: n=unknown, 25.9% Diagnosed by a low level of FT4, with a low or normal TSH	Latency time from end of treatment: TSHD: mean 61.6 months (95% CI 44.7-77.4)	SB: high risk AB: high risk DB: unclear

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias low in 1/4, high in 2/4, unclear in 1/4; Attrition bias low in 2/4, high in 2/4; Detection bias unclear in 4/4
Consistency:	0	No important inconsistency, although the latency times vary among the studies
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, four studies included, but three studies had small sample sizes and low number of events
Publication bias:	0	Unlikely
Quality of evidence	⊕⊕⊖⊖ LOW	
Conclusion:	The *overall* average latency time of TSHD in childhood cancer survivors (CNS tumor and non-CNS tumor) diagnosed before the age of 25 years ranges from 1.8 to 5.1 years ranging from minimal 0.02 years to at least 11.9 years. The average latency time of TSHD *after tumor diagnosis* in childhood cancer survivors (CNS tumor and non-CNS tumor) diagnosed before the age of 25 years ranges from 2.8 to 4.5 years ranging from minimal 0.02 to at least 11.9 years. (4 studies; 937 participants; 82 events (in 3/4 studies), unknown number of events (in 1/4))		

Abbreviations: AB, attrition bias; AMORE, Ablative surgery, Mould brachytherapy and surgical Reconstruction; CAYA, childhood, adult and young adult; CI, confidence interval; CNS, central nervous system; DB, detection bias; EBRT: external beam (conventional) radiotherapy; Gy, Gray; FT4, free thyroxine; n.a., not applicable; RT, radiotherapy; SB, selection bias; TSH, thyroid-stimulating hormone; TSHD, thyroid-stimulating hormone deficiency; yr, year.

iii. What is the latency time to develop LH/FSHD in childhood cancer survivors (CNS tumor and non-CNS tumor) treated with radiotherapy?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Latency time	Risk of bias
1a. Latency time LH/FSHD after radiotherapy (n=2 studies)	Clement 2016	718 CAYA CNS tumor survivors	6.6 (2.0-13.4)	35.9% RT *RT details;* Cranial RT, n=144, RT dose, median 54.0 Gy (range 12.5-60.0) Craniospinal RT, n=114, RT dose, median 24.0 Gy (range 18.0-39.7)	Prevalence at last follow-up LH/FSHD: n=20 (4.2% of evaluable patients) Diagnosed by low LH and/or FSH in the absence of pubertal development or use of estrogens or testosterone for diagnosis LH/FSHD	Latency time from tumor diagnosis LH/FSHD: median 4.5 yrs (range 0.2-9.5)	SB: unclear AB: high risk DB: unclear

	Clement 2016	80 CAYA head and neck rhabdomyosarcoma survivors	11.8 (2.4-22.9)	92.5% RT *RT details;* AMORE, n=25 EBRT, n=38 Proton, n=2 Initial local RT dose median 45.0 Gy (range 36.0-57.8)	Prevalence at last follow-up: LH/FSHD: n=3 (4%) Diagnosed by low FSH/LH concentrations in the absence of pubertal development (girls > 12 years B1, boys > 13 years testes volume < 4mL) and decreased sex hormone levels.	Latency time from cancer diagnosis: LH/FSHD: 10.2 yrs (range 5.5-11.6)	SB: high risk AB: low risk DB: unclear

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias high in 1/2, unclear in 1/2; Attrition bias low in 1/2, high in 1/2; Detection bias unclear in 2/2
Consistency:	0	No important inconsistency, although the latency times vary among the studies
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, only two studies included and low number of events
Publication bias:	0	Unlikely
Quality of evidence	⊕⊖⊖⊖ VERY LOW	
Conclusion:	The average latency time of LH/FSHD *after tumor diagnosis* in childhood cancer survivors (CNS tumor and non-CNS tumor) diagnosed before the age of 25 years ranges from 4.5 to 10.2 years, ranging from minimal 0.2 to at least 11.6 years. (2 studies; 798 participants; 23 events)	

Abbreviations: AB, attrition bias; AMORE, Ablative surgery, Mould brachytherapy and surgical Reconstruction; CAYA, childhood, adult and young adult; CI, confidence interval; CNS, central nervous system; DB, detection bias; EBRT: external beam (conventional) radiotherapy; FSH, follicle-stimulating hormone, Gy, Gray; LH, luteinizing hormone; LH/FSHD, luteinizing hormone and follicle-stimulating hormone deficiency; n.a., not applicable; RT, radiotherapy; SB, selection bias; yr, year.

iv. What is the latency time to develop ACTHD in childhood cancer survivors (CNS tumor and non-CNS tumor) treated with radiotherapy?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Latency time	Risk of bias
1a. Latency time ACTHD after radiotherapy (n=5 studies)	Clement 2016	718 CAYA CNS tumor survivors	6.6 (2.0-13.4)	35.9% RT *RT details;* Cranial RT, n=144, RT dose, median 54.0 Gy (range 12.5-60.0) Craniospinal RT, n=114, RT dose, median 24.0 Gy (range 18.0-39.7)	Prevalence at last follow-up ACTHD: n=31 (4.3%) Diagnosed by use of hydrocortisone maintenance or substitution under suspicion of ACTHD	Latency time from tumor diagnosis ACTHD: median 2.5 yrs (range 0.01-7.0)	SB: unclear AB: high risk DB: unclear

	Clement 2016	80 CAYA head and neck rhabdomyosarcoma survivors	11.8 (2.4-22.9)	92.5% RT *RT details;* AMORE, n=25 EBRT, n=38 Proton, n=2 Initial local RT dose median 45.0 Gy (range 36.0-57.8)	Prevalence at last follow-up: ACTHD: n=3 (4%) Diagnosed by peak cortisol <550nmol/L in response ACTH stimulation test or peak 11-deoxycortisol <200nmol/L after Metyrapone or use of hydrocortisone at follow-up	Latency time from cancer diagnosis: ACTHD: median 6.6 yrs (range 2.5-8.7)	SB: high risk AB: low risk DB: unclear
	Ramanauskienė 2014	51 CAYA CNS tumor survivors	21 months (0.25-10.6 yrs)	56.9% RT *RT details;* Cranial RT, n=13 (25.5%) Craniospinal RT, n=16 (31.4%) Mean cumulative dose, 54.2 Gy (range 45.0–60.0)	Prevalence at last follow-up ACTHD: n=1 (4.2%) Diagnosed by a morning (<10.00 AM) serum cortisol <138nmol/L	Latency time from end of treatment ACTHD: 83.4 months (95% CI 7.1-95.5)	SB: high risk AB: high risk DB: unclear
	Shalitin 2011	114 CAYA CNS tumor survivors	12.8 ± 6.25 yrs (3.7-28.7)	56.1% RT *RT details;* Cranial RT, n=55, RT dose 35-56 Gy Spinal RT, n=27, RT dose 30-54 Gy	Prevalence at last follow-up ACTHD: n=9 (7.9%) Diagnosed by peak cortisol <540 nmol/L after Synacthen test (250 µg)	Latency time from diagnosis ACTHD: mean 3.94 ± 2.44 Latency time from chemotherapy ACTHD: mean 5.05 ± 2.91 Latency time from RT ACTHD: mean 4.78 ± 3.00	SB: low risk AB: low risk DB: unclear
	Uday 2015	35 CAYA medulloblastoma survivors	18 (10-28)	100% RT *RT details;* Craniospinal RT: n=32, median dose 35 Gy and posterior fossa boost with median dose 55 Gy (range 54-55.8) Gy One patient received 35 Gy Craniospinal RT + 12 Gy posterior fossa boost One patient received 35 Gy Craniospinal RT + 28 Gy posterior fossa boost	Prevalence at last follow-up -Complete ACTHD: 13/35 (37%) -Partial ACTHD: 3 (8.5%) Complete ACTHD: peak cortisol 400 nmol/L after glucagon or ITT Partial ACTHD: peak cortisol between 400 and 450 nmol/L after glucagon or between 400 and 550 nmol/L after ITT	Latency time from end of treatment: ACTHD: median 2.9 yrs (range 9 months-7.5)	SB: high risk AB: low risk DB: unclear

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias low in 1/5, high in 3/5, unclear in 1/5; Attrition bias low in 3/5, high in 2/5; Detection bias unclear in 5/5
Consistency:	0	No important inconsistency, although the latency times vary among the studies
Directness:	0	Results are direct, population and outcomes broadly generalizable

Precision:	-1	Some imprecision, low number of events
Publication bias:	0	Unlikely
Quality of evidence	⊕⊕⊖⊖ LOW	
Conclusion:	The *overall* average latency time of ACTHD in childhood cancer survivors (CNS tumor and non-CNS tumor) diagnosed before the age of 25 years ranges from 2.5 to 7.0 years, ranging from minimal 0.01 to at least 8.7 years. The average latency time of ACTHD *after tumor diagnosis* in childhood cancer survivors (CNS tumor and non-CNS tumor) diagnosed before the age of 25 years ranges from 2.5 to 6.6 years, ranging from minimal 0.01 to at least 8.7 years. The average latency time of ACTHD *after the end of treatment* in childhood cancer survivors (CNS tumor and non-CNS tumor) diagnosed before the age of 25 years ranges from 2.9 to 7.0 years, ranging from minimal 0.75 to at least 7.5 years. (5 studies; 998 participants; 57 events)	

Abbreviations: AB, attrition bias; ACTH, adrenocorticotropic hormone; ACTHD, adrenocorticotropic hormone deficiency; AMORE, Ablative surgery, Mould brachytherapy and surgical Reconstruction; CAYA, childhood, adult and young adult; CI, confidence interval; CNS, central nervous system; DB, detection bias; EBRT: external beam (conventional) radiotherapy; Gy, Gray; ITT, insulin tolerance test; RT, radiotherapy; SB, selection bias; yr, year.

v. What is the latency time to develop CPP in childhood cancer survivors (CNS tumor and non-CNS tumor) treated with radiotherapy?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Latency time	Risk of bias
1a. Latency time CPP after radiotherapy (n=2 studies)	Clement 2016	718 CAYA CNS tumor survivors	6.6 (2.0-13.4)	35.9% RT *RT details;* Cranial RT, n=144, RT dose, median 54.0 Gy (range 12.5-60.0) Craniospinal RT, n=114, RT dose, median 24.0 Gy (range 18.0-39.7)	Prevalence at last follow-up CPP: n=48 (12.2% of evaluable patients) Onset of puberty diagnosed by Tanner B2 in girls <8 years and testes >4mL in boys >9 years.	Latency time from tumor diagnosis CPP: median 3.1 yrs (range 0.1-8.8)	SB: unclear AB: high risk DB: unclear
	Clement 2016	80 CAYA head and neck rhabdomyosarcoma survivors	11.8 (2.4-22.9)	92.5% RT *RT details;* AMORE, n=25 EBRT, n=38 Proton, n=2 Initial local RT dose median 45.0 Gy (range 36.0-57.8)	Prevalence at last follow-up: CPP: n=3 (4%) Diagnosed by pubertal development in girls < 8 years Tanner stage B2, boys < 9 years testes volume > 4 ml) in combination with a peak LH concentration of > 5 mU/L in response to GnRH stimulation test	Latency time from cancer diagnosis: CPP: 3.8 yrs (range 2.3-3.9)	SB: high risk AB: low risk DB: unclear
GRADE assessment							
Study design:	+4	Observational evidence					
Study limitations:	-1	Some limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1;					
Consistency:	0	N/A (1 study)					

Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, two studies included, but one study had small sample size and low number of events
Publication bias:	0	Unlikely
Quality of evidence	⊕⊕⊖⊖ LOW	
Conclusion:	The average latency time of CPP *after tumor diagnosis* in childhood cancer survivors (CNS tumor and non-CNS tumor) diagnosed before the age of 25 years ranges from 3.1 to 3.8 years, ranging from minimal 0.1 to at least 8.8 years. (2 studies; 798 participants; 51 events)	

Abbreviations: AB, attrition bias; AMORE, Ablative surgery, Mould brachytherapy and surgical Reconstruction; CAYA, childhood, adult and young adult; CI, confidence interval; CNS, central nervous system; CPP, central precocious puberty; DB, detection bias; EBRT: external beam (conventional) radiotherapy; Gy, Gray; GnRH, Gonadotropin-releasing hormone; RT, radiotherapy; SB, selection bias; yr, year.

b. Are there any modifying factors (e.g. steroids, surgery) that alter the latency time to develop HP dysfunction in childhood cancer survivors (CNS tumor and non-CNS tumor) treated with radiotherapy?

i. Are there any modifying factors that alter the latency time to develop GHD in childhood cancer survivors (CNS tumor and non-CNS tumor) treated with radiotherapy?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Latency time	Risk of bias
1b. Modifying factors for latency time of GHD after radiotherapy (n=2 studies)	Clayton 1991	82 CAYA CNS and non-CNS tumor survivors	4.3 (0.2-18.9)	100% RT *RT details;* Cranial RT, n=24 Craniospinal RT, n=58 RT dose to HP region Range 27-47.5 Gy <30 Gy, n=46 (56.1%) ≥30 Gy, n=36 (43.9%)	Incidence 74% of all tests Diagnosed by provocative testing (ITT); peak GH ≤15	-GHD developed more rapidly in those who received the higher RT dose, within the first 5 yrs after RT (≥30 Gy vs <30Gy, p<0.01)	SB: unclear AB: high risk DB: unclear
	Merchant 2011	192 CAYA CNS tumor survivors	60 months	100% RT *RT details;* All received conformal RT or intensity-modulated RT Ependymoma: Cranial RT dose 59.4 Gy, n=73 Cranial RT dose 54.0 Gy, n=15 Low grade glioma: Cranial RT dose 54 Gy, n=unknown	Not reported GHD diagnosed by provocative testing (arginine/L-DOPA), GH peak <7 ng/mL	Average patient would develop GHD with the following combinations of time after cranial RT and dose to hypothalamus: 12 months and >60Gy 36 months and 25-30Gy 60 months and 15-20Gy	SB: unclear AB: unclear DB: unclear
GRADE assessment							

Study design:	+4	Observational evidence
Study limitations:	-2	Serious limitations: Selection bias unclear in 2/2; Attrition bias high in 1/2, unclear in 1/2; Detection bias unclear in 2/2; Confounding high in 2/2
Consistency:	0	No important inconsistency, both studies show effect of cranial radiotherapy dose
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, two large studies included. Number of events unknown, but high number of participants
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Dose response relationship as higher doses are associated with a shorter latency time as compared to lower doses
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊖⊖ LOW	
Conclusion:	The latency time of GHD is shorter after increasing doses of cranial radiotherapy in childhood cancer survivors (CNS tumor and non-CNS tumor) diagnosed before the age of 25 years. (2 studies significant effect; 274 participants; unknown number of events (in 2/2))	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; GH, growth hormone; GHD, growth hormone deficiency; Gy, Gray; HP, hypothalamic-pituitary; ITT, insulin tolerance test; RT, radiotherapy; SB, selection bias; yr, year.

ii. **Are there any modifying factors that alter the latency time to develop TSHD in childhood cancer survivors (CNS tumor and non-CNS tumor) treated with radiotherapy?**
No studies included

iii. **Are there any modifying factors that alter the latency time to develop LH/FSHD in childhood cancer survivors (CNS tumor and non-CNS tumor) treated with radiotherapy?**
No studies included

iv. **Are there any modifying factors that alter the latency time to develop ACTHD in childhood cancer survivors (CNS tumor and non-CNS tumor) treated with radiotherapy?**
No studies included

v. **Are there any modifying factors that alter the latency time to develop CPP in childhood cancer survivors (CNS tumor and non-CNS tumor) treated with radiotherapy?**
No studies included

c. **What is the latency time to develop HP dysfunction in childhood cancer survivors (non-CNS tumor) who had brain injuries other than the malignancy (e.g. hydrocephalus or infection) and are there any modifiers?**
No studies included for all five types of HP dysfunction

d. **What is the order of occurrence in which HP dysfunction occurs in childhood cancer survivors (CNS tumor and non-CNS tumor) who have been treated with potentially high-risk treatment (i.e. radiotherapy)**
This question maybe addressed by question 1a (latency time of pituitary dysfunction).

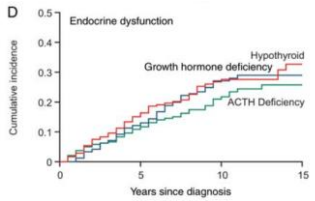
e. **What is the order of occurrence in which HP dysfunction occurs in childhood cancer survivors (CNS tumor) with a tumor in the sellar and suprasellar region versus CNS tumors located elsewhere in the brain?**
No studies included for all five types of HP dysfunction

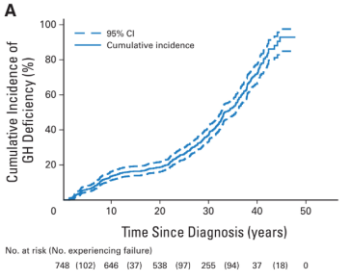
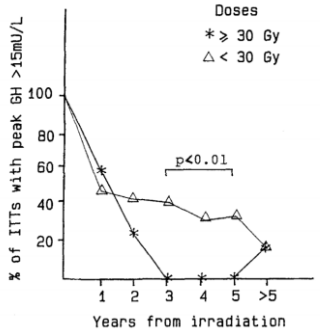
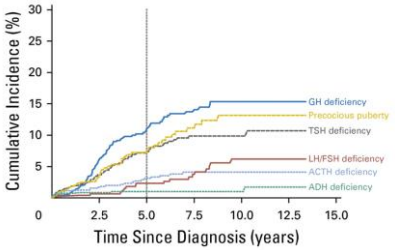
f. **What is the order of occurrence in which HP dysfunction occurs in childhood cancer survivors (non-CNS tumor) who have had brain injury?**
No studies included for all five types of HP dysfunction

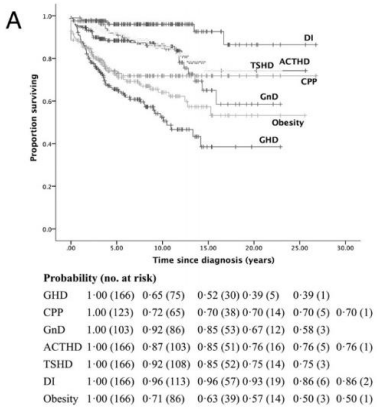
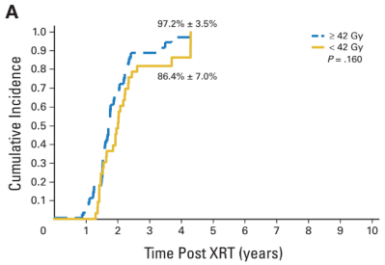
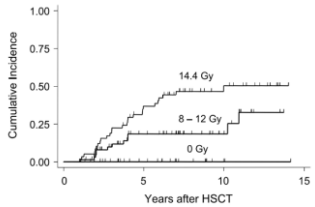
Question 2. For how long should screening for HP dysfunction continue in childhood cancer survivors (CNS tumor and non-CNS tumor) who had (repeatedly) a negative screen?

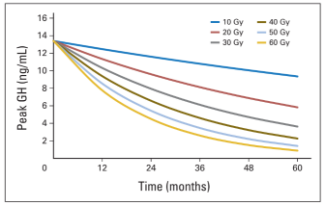
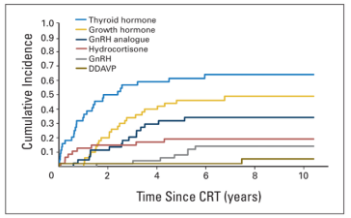
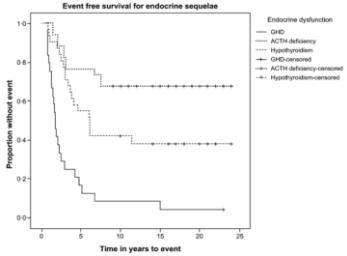
a. **Does the risk of developing HP dysfunction change (increase or decrease) over time in childhood cancer survivors (CNS tumor and non-CNS tumor)? What is the timing of such change? (i.e. is there a plateau in the cumulative incidence of HP dysfunction in childhood cancer survivors (CNS tumor and non-CNS tumor), and if so when?)**

i. **Does the risk of developing GHD change (increase or decrease) over time in childhood cancer survivors (CNS tumor and non-CNS tumor)? What is the timing of such change? (i.e. is there a plateau in the cumulative incidence of HP dysfunction in childhood cancer survivors (CNS tumor and non-CNS tumor), and if so when?)**

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence)	Cumulative incidence	Risk of bias
2a. Risk GHD over time (n=11 studies)	Armstrong 2011	240 CAYA CNS tumor survivors	10 (5-21.5)	46.3% RT *RT details;* Not reported	Not reported Diagnosed by provocative testing, GH peak cut-off value unknown	<u>Cumulative incidence at 5 years:</u> GHD: 13% (95% CI unknown) <u>Cumulative incidence at 10 years:</u> GHD: 27% (95% CI unknown) <u>Cumulative incidence at 15 years:</u> GHD: 29% (95% CI 22.2-32.5%)  Increased cumulative incidence over time	SB: unclear AB: unclear DB: unclear

	Chemaitilly 2015	748 CAYA CNS and non-CNS tumor survivors	27.3 (10.8-47.7)	100% RT *RT details;* Cranial RT dose 1-14.9 Gy, n=40 15-21.9 Gy, n=208 22-29.9 Gy, n=316 30-39.9 Gy, n=31 ≥40 Gy, n=153	Prevalence at last follow-up: GHD: n=348 (46.5%) Established by a previous diagnosis or IGF-1 z-scores <-2	 Increased cumulative incidence over time (no data reported)	SB: high risk AB: low risk DB: unclear
	Clayton 1991	82 CAYA CNS and non-CNS tumor survivors	4.3 (0.2-18.9)	100% RT *RT details;* Cranial RT, n=24 Craniospinal RT, n=58 RT dose to HP region Range 27-47.5 Gy <30 Gy, n=46 (56.1%) ≥30 Gy, n=36 (43.9%)	Incidence 74% of all tests Diagnosed by provocative testing (ITT); peak GH ≤15	 Increased cumulative incidence over time (no data reported)	SB: unclear AB: high risk DB: unclear
	Clement 2016	718 CAYA CNS tumor survivors	6.6 (2.0-13.4)	35.9% RT *RT details;* Cranial RT, n=144, RT dose, median 54.0 Gy (range 12.5-60.0) Craniospinal RT, n=114, RT dose, median 24.0 Gy (range 18.0-39.7)	Prevalence at last follow-up GHD: n=90 (12.5%) Diagnosed by provocative testing, GH peak <20-30 mU/L or diagnosis by treating physician	<u>Cumulative incidence at 5 years:</u> GHD: 11.1% (95% CI 6.2-17.4)  Increased cumulative incidence over time (no data on multiple time points reported)	SB: unclear AB: high risk DB: unclear

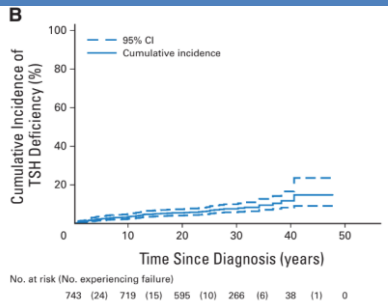
	Gan 2015	166 CAYA CNS tumor survivors	8.3 (0.04-26.8)	41.6% RT *RT details;* Focal RT to total dose 48-55 Gy	Prevalence at last follow-up: GHD: n=67 (40.3%) Diagnosed by provocative testing, GH peak <7 ng/mL	 Increased cumulative incidence over time (no data reported)	SB: low risk AB: unclear DB: unclear
	Laughton 2008	88 CAYA CNS tumor survivors	Median 4.7 to 5.1 (range 2.1-9.6) depending on risk category	100% RT *RT details* Average-risk patients (n=53): -Hypothalamus dose: median 38.6 Gy -Craniospinal dose: 23.4 Gy High-risk patients (n=35) hypothalamus: -Hypothalamus dose: median 50.5 Gy -Craniospinal dose: 39.6 Gy	Prevalence at last follow-up: GHD (assessed in n=70): n=66 (94%) Diagnosed by provocative testing, GH peak <10 µg/ml	 Increased cumulative incidence over time (no data reported)	SB: low risk AB: low risk DB: unclear
	Leung 2007	155 CAYA survivors after HCT	9 (3.1-15.9)	79.4% RT *RT details;* Dose of TBI: 14.4 Gy, n=59 8-12 Gy, n=64	Prevalence at last follow-up GHD, n=39 (25%) Diagnosed by provocative testing, GH peak <10ng/mL	 Increased cumulative incidence over time (no data reported)	SB: low risk AB: low risk DB: unclear
	Merchant 2011	192 CAYA CNS tumor survivors	60 months	100% RT *RT details;* All received conformal RT or intensity-modulated RT	Not reported GHD diagnosed by provocative testing (arginine/L-DOPA), GH peak <7 ng/mL	Average patient would develop GHD with the following combinations of time after cranial RT and dose to hypothalamus: 12 months and >60Gy; 36 months and 25-30Gy; 60 months and 15-20Gy.	SB: unclear AB: unclear DB: unclear

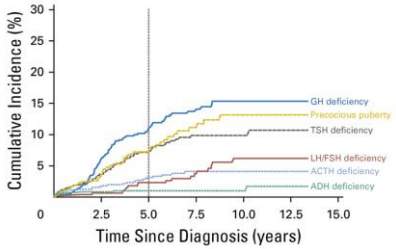
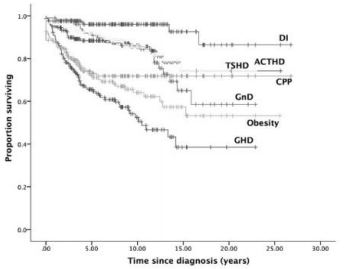
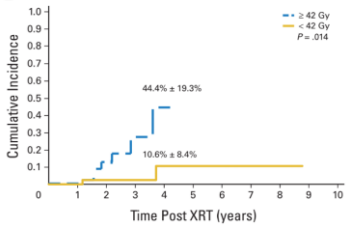
				Ependymoma: Cranial RT dose 59.4 Gy, n=73 Cranial RT dose 54.0 Gy, n=15 Low grade glioma: Cranial RT dose 54 Gy, n=unknown		 Increased cumulative incidence over time.	
	Merchant 2009	78 CAYA CNS tumor survivors	Not reported	100% RT *RT details;* Dose 54 Gy in 6 weeks (1.8 Gy fractions) All received conformal RT or intensity-modulated RT (n=3)	Not reported Diagnosed by provocative testing (ATT/L-DOPA), GH peak <10 ng/mL	<u>Cumulative incidence at 5 years after RT (n=50)</u> GH replacement: 46% ± 7.2 <u>Cumulative incidence at 10 years after RT</u> GH replacement: 48.9% ± 7.4  Increased cumulative incidence over time	SB: low risk AB: high risk DB: unclear
	Uday 2015	35 CAYA medulloblastoma survivors	18 (10-28)	100% RT *RT details;* Craniospinal RT: n=32, median dose 35 Gy and posterior fossa boost with median dose 55 Gy (range 54-55.8) Gy One patient received 35 Gy Craniospinal RT + 12 Gy posterior fossa boost One patient received 35 Gy Craniospinal RT + 28 Gy posterior fossa boost	Prevalence at last follow-up -Complete GHD: 28/35 (80%) -Partial GHD: 6/35 (17%) Complete GHD: peak GH level <3 µg/L in adults, and <7 µg/L in children Partial GHD: peak GH level between 3 and 7 µg/L in adults	 Increased cumulative incidence over time	SB: high risk AB: low risk DB: unclear
	Yock 2016	59 CAYA medulloblastoma survivors	7.0 (IQR 5.2-8.6)	100% RT *RT details;* HP dose <40 GyRBE, n=37 ≥40 GyRBE, n=22 All received proton RT (6/59 (10%) received <20% of RT as photons)	Not reported Definition GHD not reported, neuroendocrine assessment with IGF-1	<u>Cumulative incidence at 3 years after RT</u> GHD: 22% (95% CI 12-33%) <u>Cumulative incidence at 5 years after RT</u> GHD: 46% (95% CI 33-59%) <u>Cumulative incidence at 7 years after RT</u> GHD: 55% (95% CI 40-68%)	SB: high risk AB: low risk DB: unclear
GRADE assessment							

Study design: Study limitations:	+4 -1	Observational evidence Some limitations: Selection bias low in 4/11, high in 3/11, unclear in 4/11; Attrition bias low in 5/11, high in 3/11, unclear in 3/11; Detection bias unclear in 11/11
Consistency: Directness:	0 0	No important inconsistency, all show increased incidence over time, although the presence of a plateau may be present in two of eleven studies. Results are direct, population and outcomes broadly generalizable
Precision: Publication bias:	0 0	No important imprecision, high percentage of events Unlikely
Quality of evidence	⊕⊕⊕⊖ MODERATE	
Conclusion:	The cumulative incidence of GHD increases over time which does not seem to plateau in childhood cancer survivors (CNS tumor and non-CNS tumor) diagnosed before the age of 25 years. (11 studies; 2,561 participants; 638 events (in 6/11 studies); unknown number of events (in 5/11))	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CI, confidence interval; CNS, central nervous system; DB, detection bias; GH, growth hormone; GHD, growth hormone deficiency; Gy, Gray; GyRBE, gray relative biological effectiveness; HCT, hematopoietic cell transplantation; HP, hypothalamic-pituitary; IGF-1, insulin-like growth factor-1; ITT, insulin tolerance test; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; yr, year.

ii. Does the risk of developing TSHD change (increase or decrease) over time in childhood cancer survivors (CNS tumor and non-CNS tumor)? What is the timing of such change? (i.e. is there a plateau in the cumulative incidence of HP dysfunction in childhood cancer survivors (CNS tumor and non-CNS tumor), and if so when?)

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence)	Cumulative incidence	Risk of bias
2a. Risk TSHD over time (n=5 studies)	Chemaitilly 2015	748 CAYA CNS and non-CNS tumor survivors	27.3 (10.8-47.7)	100% RT *RT details;* Cranial RT dose 1-14.9 Gy, n=40 15-21.9 Gy, n=208 22-29.9 Gy, n=316 30-39.9 Gy, n=31 ≥40 Gy, n=153	Prevalence at last follow-up: TSHD: n=56 (7.5%) Established by a previous diagnosis or FT4 <0.9 ng/dL with TSH<4 mIU/L	 Increased cumulative incidence over time (no data reported)	SB: high risk AB: low risk DB: unclear
	Clement 2016	718 CAYA CNS tumor survivors	6.6 (2.0-13.4)	35.9% RT *RT details;* Cranial RT, n=144, RT dose, median 54.0 Gy (range 12.5-60.0) Craniospinal RT, n=114, RT dose, median 24.0 Gy (range 18.0-39.7)	Prevalence at last follow-up TSHD: n=66 (9.1%) Diagnosed by low FT4 concentrations with low, normal or mildly raised TSH	Cumulative incidence at 5 years: TSHD: 7.2% (95% CI 3.0-13.9)	SB: unclear AB: high risk DB: unclear

					 Increased cumulative incidence over time (no data on multiple time points reported)	
Gan 2015	166 CAYA CNS tumor survivors	8.3 (0.04-26.8)	41.6% RT *RT details;* Focal RT to total dose 48-55 Gy	Prevalence at last follow-up: TSHD: n=22 (13.3%) Diagnosed by low FT4 concentrations with inappropriately normal/ low TSH	A  **Probability (no. at risk)** GHD 1·00 (166) 0·65 (75) 0·52 (30) 0·39 (5) 0·39 (1) CPP 1·00 (123) 0·72 (65) 0·70 (38) 0·70 (14) 0·70 (5) 0·70 (1) GnD 1·00 (103) 0·92 (86) 0·85 (53) 0·67 (12) 0·58 (3) ACTHD 1·00 (166) 0·87 (103) 0·85 (51) 0·76 (16) 0·76 (5) 0·76 (1) TSHD 1·00 (166) 0·92 (108) 0·85 (52) 0·75 (14) 0·75 (3) DI 1·00 (166) 0·96 (113) 0·96 (57) 0·93 (19) 0·86 (6) 0·86 (2) Obesity 1·00 (166) 0·71 (86) 0·63 (39) 0·57 (14) 0·50 (3) 0·50 (1) Increased cumulative incidence over time (no data reported)	SB: low risk AB: unclear DB: unclear
Laughton 2008	88 CAYA CNS tumor survivors	Median 4.7 to 5.1 (range 2.1-9.6) depending on risk category	100% RT *RT details* Average-risk patients (n=53): -Hypothalamus dose: median 38.6 Gy -Craniospinal dose: 23.4 Gy High-risk patients (n=35) hypothalamus: -Hypothalamus dose: median 50.5 Gy -Craniospinal dose: 39.6 Gy	Prevalence at last follow-up: TSHD (assessed in n=87): n=9 (10%) Diagnosed by a FT4 below the normal range, with a normal or low TSH level.	B  Increased cumulative incidence over time (no data reported)	SB: low risk AB: low risk DB: unclear

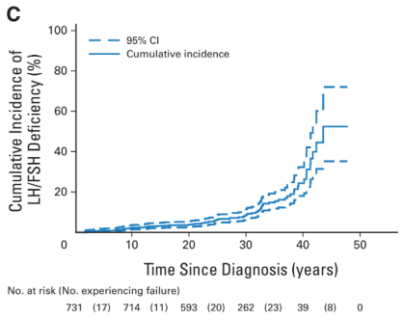
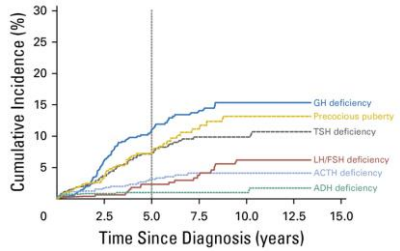
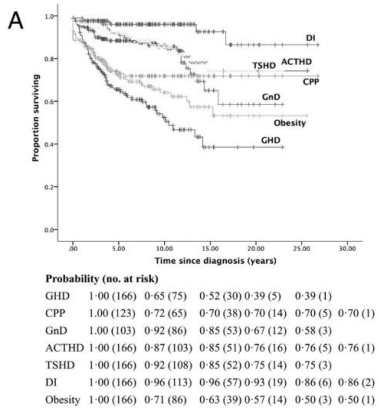
	Ramanauskienė 2014	51 CAYA CNS tumor survivors	21 months (0.25-10.6 yrs)	56.9% RT *RT details;* Cranial RT, n=13 (25.5%) Craniospinal RT, n=16 (31.4%) Mean cumulative dose, 54.2 Gy (range 45.0–60.0)	Prevalence at last follow-up TSHD: n=unknown, 25.9% Diagnosed by a low level of FT4, with a low or normal TSH	<u>Cumulative incidence at 1 year after end of treatment</u> TSHD: 4.8% ± 4.6% <u>Cumulative incidence at 2 years after end of treatment</u> TSHD: 33.7% ± 11.4% <u>Cumulative incidence at 3 years after end of treatment</u> TSHD: 33.7% ± 11.4% <u>Cumulative incidence at 4 years after end of treatment</u> TSHD: 33.7% ± 11.4% <u>Cumulative incidence at 5 years after end of treatment</u> TSHD: 33.7% ± 11.4% Increased cumulative incidence over time	SB: high risk AB: high risk DB: unclear

GRADE assessment		
<u>Study design:</u> <u>Study limitations:</u>	+4 -1	Observational evidence Some limitations: Selection bias low in 2/5, high in 2/5, unclear in 1/5; Attrition bias low in 2/5, high in 2/5, unclear in 1/5; Detection bias unclear in 5/5
<u>Consistency:</u> <u>Directness:</u>	0 0	No important inconsistency, all show increased incidence over time, although the presence of a plateau may be present in two of five studies. Results are direct, population and outcomes broadly generalizable
<u>Precision:</u> <u>Publication bias:</u>	-1 0	Some imprecision, low number of events in multiple studies Unlikely
Quality of evidence	⊕⊕⊖⊖ LOW	
Conclusion:	The cumulative incidence of TSHD increases over time in childhood cancer survivors (CNS tumor and non-CNS tumor) diagnosed before the age of 25 years. (5 studies; 1,771 participants; 153 events (in 4/5 studies); unknown number of events (in 1/5))	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CI, confidence interval; CNS, central nervous system; DB, detection bias; FT4, free thyroxine; Gy, Gray; RT, radiotherapy; SB, selection bias; TSH, thyroid-stimulating hormone; TSHD, thyroid-stimulating hormone deficiency; yr, year.

iii. Does the risk of developing LH/FSHD change (increase or decrease) over time in childhood cancer survivors (CNS tumor and non-CNS tumor)? What is the timing of such change? (i.e. is there a plateau in the cumulative incidence of HP dysfunction in childhood cancer survivors (CNS tumor and non-CNS tumor), and if so when?)

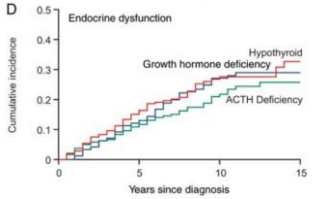
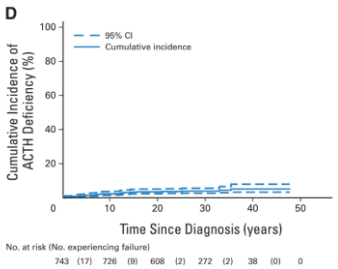
Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence)	Cumulative incidence	Risk of bias

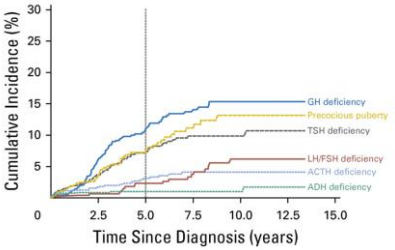
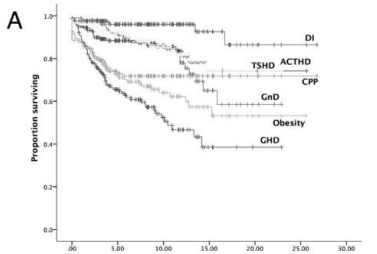
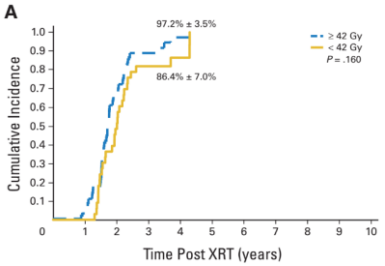
2a. Risk LH/FSHD over time (n=3 studies)	Chemaitilly 2015	748 CAYA CNS and non-CNS tumor survivors	27.3 (10.8-47.7)	100% RT *RT details;* Cranial RT dose 1-14.9 Gy, n=40 15-21.9 Gy, n=208 22-29.9 Gy, n=316 30-39.9 Gy, n=31 ≥40 Gy, n=153	Prevalence at last follow-up: LH/FSHD: n=79 (10.8%) Established by a previous diagnosis or total testosterone <200ng/dL coincided with LH<7 IU/L and FSH <9.2 IU/L in males. In amenorrheic women <40 yrs old, estradiol <17 pg/mL and FSH <11.2 IU/L	 Increased cumulative incidence over time (no data reported)	SB: high risk AB: low risk DB: unclear
	Clement 2016	718 CAYA CNS tumor survivors	6.6 (2.0-13.4)	35.9% RT *RT details;* Cranial RT, n=144, RT dose, median 54.0 Gy (range 12.5-60.0) Craniospinal RT, n=114, RT dose, median 24.0 Gy (range 18.0-39.7)	Prevalence at last follow-up LH/FSHD: n=20 (4.2% of evaluable patients) Diagnosed by low LH and/or FSH in the absence of pubertal development or use of estrogens or testosterone for diagnosis LH/FSHD	<u>Cumulative incidence at 5 years:</u> LH/FSHD: 1.7% (95% CI 0.0-11.1)  Increased cumulative incidence over time (no data on multiple time points reported)	SB: unclear AB: high risk DB: unclear
	Gan 2015	166 CAYA CNS tumor survivors	8.3 (0.04-26.8)	41.6% RT *RT details;* Focal RT to total dose 48-55 Gy	Prevalence at last follow-up: LH/FSHD: n=21/103 (20.4%) Diagnosed by absence of pubertal development or pubertal arrest with undetectable testosterone/estradiol and/or abnormal GnRH testing	 Increased cumulative incidence over time (no data reported)	SB: low risk AB: unclear DB: unclear
GRADE assessment							
<u>Study design:</u>	+4	Observational evidence					

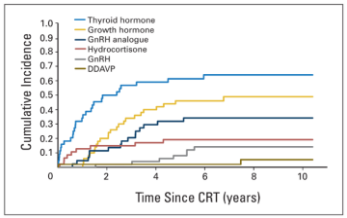
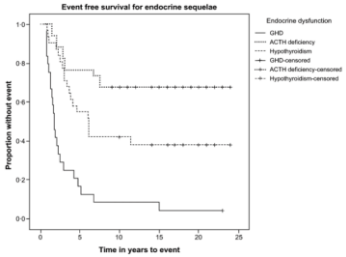
Study limitations:	-1	Some limitations: Selection bias low in 1/3, high in 1/3, unclear in 1/3; Attrition bias low in 1/3, high in 1/3, unclear in 1/3; Detection bias unclear in 3/3
Consistency: Directness:	0 0	No important inconsistency, all studies who increased incidence over time, although the presence of a plateau may be present in one of the studies. Results are direct, population and outcomes broadly generalizable
Precision: Publication bias:	-1 0	Some imprecision, low number of events Unlikely
Quality of evidence	⨁⨁⨀⨀ LOW	
Conclusion:	The cumulative incidence of LH/FSHD increases over time in childhood cancer survivors (CNS tumor and non-CNS tumor) diagnosed before the age of 25 years. (3 studies; 1632 participants; 120 events)	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CI, confidence interval; CNS, central nervous system; DB, detection bias; FSH, follicle-stimulating hormone, Gy, Gray; GnRH, Gonadotropin-releasing hormone; LH, luteinizing hormone; LH/FSHD, luteinizing hormone and follicle-stimulating hormone deficiency; RT, radiotherapy; SB, selection bias; yr, year.

iv. Does the risk of developing ACTHD change (increase or decrease) over time in childhood cancer survivors (CNS tumor and non-CNS tumor)? What is the timing of such change? (i.e. is there a plateau in the cumulative incidence of HP dysfunction in childhood cancer survivors (CNS tumor and non-CNS tumor), and if so when?)

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence)	Cumulative incidence	Risk of bias
2a. Risk ACTHD over time (n=9 studies)	Armstrong 2011	240 CAYA CNS tumor survivors	10 (5-21.5)	46.3% RT *RT details;* Not reported	Not reported Diagnosed by provocative testing, cut-off value unknown	Cumulative incidence at 5 years: ACTHD: 12% (95% CI unknown) Cumulative incidence at 10 years: ACTHD: 22% (95% CI unknown) Cumulative incidence at 15 years: ACTHD: 26% (95% CI 18.9-32.5%)  Increased cumulative incidence over time	SB: unclear AB: unclear DB: unclear
	Chemaitilly 2015	748 CAYA CNS and non-CNS tumor survivors	27.3 (10.8-47.7)	100% RT *RT details;* Cranial RT dose 1-14.9 Gy, n=40 15-21.9 Gy, n=208 22-29.9 Gy, n=316 30-39.9 Gy, n=31 ≥40 Gy, n=153	Prevalence at last follow-up: ACTHD: n=30 (4.0%) Established by a previous diagnosis or 08.00 AM cortisol <5µg/dL	 Increased cumulative incidence over time	SB: high risk AB: low risk DB: unclear

					(no data reported)	
	Clement 2016	718 CAYA CNS tumor survivors	6.6 (2.0-13.4)	35.9% RT *RT details;* Cranial RT, n=144, RT dose, median 54.0 Gy (range 12.5-60.0) Craniospinal RT, n=114, RT dose, median 24.0 Gy (range 18.0-39.7)	Prevalence at last follow-up ACTHD: n=31 (4.3%) Diagnosed by use of hydrocortisone maintenance or substitution under suspicion of ACTHD	<u>Cumulative incidence at 5 years:</u> ACTHD: 2.9% (95% CI 0.4-10.6)  Increased cumulative incidence over time (no data on multiple time points reported)	SB: unclear AB: high risk DB: unclear
	Gan 2015	166 CAYA CNS tumor survivors	8.3 (0.04-26.8)	41.6% RT *RT details;* Focal RT to total dose 48-55 Gy	Prevalence at last follow-up: ACTHD: n=22 (13.3%) Diagnosed by provocative testing, peak cortisol <500nmol/L	 **Probability (no. at risk)** GHD 1·00 (166) 0·65 (75) 0·52 (30) 0·39 (5) 0·39 (1) CPP 1.00 (123) 0·72 (65) 0·70 (38) 0·70 (14) 0·70 (5) 0·70 (1) GnD 1.00 (103) 0·92 (86) 0·85 (53) 0·67 (12) 0·58 (3) ACTHD 1·00 (166) 0·87 (103) 0·85 (51) 0·76 (16) 0·76 (5) 0·76 (1) TSHD 1·00 (166) 0·92 (108) 0·85 (52) 0·75 (14) 0·75 (3) DI 1·00 (166) 0·96 (113) 0·96 (57) 0·93 (19) 0·86 (6) 0·86 (2) Obesity 1·00 (166) 0·71 (86) 0·63 (39) 0·57 (14) 0·50 (3) 0·50 (1) Increased cumulative incidence over time (no data reported)	SB: low risk AB: unclear DB: unclear
	Laughton 2008	88 CAYA CNS tumor survivors	Median 4.7 to 5.1 (range 2.1-9.6) depending on risk category	100% RT *RT details* Average-risk patients (n=53): -Hypothalamus dose: median 38.6 Gy -Craniospinal dose: 23.4 Gy High-risk patients (n=35) hypothalamus: -Hypothalamus dose: median 50.5 Gy -Craniospinal dose: 39.6 Gy	Prevalence at last follow-up: ACTHD (assessed in n=76): n=33 (43%) Diagnosed by cortisol level after 20 minutes <18µg/dL after 1µg ACTH test or 11-deoxycortisol level ≤7ng/dL after metyrapone test	 Increased cumulative incidence over time (no data reported)	SB: low risk AB: low risk DB: unclear
	Merchant 2009	78 CAYA CNS tumor	Not reported	100% RT	Prevalence at 24	<u>Cumulative incidence at 5 years after RT</u>	SB: low risk

		survivors		*RT details;* Dose 54 Gy in 6 weeks (1.8 Gy fractions) All received conformal RT or intensity-modulated RT (n=3)	months after radiotherapy: Glucocorticoid: n=11 (22%) Diagnosed by 1-µg ACTH test, cut off-value ≤18 µg/dL or 11-deoxycortisol level ≤7ng/dL after metyrapone test	<u>(n=50)</u> Glucocorticoid replacement: 19.2% ± 5.8 <u>Cumulative incidence at 10 years after RT</u> Glucocorticoid replacement: 19.2% ± 5.8  Increased cumulative incidence over time	AB: high risk DB: unclear
	Uday 2015	35 CAYA medulloblastoma survivors	18 (10-28)	100% RT *RT details;* Craniospinal RT: n=32, median dose 35 Gy and posterior fossa boost with median dose 55 Gy (range 54-55.8) Gy One patient received 35 Gy Craniospinal RT + 12 Gy posterior fossa boost One patient received 35 Gy Craniospinal RT + 28 Gy posterior fossa boost	Prevalence at last follow-up -Complete ACTHD: 13/35 (37%) -Partial ACTHD: 3 (8.5%) Complete ACTHD: peak cortisol 400 nmol/L after glucagon or ITT Partial ACTHD: peak cortisol between 400 and 450 nmol/L after glucagon or between 400 and 550 nmol/L after ITT	 Increased cumulative incidence over time (no data reported)	SB: high risk AB: low risk DB: unclear
	Yock 2016	59 CAYA medulloblastoma survivors	7.0 (IQR 5.2-8.6)	100% RT *RT details;* HP dose <40 GyRBE, n=37 ≥40 GyRBE, n=22 All received proton RT (6/59 (10%) received <20% of RT as photons)	Not reported Definition ACTHD not reported, neuroendocrine assessment with morning cortisol	<u>Cumulative incidence at 3 years after RT</u> ACTHD: 5% (95% CI 1-13%) <u>Cumulative incidence at 5 years after RT</u> ACTHD: 9% (95% CI 3-17%) <u>Cumulative incidence at 7 years after RT</u> ACTHD: 9% (95% CI 3-17%) Increased cumulative incidence over time	SB: high risk AB: low risk DB: unclear
	Ramanauskienė 2014	51 CAYA CNS tumor survivors	21 months (0.25-10.6)	56.9% RT *RT details;* Cranial RT, n=13 (25.5%) Craniospinal RT, n=16	Prevalence at last follow-up ACTHD: n=1 (4.2%) Diagnosed by a morning (<10.00	<u>Cumulative incidence at 1 year after end of treatment</u> ACTHD: 0% <u>Cumulative incidence at 2 years after end</u>	SB: high risk AB: high risk DB: unclear

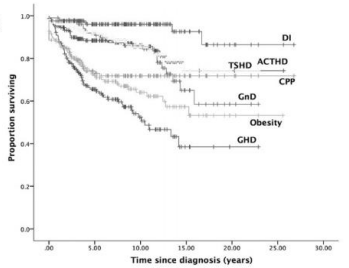
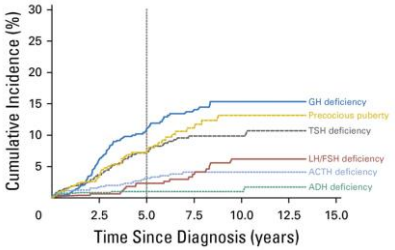
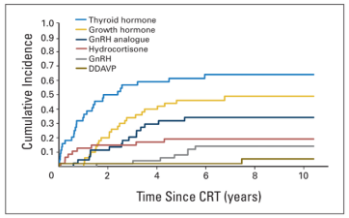
			(31.4%) Mean cumulative dose, 54.2 Gy (range 45.0–60.0)	AM) serum cortisol <138nmol/L	<u>of treatment</u> ACTHD: 9.1% ± 8.7% <u>Cumulative incidence at 3 years after end of treatment</u> ACTHD: 9.1% ± 8.7% <u>Cumulative incidence at 4 years after end of treatment</u> ACTHD: 9.1% ± 8.7% <u>Cumulative incidence at 5 years after end of treatment</u> ACTHD: 9.1% ± 8.7% Increased cumulative incidence over time	

GRADE assessment		
<u>Study design:</u> <u>Study limitations:</u>	+4 -1	Observational evidence Some limitations: Selection bias low in 3/9, high in 4/9, unclear in 2/9; Attrition bias low in 4/9, high in 3/9, unclear in 2/9; Detection bias unclear in 9/9
<u>Consistency:</u> <u>Directness:</u>	0 0	No inconsistency, all show increased incidence over time, although the presence of a plateau may be present in five of nine studies. Results are direct, population and outcomes broadly generalizable
<u>Precision:</u> <u>Publication bias:</u>	-1 0	Some imprecision, low number of events Unlikely
Quality of evidence	⨁⨁⨀⨀ LOW	
Conclusion:	The cumulative incidence of ACTHD increases over time in childhood cancer survivors (CNS tumor and non-CNS tumor) diagnosed before the age of 25 years. (9 studies; 2,183 participants; 141 events (in 7/9 studies); unknown number of events (in 2/9))	

Abbreviations: AB, attrition bias; ACTH, adrenocorticotropic hormone; ACTHD, adrenocorticotropic hormone deficiency; CAYA, childhood, adult and young adult; CI, confidence interval; CNS, central nervous system; DB, detection bias; Gy, Gray; GyRBE, gray relative biological effectiveness; HP, hypothalamic-pituitary; ITT, insulin tolerance test; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; yr, year.

v. Does the risk of developing CPP change (increase or decrease) over time in childhood cancer survivors (CNS tumor and non-CNS tumor)? What is the timing of such change? (i.e. is there a plateau in the cumulative incidence of HP dysfunction in childhood cancer survivors (CNS tumor and non-CNS tumor), and if so when?)

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence)	Cumulative incidence	Risk of bias

2a. Risk CPP over time (n=3 studies)	Gan 2015	166 CAYA CNS tumor survivors	8.3 (0.04-26.8)	41.6% RT *RT details;* Focal RT to total dose 48-55 Gy	Prevalence at last follow-up: CPP: n=32/123 (26.0%) Diagnosed by Tanner staging, pubertal concentrations of testosterone/estradiol and/or pubertal response to provocative testing	A  **Probability (no. at risk)** GHD 1·00 (166) 0·65 (75) 0·52 (30) 0·39 (5) 0·39 (1) CPP 1.00 (123) 0·72 (65) 0·70 (38) 0·70 (14) 0·70 (5) 0·70 (1) GnD 1.00 (103) 0·92 (86) 0·85 (53) 0·67 (12) 0·58 (3) ACTHD 1·00 (166) 0·87 (103) 0·85 (51) 0·76 (16) 0·76 (5) 0·76 (1) TSHD 1·00 (166) 0·92 (108) 0·85 (52) 0·75 (14) 0·75 (3) DI 1·00 (166) 0·96 (113) 0·96 (57) 0·93 (19) 0·86 (6) 0·86 (2) Obesity 1·00 (166) 0·71 (86) 0·63 (39) 0·57 (14) 0·50 (3) 0·50 (1) Increased cumulative incidence over time (no data reported)	SB: low risk AB: unclear DB: unclear
	Clement 2016	718 CAYA CNS tumor survivors	6.6 (2.0-13.4)	35.9% RT *RT details;* Cranial RT, n=144, RT dose, median 54.0 Gy (range 12.5-60.0) Craniospinal RT, n=114, RT dose, median 24.0 Gy (range 18.0-39.7)	Prevalence at last follow-up CPP: n=48 (12.2% of evaluable patients) Onset of puberty diagnosed by Tanner B2 in girls <8 years and testes >4mL in boys >9 years.	<u>Cumulative incidence at 5 years:</u> CPP: 4.0% (95% CI 0.9-11.1)  Increased cumulative incidence over time (no data on multiple time points reported)	SB: unclear AB: high risk DB: unclear
	Merchant 2009	78 CAYA CNS tumor survivors	Not reported	100% RT *RT details;* Dose 54 Gy in 6 weeks (1.8 Gy fractions) All received conformal RT or intensity-modulated RT (n=3)	Prevalence at 24 months after radiotherapy: GnRH analog: n=11 (22%) Diagnosed by clinical and laboratory evidence of CPP, with abnormal GnRH stimulation test	<u>Cumulative incidence at 5 years after RT (n=50)</u> GnRH analog therapy: 31.8% ± 7.1 <u>Cumulative incidence at 10 years after RT</u> GnRH analog therapy: 34.2% ± 7.3  Increased cumulative incidence over time	SB: low risk AB: high risk DB: unclear
GRADE assessment							

Study design: Study limitations:	+4 -1	Observational evidence Some limitations: Selection bias low in 2/3, unclear in 1/3; Attrition bias high in 2/3, unclear in 1/3; Detection bias unclear in 3/3
Consistency: Directness:	0 0	No important inconsistency, all studies who increased incidence over time. Results are direct, population and outcomes broadly generalizable
Precision: Publication bias:	-1 0	Some imprecision, low number of events Unlikely
Quality of evidence	⊕⊕⊖⊖ LOW	
Conclusion:	The cumulative incidence of CPP increases over time in childhood cancer survivors (CNS tumor and non-CNS tumor) diagnosed before the age of 25 years. (3 studies; 962 participants; 91 events)	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CI, confidence interval; CNS, central nervous system; CPP, central precocious puberty; DB, detection bias; Gy, Gray; GnRH, Gonadotropin-releasing hormone; RT, radiotherapy; SB, selection bias; yr, year.

b. Are there any modifying factors that alter the cumulative incidence to develop HP dysfunction in childhood cancer survivors (CNS tumor and non-CNS tumor) treated with potentially high-risk treatment (i.e. radiotherapy)?
No studies included for all five types of HP dysfunction

WG3; What surveillance modality should be used?

Question 1. Which screening modality is most sensitive and specific for detecting GHD in CCS?

a. What is the diagnostic value of IGF-1 measurements versus GH stimulation tests (preferably gold standard, ITT or glucagon) for detecting GHD in *pediatric* CS?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Age at testing (median/mean, range) yr	Testing modalities	Events (prevalence)	Effect size	Risk of bias
2a. IGF-1 and vs GH stimulation test in children (n=4)	Hua 2012	106 CAYA brain tumor 'survivors'	3 (0.4-5.8)	5.6 (1.1-16.6)	Diagnostic test: IGF-1 (standardized in z-scores) Reference test: GH stimulation test; arginine and L-dopa test (peak GH <7 ng/ml)	Prevalence not reported Definition GHD: peak GH <7 ng/ml	Model with IGF-1 z-score, weight and hypothalamic dose Sensitivity: 80% Specificity: 78% NPV: not reported PPV: not reported AUC: 0.883 (cut-off 0.3) Model with IGF-1 alone Sensitivity: not reported Specificity: not reported NPV: not reported PPV: not reported AUC: 0.651	SB: unclear VB: high risk I/TB: unclear
	Sklar 1993	20 CAYA survivors	2.7 (2-7)	9.4 (5.6-16)	Diagnostic test: IGF-1 (standardized in z-scores)	GHD: n=15, defined by peak GH	IGF-1 Sensitivity: 66%	SB: unclear VB: unclear

					Reference test: GH stimulation test: clonidine and L-dopa	<10µg/ml in at least two dynamic GH tests	Specificity: 100% PPV, NPV, AUC not reported	I/TB: unclear
	Tillmann 1998	28 CAYA survivors	CNS tumor: 4.2 ± 4.0 (0.4-14.2) ALL: 6.7 ± 3.2 (1.3-10.9)	CNS tumor: 12.4 ± 5.5 (7.0-24.3) ALL: 11.8 ± 2.5 (7.8-17.4)	Diagnostic test IGF-1 (standardized in SDS) Reference test: GH stimulation tests; arginine (n=20), glucagon (n=12), insulin (n=10), clonidine (n=6)	GHD: n=15, defined by peak GH <7.5 ng/ml	IGF-1 Sensitivity: 47% Specificity: 77% PPV, NPV, AUC not reported	SB: unclear VB: high risk I/TB: unclear
	Sfeir 2018 (n=15 studies, Sklar 1993 and Tillmann 1998 are included)	477 CAYA survivors	Could not be calculated	Could not be calculated	Diagnostic test: Reference test: Arginine (n=2), Arginine /ITT/Exercise (n=1), GHRH/arginine/IGF-1/IGFBP-3 (n=1), GHRH/arginine (n=1), GHRH (n=1), GHRH/IGF-1 (n=1), GHRH/IGFBP-3 (n=1), hpGRF1 (n=1), IGF-1/IGFBP-3 (n=5), IGFBP-3 (n=1), Reference test: Arginine/Glucagon/ITT/Clonidine (n=1), ITT/arginine (n=3), ITT (n=4), Arginine/Levodopa (n=1), Clonidine/Levodopa (n=1), 24h GH (n=2), nocturnal GH (n=1), one or more GH stimulation tests (n=1), not reported (n=1)	Prevalence not reported	IGF-1: sensitivity between 47% to 66%, specificity between 77% and 100% GH profiles (nocturnally or 24-hour): insufficient data available Dynamic testing: most accurate, and ITT (alone or in combination with arginine) most commonly used	SB: n.a. VB: n.a. I/TB: n.a.

GRADE assessment		
Study design:	+4	Observational evidence for diagnostic questions
Study limitations:	-1	Some limitations: Selection bias unclear in 3/4, n.a. in 1/4; Verification bias high in 2/4, unclear in 1/4, n.a. in 1/4; Index test bias unclear in 3/4, n.a. in 1/4
Consistency:	-1	Some inconsistency, differences in sensitivity and specificity ranges about 20% or more among different studies
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, low number of events
Publication bias:	0	Unlikely
Quality of evidence	⊕⊖⊖⊖ VERY LOW	
Conclusion:	The diagnostic value of IGF-1 to detect GHD in CCS is moderate (sensitivity ranged from 47% to 80%, specificity ranged from 77% to 100%) (3 original studies; 154 participants; 30 events (in 1/3 studies), unknown number of events (in 1/3), 1 systematic review)	

Abbreviations: ALL, acute lymphoblastic leukemia; AUC, area under the curve; CAYA, childhood, adult and young adult; CF, confounding; CNS tumor, central nervous system tumor; GH, growth hormone; GHD, growth hormone deficiency; I/TB, index/reference test bias; IGF-1, insulin-like growth factor-1; IGFBP-3, Insulin-like growth factor-binding protein 3; ITT, insulin tolerance test; n.a., not applicable; NPV, negative predictive value; PPV, positive predictive value; SB, selection bias; SDS, standard deviation scores; VB, verification bias.

a. What is the diagnostic value of IGF-1 and IGFBP-3 measurements versus GH stimulation tests (preferably gold standard, ITT or glucagon) for detecting GHD in *pediatric* CS?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Age at testing (median/mean, range) yr	Testing modalities	Events (prevalence)	Effect size	Risk of bias
2a. IGF-1 and IGFBP-3 vs GH stimulation test in children (n=3)	Hua 2012	106 CAYA brain tumor 'survivors'	3 (0.4-5.8)	5.6 (1.1-16.6)	Diagnostic test: IGFBP-3 (standardized in z-scores) Reference test: GH stimulation test; arginine and L-dopa test (peak GH <7 ng/ml)	Prevalence not reported Definition GHD: peak GH <7 ng/ml	Model with IGFBP-3 alone Sensitivity: not reported Specificity: not reported NPV: not reported PPV: not reported AUC 0.617	SB: unclear VB: high risk I/TB: unclear
	Sklar 1993	20 CAYA survivors	2.7 (2-7)	9.4 (5.6-16)	Diagnostic test: IGFBP-3 (standardized in z-scores) Reference test: GH stimulation test: clonidine and L-dopa	GHD: n=15, defined by peak GH <10µg/ml in at least two dynamic GH tests	IGFBP-3 Sensitivity: 20% Specificity: 100% PPV, NPV, AUC not reported	SB: unclear VB: unclear I/TB: unclear
	Sfeir 2018 (n=15 studies, Sklar 1993 and Tillmann 1998 are included)	477 CAYA survivors	Could not be calculated	Could not be calculated	Diagnostic test: Reference test: Arginine (n=2), Arginine /ITT/Exercise (n=1), GHRH/arginine/IGF-1/IGFBP-3 (n=1), GHRH/arginine (n=1), GHRH (n=1), GHRH/IGF-1 (n=1), GHRH/IGFBP-3 (n=1), hpGRF1 (n=1), IGF-1/IGFBP-3 (n=5), IGFBP-3 (n=1), Reference test: Arginine/Glucagon/ITT/Clonidine (n=1), ITT/arginine (n=3), ITT (n=4), Arginine/Levodopa (n=1), Clonidine/Levodopa (n=1), 24h GH (n=2), nocturnal GH (n=1), one or more GH stimulation tests (n=1), not reported (n=1)	Prevalence not reported	IGFBP-3: sensitivity 20%, specificity not reported IGF-1 and IGFBP-3 had a strong correlation, but simultaneous use did not increase diagnostic accuracy GH profiles (nocturnally or 24-hour): insufficient data available Dynamic testing: most accurate, and ITT (alone or in combination with arginine) most commonly used	SB: n.a. VB: n.a. I/TB: n.a.

GRADE assessment		
Study design:	+4	Observational evidence for diagnostic questions
Study limitations:	-2	Serious limitations: Selection bias unclear in 2/3, n.a. in 1/3; Verification bias high in 1/3, unclear in 1/3, n.a. in 1/3; Index test bias unclear in 2/3, n.a. in 1/3
Consistency:	N/A	Only one study assessed sensitivity and specificity, and the other study only reported AUC
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, low number of events
Publication bias:	0	Unlikely
Quality of evidence	⊕⊖⊖⊖ VERY LOW	
Conclusion:	The diagnostic value of IGFBP-3 to detect GHD in CCS is moderate (sensitivity is 20%, specificity is 100%, AUC 0.617) (2 original studies; 126 participants; 15 events (in 1/2 studies), unknown number of events (in 1/2), 1 systematic review)	

Abbreviations: AUC, area under the curve; CAYA, childhood, adult and young adult; CF, confounding; GH, growth hormone; GHD, growth hormone deficiency; I/TB, index/reference test bias; IGF-1, insulin-like growth factor-1; IGFBP-3, Insulin-like growth factor-binding protein 3; ITT, insulin tolerance test; n.a., not applicable; NPV, negative predictive value; PPV, positive predictive value; SB, selection bias; SDS, standard deviation scores; VB, verification bias.

b. What is the diagnostic value of height plotted in a growth chart versus GH stimulation tests (preferably gold standard, ITT or glucagon) for detecting GHD in *prepubertal pediatric* CS?
No studies included

c. What is the diagnostic value of IGF-1 and IGFBP-3 measurements versus GH stimulation tests (preferably gold standard, ITT or glucagon) for detecting GHD in *adult* CCS?
No studies included. Only studies included that compare two dynamic GH tests in adults

Question 2. Which screening modality is most sensitive and specific for detecting central hypothyroidism in CCS?

a. What is the diagnostic value of FT4, FT3, TSH and FT4/FT3 ratio and serial measurements for detecting central hypothyroidism versus a TRH test or nocturnal TSH surge in CCS (or the normal population)?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Age at testing (median/mean, range) yr	Testing modalities	Events (prevalence)	Effect size	Risk of bias
8a. FT4, FT3, TSH and FT4/FT3 ratio vs TRH test or nocturnal TSH surge (n=2)	Darzy 2005	37 CAYA survivors	11.5 (2-29)	21.5 (17-53.7)	Diagnostic test: nocturnal TSH surge or TRH test Reference test: FT4 concentration	TSHD: n=0 all were euthyroid (=FT4 above lower limit reference range)	-No correlation FT4 concentration and basal or stimulated TSH, TSH decline after TRH or nocturnal TSH surge -No difference between FT4 concentration in lowest third of reference interval, or higher FT4, regarding TSH responses to TRH test, maximum and nocturnal TSH surges	SB: unclear VB: low risk I/TB: unclear
	Rose 1999	208 CAYA survivors	6.1 (1-16)	Not reported (pediatric age)	Diagnostic test nocturnal TSH surge or TRH test Reference test nocturnal TSH surge or TRH test	TSHD: n=62 (if blunted TSH surge, or delayed TSH peak after TRH or delayed TSH decline after TRH), n=5 had FT4 slightly less than lower border of reference range	-57 (92%) of TSHD would have been missed using FT4 reference ranges -Sensitivity: Blunted TSH surge 71% -Sensitivity: delayed peak after TRH 21% -Sensitivity: delayed decline after TRH 42%	SB: unclear VB: high risk I/TB: unclear

			-Sensitivity: blunted peak after TRH 17%
GRADE assessment			
Study design:	+4	Observational evidence for diagnostic questions	
Study limitations:	-1	Some limitations: Selection bias unclear in 2/2; Verification bias low in 1/2, high in 1/2; Index test bias unclear in 2/2	
Consistency:	-1	Important inconsistency, one study in favor of using nocturnal TSH surge or TRH test, one study against using these tests	
Directness:	0	Results are direct, population and outcomes broadly generalizable	
Precision:	-1	Some imprecision, low number of events as almost all patients were thyroid defined by FT4 concentrations below the reference range	
Publication bias:	0	Unlikely	
Quality of evidence	⊕⊖⊖⊖ VERY LOW		
Conclusion:	The correlation between nocturnal TSH surge and FT4 concentrations to detect TSHD in CCS is low (no correlation between nocturnal TSH surge and FT4 concentrations) (1 study; 37 participants; 0 events) The correlation between TSH peak after TRH test and FT4 concentrations to detect TSHD in CCS is low (no correlation between TSH peak after TRH test and FT4 concentrations) (1 study; 37 participants; 0 events) The correlation between TSH decline after TRH test and FT4 concentrations to detect TSHD in CCS is low (no correlation between TSH decline after TRH and FT4 concentrations) (1 study; 37 participants; 0 events) The diagnostic values of these parameters vs. FT4 concentrations in the other study (Rose et al.) could not be determined, as they were not separately assessed against the golden standard.		

Abbreviations: CAYA, childhood, adult and young adult; CF, confounding; FT3, free triiodothyronine; FT4, Free thyroxine; I/TB, index/reference test bias; n.a., not applicable; SB, selection bias; Total T4, total thyroxine; TRH, thyrotropin releasing hormone; TSH, thyroid stimulating hormone; TSHD, thyroid stimulating hormone deficiency; VB, verification bias.

Question 3: Which screening modality is most sensitive and specific for detecting LH/FSHD in CCS?

a. What is the diagnostic value of Tanner stage, bone age, LH, FSH and sex steroids measurements for detecting central hypogonadism in prepubertal girls at B1 >12 years or boys age 13 with prepubertal testes?

No studies included

b. What is the inter-observer variability and likelihood performance for defining Tanner stages between health care providers from different specialties?

No studies included

Question 4: Which screening modality is most sensitive and specific for detecting central hypocortisolism in pediatric CCS?

a. What is the diagnostic value of morning plasma cortisol (total and free), ACTH, saliva cortisol or morning glucose (in young children) measurements versus dynamic testing (preferably ITT) for detecting central hypocortisolism in *pediatric* CS?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Age at testing (median/mean, range) yr	Testing modalities	Events (prevalence)	Effect size	Risk of bias

4a. morning cortisol vs. ITT in children (n=1)	Patterson 2009	78 CAYA survivors	5.8 ± 4.0	Not reported (pediatric age)	Diagnostic test: 08.00 AM cortisol or LDCT (<1mcg) Reference test: LDCT (<1mcg) or SDCT (225 mcg)	ACTHD: 75% after 08.00 AM cortisol (≤365 nmol/L) ACTHD: 69% after random cortisol (≤365 nmol/L) ACTHD: 35% after LDCT (<500 nmol/L) ACTHD: 11% after SDCT (<500 nmol/L)	- 08.00 AM cortisol and LDCT, Kappa=0.25, agreement 63%, P=NS - Random cortisol and LDCT, Kappa=0.03, agreement 51%, P=NS - LDCT and SDCT, Kappa=0.39, P<0.05), 68% of patients who failed LDCT, passed SDCT	SB: unclear VB: high risk I/TB: unclear

GRADE assessment		
Study design:	+4	Observational evidence for diagnostic questions
Study limitations:	-1	Some limitations: Selection bias unclear in 1/1; Verification bias high in 1/1; Index test bias unclear in 1/1
Consistency:	0	N/A (1 study)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, only 1 study included and low number of events
Publication bias:	0	Unlikely
Quality of evidence	⨁⊖⊖⊖ VERY LOW	
Conclusion:	The agreement between morning cortisol and LDCT to detect ACTHD in CCS is poor (Agreement 63%, kappa 0.25) (1 study; 78 participants; unknown number of events (in 1/1))	

Abbreviations: ACTHD, adrenocorticotropic hormone deficiency; CAYA, childhood, adult and young adult; CF, confounding; I/TB, index/reference test bias; ITT, insulin tolerance test; LDCT, low-dose corticotropin test; n.a., not applicable; NS, not significant; SB, selection bias; SDCT, standard-dose corticotropin test; VB, verification bias.

b. What is the diagnostic value of morning plasma cortisol (total and free), ACTH and saliva cortisol measurements versus an ITT for detecting central hypocortisolism in adult CCS (or the normal population)?

No systematic searches needed, refer to existing guidelines

c. What is the influence of steroid use (topical/oral/inhaled) on the testing results of the corticotropic axis for detecting hypocortisolism in pediatric CS?

No studies included

Question 5: Which screening modality is most sensitive and specific for detecting CPP in CCS?

c. What is the diagnostic value of screening with Tanner stage and/or growth velocity versus measuring LH, FSH and sex steroid levels or LHRH (or GnRH agonist) testing, or pelvic ultrasound (only in girls) or bone age in girls B2 <8 years or boys with pubertal testis (>4mL) or other signs of virilization <9y/o for detecting CPP?

No studies included

d. What is the diagnostic value of testes volume for detecting CPP changed in boys treated with gonadotoxic therapy?

No studies included

WG4; What should be done when abnormalities are identified?

1. What is the risk of secondary tumors in CAYA cancer survivors treated with GH therapy vs. no GH therapy?

a. What is the risk of secondary tumors in CAYA cancer survivors treated with GH therapy vs. no GH therapy?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
1a. Risk secondary tumors (all different types) after GH therapy (n=8 studies)	Bakker 2007	66 CAYA CNS and non-CNS tumor survivors GH Tx, n=23 No GH Tx, n=43	7.7 (2.0-17.0) since tumor treatment 4.2 (0.5-7.7) since start GH Tx	100% RT *RT details;* TBI 5.0 Gy, n=1 (1.5%) TBI 7.0 Gy, n=9 (13.6%) TBI 7.5 Gy, n=37 (56.1%) TBI 8.0 Gy, n=2 (3.0%) TBI 2x6.0 Gy, n=17 (25.8%)	GH Tx, n=2 1 osteosarcoma, 1 papillary thyroid carcinoma No GH Tx, n=1 1 schwannoma	Not reported, only descriptive outcomes	SB: unclear AB: high risk DB: unclear CF: high risk
	Brignardello 2015	49 CAYA CNS and non-CNS tumor survivors GH Tx, n=26 No GH Tx, n=23	Not reported	91.8% RT Cranial RT, n=32 (65.3%) TBI, n=10 (20.4%) Cranial RT + TBI, n=3 (6.1%)	GH Tx, n=10 5 meningioma, 3 basal cell carcinoma, 1 thoracic spinal neurinoma, 1 papillary thyroid carcinoma No GH Tx, n=9 5 meningioma, 3 basal cell carcinoma, 1 melanoma skin cancer	Hazard ratio (95% CI) GH Tx (yes vs. no) 3.74 (0.85-16.43) Adjustments Gender (male vs. female) 0.39 (0.11-1.43) Age at primary cancer (every 5 years) 1.46 (0.72-2.96) Cancer type (brain tumors vs. hematologic malignancies) 0.26 (0.05-1.33)	SB: low risk AB: low risk DB: unclear CF: high risk
	Ergun-Longmire 2006[1]	14,108 CAYA CNS and non-CNS tumor survivors GH Tx, n=361 No GH Tx, n=13,747	Not reported	Not reported	GH Tx, n=20 9 meningioma, 3 osteosarcoma, 2 glioma, 1 astrocytoma, 1 mucoepidermoid carcinoma, 1 adenocarcinoma, 1 spindle cell sarcoma, 1 sarcoma, 1 papillary thyroid carcinoma No GH Tx, n=555	Rate ratio (95% CI) GH Tx (yes vs. no) 2.15 (1.33-3.47)* Adjustments Gender (male vs. female) 0.52 (0.43-0.63)* Age at diagnosis: 1.07 (1.06-1.09)* Alkylating agent (yes vs. no)	SB: low risk AB: high risk DB: unclear CF: low risk

					69 meningioma, 486 other tumors	1.30 (1.09-1.56)* Radiation (yes vs. no) 2.88 (2.20-3.78)*	
	Leung 2002	587 CAYA non-CNS tumor survivors GH Tx, n=43 No GH Tx, n=544	15.6 (7.3-22.1) since tumor diagnosis	57.9% RT *RT details;* not reported	GH Tx, n=2 1 sclerosing sweat duct carcinoma, 1 myelodysplastic syndrome No GH Tx, n=16 No details reported	Cumulative incidence secondary tumors similar in survivors treated with GH vs. survivors not treated with GH in 11-year landmark analysis (P = 0.45 in Gray's test)	SB: low risk AB: low risk DB: unclear CF: high risk
	Mackenzie 2011	220 childhood and adult CNS tumor survivors GH Tx, n=110 No GH Tx, n=110	14.5 (11-22) follow-up	100% RT *RT details;* Cranial RT 40 Gy, n=220 (100%)	GH Tx, n=5 in childhood onset malignancy 4 meningioma, 1 malignant nerve sheath tumor No GH Tx, n=2 in childhood onset malignancy 2 meningioma	Incidence of secondary tumors similar in survivors treated with GH vs. survivors not treated with GH (P = NS)	SB: high risk AB: low risk DB: unclear CF: high risk
	Patterson 2014[1]	12,098 CAYA CNS and non-CNS tumor survivors GH Tx, n=338 No GH Tx, n=11,760	Not reported	35.4% RT *RT details;* Cranial RT <10 Gy, n=383 (3.2%) Cranial RT 10-19.9 Gy, n=1200 (9.9%) Cranial RT 20-29.9 Gy, n=1353 (11.2%) Cranial RT 30-45 Gy, n=331 (2.7%) Cranial RT >45 Gy, n=1010 (8.3%)	GH Tx, n=16 10 meningioma, 6 glioma No GH Tx, n=203 138 meningioma, 49 glioma, 16 other CNS secondary tumor	Rate ratio (95% CI) Any CNS secondary tumor, GH Tx (yes vs. no) 1.0 (0.6-1.8) Meningioma, GH Tx (yes vs. no) 0.8 (0.4-1.7) Glioma, GH Tx (yes vs. no) 1.9 (0.7-4.8) Adjustments for any CNS secondary tumor Gender (female vs. male)1.6 (1.2-2.2)* Age at primary cancer diagnosis (0-4 years vs. ≥15 years) 4.8 (2.4-9.7)* Age at primary cancer diagnosis (5-9 years vs. ≥15 years) 2.5 (1.3-4.7)* Age at primary cancer diagnosis (10-14 years vs. ≥15 years) 1.7 (0.9-3.0) CRT ≤45 Gy and <10 years between CRT and CNS neoplasm vs. no CRT, 9.5 (4.3-20.8)* CRT ≤45 Gy and 10-19 years	SB: low risk AB: unclear DB: unclear CF: low risk

					between CRT and CNS neoplasm vs. no CRT, 11.1 (6.3-19.5)* CRT ≤45 Gy and ≥20 years between CRT and CNS neoplasm vs. no CRT, 9.9 (5.5-17.5)* CRT >45 Gy and <10 years between CRT and CNS neoplasm vs. no CRT, 23.9 (10.2-55.9)* CRT >45 Gy and 10-19 years between CRT and CNS neoplasm vs. no CRT, 24.9 (13.6-45.8)* CRT >45 Gy and ≥20 years between CRT and CNS neoplasm vs. no CRT, 25.3 (14.0-46.0)* Intrathecal methotrexate (yes vs. no) 1.3 (0.8-2.0) Estrogen and/or progesterone (yes vs. no) 0.7 (0.5-1.2) Alkylating agents (yes vs. no) 0.7 (0.5-1.0)	
	Sklar 2002[1]	13,222 CAYA CNS and non-CNS tumor survivors GH Tx, n=354 No GH Tx, n=12,868	6.2 (0.4-20.6) since start GH Tx	Not reported	GH Tx, n=15 6 meningioma, 3 osteogenic sarcoma, 1 astrocytoma, 1 glioma, 1 mucoepidermoid carcinoma, 1 adenocarcinoma, 1 spindle cell sarcoma, 1 sarcoma No GH Tx, n=344 No details reported	Relative risk (95% CI) GH Tx (yes vs. no) 3.21 (1.88-5.46)* Adjustments Radiation (yes vs. no) 2.71 (1.94-3.79)* Age at diagnosis (risk/yr) 1.06 (1.02-1.08)* Alkylating agent (yes vs. no) 1.44 (1.15-1.79)* Gender (male vs. female) 0.55 (0.44-0.69)*	SB: high risk AB: unclear DB: unclear CF: low risk
	Woodmansee 2013	701 CAYA CNS and non-CNS tumor survivors GH Tx, n=646 No GH Tx, n=55	< 3 follow-up	Not reported	GH Tx, n=30 8 meningioma, 1 bone sarcoma, 1 bone cyst, 1 ALL, 1 AML, 1 lingual granular cell tumor, 1 low-grade astrocytoma, 1 low-grade glioma, 1 myelodysplastic syndrome, 1 spinal cord	Not reported, only descriptive outcomes	SB: low risk AB: high risk DB: unclear CF: high risk

					neoplasm, 1 pheochromocytoma, 1 osteochondroma, 1 neuroblastoma, 1 Ewing sarcoma, 1 malignant melanoma, 2 basal cell carcinoma, 1 hepatic adenoma, 1 glioblastoma multiforme, 1 benign nervous system neoplasm, 1 gastrointestinal stromal tumor, 1 glioblastoma, 1 thyroid carcinoma No GH Tx, n=2 1 glioblastoma multiforme, 1 breast cancer		
1b. Risk secondary tumors (all different types) after GH therapy (n=1 meta-analysis)	Tamhane 2018 (including Leung 2002, Ergun-Longmire 2006, Mackenzie 2011, Woodmansee (2x), Brignardello 2015)	n.a.	n.a.	n.a.	n.a.	Overall OR (95% CI) GH therapy (yes vs. no) 1.34 (0.92-1.96) I-squared=0.0%, p=0.896	n.a.

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-2	Serious limitations: Selection bias low in 5/8, high in 2/8, unclear in 1/8; Attrition bias low in 3/8, high in 3/8, unclear in 2/8; Detection bias unclear in 8/8; Confounding low in 3/8, high in 5/8
Consistency:	-1	Some inconsistency, 2 studies show significant effect of GH Tx, 4 studies show non-significant effects and in 2 studies the effect could not be determined
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊖⊖⊖ VERY LOW	
Conclusion:	There is a suggestion for possible significant effect of GH therapy on the occurrence of secondary tumors in childhood cancer survivors (CNS tumor and non-CNS tumor) diagnosed before the age of 25 years, but in a recent meta-analysis, no significant effect was observed. (4 studies non-significant effect, 2 studies significant effect from similar cohort, effect could not be determined in 2 studies; 1 meta-analysis non-significant effect, 41,051 participants; 1232 events; 4 multivariable analyses, 1 systematic analysis)	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; GH, growth hormone; GH Tx, growth hormone therapy; Gy, Gray; NS, not significant; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; yr, year.

*Statistically significant outcome

[1] Overlap in included patients in studies of Ergun-Longmire 2006, Patterson 2014 and Sklar 2002

2. What is the risk of tumor recurrence in CAYA cancer survivors treated with GH therapy vs. no GH therapy?

a. What is the risk of tumor recurrence in CAYA cancer survivors treated with GH therapy vs. no GH therapy?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Radiotherapy	Events (prevalence/incidence)	Effect size	Risk of bias
2. Risk tumor recurrence after GH therapy (n=8 studies)	Bakker 2007	66 CAYA CNS and non-CNS tumor survivors GH Tx, n=23 No GH Tx, n=43	7.7 (2.0-17.0) since tumor treatment 4.2 (0.5-7.7) since start GH Tx	100% RT *RT details;* TBI 5.0 Gy, n=1 (1.5%) TBI 7.0 Gy, n=9 (13.6%) TBI 7.5 Gy, n=37 (56.1%) TBI 8.0 Gy, n=2 (3.0%) TBI 2x6.0 Gy, n=17 (25.8%)	GH Tx, n=1 No GH Tx, n=6	Not reported, only descriptive outcomes	SB: unclear AB: high risk DB: unclear CF: high risk
	Corrias 1997	125 CAYA CNS tumor survivors GH Tx, n=25 No GH Tx, n=100	Not reported	100% RT RT details; Cranial RT 40-50 Gy, n=8 (32%) RT on the whole brain 34-36 Gy, posterior fossa 10-14 Gy, 10-36 Gy on the spine, n=17 (68%)	GH Tx, n=4 No GH Tx, n=18	No significant difference in tumor relapse between GH treated and non-GH treated CAYA survivors (P value not reported)	SB: unclear AB: low risk DB: unclear CF: high risk
	Leung 2002	587 CAYA non-CNS tumor survivors GH Tx, n=43 No GH Tx, n=544	15.6 (7.3-22.1) since tumor diagnosis	57.9% RT *RT details;* not reported	GH Tx, n=0 No GH Tx, n=8	Cumulative incidence tumor recurrence similar in survivors treated with GH vs. survivors not treated with GH (P = 0.70 in Gray's test)	SB: low risk AB: low risk DB: unclear CF: high risk
	Mackenzie 2011	220 CAYA CNS tumor survivors GH Tx, n=110 No GH Tx, n=110	14.5 (11-22) since tumor treatment	100% RT *RT details;* Cranial RT 40 Gy, n=220 (100%)	GH Tx, n=0 in childhood onset malignancy No GH Tx, n=4 in childhood onset malignancy	Incidence of tumor recurrence similar in survivors treated with GH vs. survivors not treated with GH (P = NS)	SB: high risk AB: low risk DB: unclear CF: high risk
	Ogilvy-Stuart 1992	368 CAYA CNS and non-CNS tumor survivors GH Tx, n=62 No GH Tx, n=306	Not reported	100% RT RT details; Cranial RT 30 Gy, n=47 of GH treated, boost 15 Gy in 36 of 47	Brain tumor recurrence: GH Tx, n=5 No GH Tx, n=42	Relative risk (95% CI) Brain tumor recurrence: GH Tx (yes vs. no) 0.82 (0.28-2.37) ALL recurrence: not reported	SB: unclear AB: high risk DB: unclear CF: low risk

				Cranial RT 24 Gy, n=15 of GH treated	ALL recurrence: GH Tx, n=1 No GH Tx, n=11		
	Packer 2001	545 CAYA CNS tumor survivors GH Tx, n=167 No GH Tx, n=375	Not reported	Not reported	Not reported	Relative risk (95% CI) progression-free survival For infants (<3 years) : GH Tx (yes vs. no) 0.710 (0.648-4.267) For older children (≥3 years): GH Tx (yes vs. no) 0.648 (0.365-1.150)	SB: low risk AB: low risk DB: unclear CF: high risk
	Sklar 2002	12,039 13,222 CAYA CNS and non-CNS tumor survivors GH Tx, n=297 No GH Tx, n=11,742	6.2 (0.4-20.6) since GH Tx	Not reported	GH Tx, n=6 No GH Tx, n=502	Relative risk (95% CI) GH Tx (yes vs. no) 0.83 (0.37-1.86)	SB: high risk AB: unclear DB: unclear CF: low risk
	Swerdlow 2000	1071 CAYA CNS tumor survivors GH Tx, n=180 No GH Tx, n=891	6.4 (maximum 20) since GH Tx	100% RT *RT details;* not reported	GH Tx, n=35 No GH Tx, n=434	Relative risk (95% CI) GH Tx (yes vs. no) 0.6 (0.4-0.9)*	SB: low risk AB: unclear DB: unclear CF: low risk

GRADE assessment		
Study design:	+4	Observational evidence
Study limitations:	-1	Some limitations: Selection bias low in 3/8, high in 2/8, unclear in 3/8; Attrition bias low in 4/8, high in 2/8, unclear in 2/8; Detection bias unclear in 8/8; Confounding low in 3/8, high in 5/8
Consistency:	0	No important inconsistency, none of the studies show increased risk of GH Tx
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding	0	No plausible confounding
Quality of evidence	⊕⊕⊕⊖ MODERATE	
Conclusion:	There is no significant effect of GH therapy on the occurrence of tumor recurrence in childhood cancer survivors (CNS tumor and non-CNS tumor) diagnosed before the age of 25 years. (7 studies non-significant effect, effect could not be determined in 1 study; 15,021 participants; 1077 events (in 7/8), unknown number of events (in 1/8); 4 multivariable analyses)	

Abbreviations: AB, attrition bias; CAYA, childhood, adult and young adult; CF, confounding; CI, confidence interval; CNS, central nervous system; DB, detection bias; GH, growth hormone; GH Tx, growth hormone therapy; Gy, Gray; NS, not significant; RT, radiotherapy; SB, selection bias; TBI, total body irradiation; yr, year.
*Statistically significant outcome