Conclusions of evidence from the systematic literature search for hypothalamic-pituitary dysfunction surveillance for CAYA cancer survivors

Who needs surveillance?	
Risk GHD in CAYA cancer survivors (CNS tumor)	**Quality of evidence**
Increased risk after *cranial radiotherapy* vs. no cranial radiotherapy	⊕⊕⊕⊕ HIGH (6,28,34,35)
Increased risk after *higher doses of cranial radiotherapy* vs. lower doses	⊕⊕⊕⊕ HIGH (36-38)
Unknown risk after different *fractionation schedules*	No studies
No significant effect after different *types of radiotherapy (proton vs. photon)*	⊕⊖⊖⊖ VERY LOW (40)
No significant effect of *spinal radiotherapy* vs. no spinal radiotherapy	⊕⊖⊖⊖ VERY LOW (35)
No significant effect of *chemotherapy* vs. no chemotherapy in addition to cranial radiotherapy	⊕⊕⊕⊕ HIGH (28,38)
Unknown risk after *chemotherapy* vs. no chemotherapy, without exposure to radiotherapy	No studies
No increased risk after *neurosurgery* vs. *no neurosurgery*	⊕⊕⊖⊖ LOW (6,28)
Increased risk after higher number of neurosurgeries vs. lower number	⊕⊕⊖⊖ LOW (34)
Increased risk in *males* vs. females	⊕⊕⊖⊖ LOW (6,38,40)
No significant effect of *neurofibromatosis type 1*	⊕⊕⊖⊖ LOW (28)
Increased risk after *hydrocephalus* or CSF shunt vs. no hydrocephalus or CSF shunt	⊕⊕⊖⊖ LOW (6,37)
Increased risk after *younger age at tumor diagnosis/treatment* vs. older age	⊕⊕⊖⊖ LOW (6,35,36,38,40)
Increased risk after *longer follow-up* vs. shorter follow-up	⊕⊕⊖⊖ LOW (6,36-38)
Increased risk in *later treatment era (i.e., 2005–2010)* vs. earlier treatment era (i.e., 1980–1996)	⊕⊕⊕⊖ MODERATE (34)
Unknown risk for different *ethnicities/races, histologies/tumor types, genetic profiles*, *age at follow-up*	No studies
Risk GHD in CAYA cancer survivors (non-CNS tumor)	**Quality of evidence**
Increased risk after *radiotherapy to the head and neck region* vs. no radiotherapy	⊕⊕⊕⊕ HIGH (41-43)
Increased risk after *higher doses of radiotherapy to the head and neck region* vs. lower doses	⊕⊕⊕⊖ MODERATE (8,44,45)
Increased risk after *total body irradiation* vs. no total body irradiation	⊕⊖⊖⊖ VERY LOW (42,43)
Unknown risk after different fractionation schedules, types of radiotherapy and spinal radiotherapy	No studies
Unknown risk after *chemotherapy* with or without exposure to radiotherapy	No studies
Unknown risk after *brain injury* vs. no brain injury	No studies

No significant effect of different *ethnicities/races*	⊕⊕⊖⊖ LOW (8)
Increased risk after *younger age at tumor diagnosis/treatment* vs. older age	⊕⊕⊖⊖ LOW (8,44,45)
Increased risk after *younger age at follow-up* vs. older age	⊕⊕⊖⊖ LOW (8,43)
Increased risk after *longer follow-up* vs. shorter follow-up	⊕⊖⊖⊖ VERY LOW (43,44)
Unknown risk in *males, different histologies/tumor types, genetic profiles*	No studies
Risk TSHD in CAYA cancer survivors (CNS tumor)	**Quality of evidence**
Increased risk after *cranial radiotherapy* vs. no cranial radiotherapy	⊕⊕⊖⊖ LOW (6)
Unknown risk after different doses of cranial radiotherapy, fractionation schedules, types of radiotherapy and spinal radiotherapy	No studies
Unknown risk after *chemotherapy* with or without exposure to radiotherapy	No studies
No significant effect after *neurosurgery* vs. *no neurosurgery*	⊕⊕⊖⊖ LOW (6)
Increased risk in *males* vs. females	⊕⊕⊖⊖ LOW (6)
No significant effect after *hydrocephalus* vs. no hydrocephalus	⊕⊕⊖⊖ LOW (6)
No significant effect of *younger age at tumor diagnosis/treatment* vs. older age	⊕⊕⊖⊖ LOW (6)
No significant effect after *longer follow-up* vs. shorter follow-up	⊕⊕⊖⊖ LOW (6)
Unknown risk for different *ethnicities/races, presence of neurofibromatosis, histologies/tumor types, genetic profiles, ages at follow-up and treatment eras*	No studies
Risk TSHD in CAYA cancer survivors (non-CNS tumor)	**Quality of evidence**
Unknown risk after *radiotherapy to the head and neck region* vs. no radiotherapy	No studies
Increased risk after *higher doses of radiotherapy to the head and neck region* vs. lower doses	⊕⊕⊕⊖ MODERATE (8)
Unknown risk after *total body irradiation*, *different fractionation schedules, types of radiotherapy, spinal radiotherapy, chemotherapy with or without exposure to radiotherapy and brain injury*	No studies
Increased risk in patients with *white ethnicity* vs. non-white ethnicity	⊕⊕⊖⊖ LOW (8)
Increased risk after *younger age at follow-up* vs. older age	⊕⊕⊖⊖ LOW (8)
No significant effect of *longer follow-up* vs. shorter follow-up	⊕⊕⊖⊖ LOW (8)
Unknown risk in *males, different histologies/tumor types, genetic profiles and ages at tumor diagnosis/treatment*	No studies
Risk LH/FSHD in CAYA cancer survivors (CNS tumor)	**Quality of evidence**
Increased risk after *cranial radiotherapy* vs. no cranial radiotherapy	⊕⊕⊖⊖ LOW (34)
Unknown risk after different doses of cranial radiotherapy, fractionation schedules, types of radiotherapy and spinal radiotherapy	No studies
Unknown risk after *chemotherapy* with or without exposure to radiotherapy	No studies
Unknown risk after *neurosurgery* vs. no neurosurgery	No studies

Unknown risk in *males, different ethnicities/races, presence of neurofibromatosis, hydrocephalus, different histologies/tumor types, genetic profiles, ages at tumor diagnosis/treatment, ages at follow-up, follow-up durations and treatment eras*	No studies
Risk LH/FSHD in CAYA cancer survivors (non-CNS tumor)	**Quality of evidence**
Unknown risk after *radiotherapy to the head and neck region* vs. no radiotherapy	No studies
Increased risk after *higher doses of radiotherapy to the head and neck region* vs. lower doses	⊕⊕⊕⊖ MODERATE (8)
Unknown risk after *total body irradiation*, *different fractionation schedules, types of radiotherapy, spinal radiotherapy, chemotherapy with or without exposure to radiotherapy and brain injury*	No studies
Increased risk in *males* vs. females	⊕⊕⊖⊖ LOW (8)
Increased risk in patients with *white ethnicity* vs. non-white ethnicity	⊕⊕⊖⊖ LOW (8)
No significant effect of *longer follow-up* vs. shorter follow-up	⊕⊕⊖⊖ LOW (8)
Unknown risk after *different histologies/tumor types, genetic profiles, ages at tumor diagnosis/treatment and ages at follow-up*	No studies
Risk ACTHD in CAYA cancer survivors (CNS tumor)	**Quality of evidence**
Increased risk after *cranial radiotherapy* vs. no cranial radiotherapy	⊕⊕⊕⊖ MODERATE (28,34)
Increased risk after *higher doses of cranial radiotherapy* vs. lower doses	⊕⊕⊖⊖ LOW (39)
Unknown risk after different *fractionation schedules*	No studies
Unknown risk after treatment with different *types of radiotherapy*	No studies
No significant effect of *spinal radiotherapy* vs. no spinal radiotherapy	⊕⊖⊖⊖ VERY LOW (39)
No increased risk of *chemotherapy* vs. no chemotherapy in addition to cranial radiotherapy	⊕⊕⊕⊖ MODERATE (28,34,39)
Unknown risk after *chemotherapy* vs. no chemotherapy, without exposure to radiotherapy	No studies
No significant effect after *neurosurgery* vs. *no neurosurgery*	⊕⊕⊖⊖ LOW (28)
Increased risk in *males* vs. females	⊕⊕⊕⊖ MODERATE (28,34,39)
No significant effect of *younger age at tumor diagnosis/treatment* vs. older age	⊕⊖⊖⊖ VERY LOW (39)
No significant effect after *longer follow-up* vs. shorter follow-up	⊕⊖⊖⊖ VERY LOW (39)
Increased risk in *later treatment era (i.e., 1997–2007)* vs. earlier treatment era (i.e., 1985–1996)	⊕⊕⊖⊖ LOW (28)
Unknown risk for *different ethnicities/races, presence of neurofibromatosis, hydrocephalus, different histologies/tumor types, genetic profiles and ages at follow-up*	No studies

Risk ACTHD in CAYA cancer survivors (non-CNS tumor)	**Quality of evidence**
Unknown risk after *radiotherapy to the head and neck region* vs. no radiotherapy	No studies
Increased risk after *higher doses of radiotherapy to the head and neck region* vs. lower doses	⊕⊕⊖⊖ LOW (8)
Unknown risk after *total body irradiation*, *different fractionation schedules, types of radiotherapy, spinal radiotherapy, chemotherapy with or without exposure to radiotherapy and brain injury*	No studies
Increased risk after *shorter follow-up* vs. longer follow-up	⊕⊕⊖⊖ LOW (8)
Unknown risk in *males, different ethnicities/races, histologies/tumor types, genetic profiles, ages at tumor diagnosis/treatment and ages at follow-up*	No studies
Risk CPP in CAYA cancer survivors (CNS tumor)	**Quality of evidence**
Increased risk after *cranial radiotherapy* vs. no cranial radiotherapy	⊕⊕⊖⊖ LOW (6)
Unknown risk after different doses of radiotherapy, fractionation schedules, types of radiotherapy and spinal radiotherapy	No studies
No increased risk of *chemotherapy* vs. no chemotherapy in addition to cranial radiotherapy	⊕⊕⊖⊖ LOW (34)
Unknown risk after *chemotherapy* vs. no chemotherapy, without exposure to radiotherapy	No studies
No significant effect after *neurosurgery* vs. *no neurosurgery*	⊕⊕⊖⊖ LOW (6)
Increased risk in *males* vs. females	⊕⊕⊖⊖ LOW (6,34)
Increased risk after *hydrocephalus* vs. no hydrocephalus	⊕⊕⊖⊖ LOW (6)
No significant effect of *younger age at tumor diagnosis/treatment* vs. older age	⊕⊕⊖⊖ LOW (6)
No significant effect after *longer follow-up* vs. shorter follow-up	⊕⊕⊖⊖ LOW (6)
Unknown risk for *different ethnicities/races, presence of neurofibromatosis, different histologies/tumor types, genetic profiles, ages at follow-up and treatment eras*	No studies
Risk CPP in childhood cancer survivors (non-CNS tumor)	**Quality of evidence**
Unknown risk after *radiotherapy to the head and neck region, different doses of radiotherapy, total body irradiation, fractionation schedules, types of radiotherapy, spinal radiotherapy, chemotherapy with or without exposure to radiotherapy and brain injury*	No studies
Unknown risk in *males, different ethnicities/races, histologies/ tumor types, genetic profiles, ages at tumor diagnosis/treatment, ages at follow-up and follow-up durations*	No studies

Abbreviations: ACTHD= adrenocorticotropic hormone deficiency, CAYA= childhood and young adult, CCP= central precocious puberty, CNS= central nervous system, GHD= growth hormone deficiency, HP= hypothalamic-pituitary, LH/FSHD= luteinizing hormone/follicle-stimulating hormone deficiency, TSHD= thyroid stimulating hormone deficiency.

When should surveillance be initiated? **At what frequency and for how long should surveillance be performed?**	
Risk <u>GHD</u> in CAYA CNS and non-CNS tumor survivors	**Quality of evidence**
• Overall average latency time ranges from <1 to 4.4 years, ranging from minimal 0.05 years to at least 15 years • Average latency time *after tumor diagnosis* ranges from 1.4 to 4.4 years, ranging from minimal 0.05 to at least 11.1 years • Average latency time *after start radiotherapy* ranges from <1 to 3.96 years, ranging from minimal 0.9 to at least 4.3 years	⊕⊕⊕⊖ MODERATE (6,35-37,45-51)
Shorter latency time after *higher doses of radiotherapy* vs. lower doses	⊕⊕⊖⊖ LOW (36,37)
Cumulative incidence increases over time which does not seem to plateau	⊕⊕⊕⊖ MODERATE (6,8,28,34,36,37,45,49,51,53,54)
Modifying factors of cumulative incidence unknown	No studies
Risk <u>TSHD</u> in CAYA CNS and non-CNS tumor survivors	**Quality of evidence**
• Overall average latency time ranges from 1.8 to 5.1 years, ranging from minimal 0.02 years to at least 11.9 years • Average latency time *after tumor diagnosis* ranges from 2.8 to 4.5 years, ranging from minimal 0.02 to at least 11.9 years	⊕⊕⊖⊖ LOW (6,47,49,52)
Modifying factors of latency time unknown	No studies
Cumulative incidence increases over time; presence of plateau can not be assessed	⊕⊕⊖⊖ LOW (6,8,34,49,52)
Modifying factors of cumulative incidence unknown	No studies
Risk <u>LH/FSHD</u> in CAYA CNS and non-CNS tumor survivors	**Quality of evidence**
Average latency time *after tumor diagnosis* ranges from 4.5 to 10.2 years, ranging from minimal 0.2 to at least 11.6 years	⊕⊖⊖⊖ VERY LOW (6,47)
Modifying factors of latency time unknown	No studies
Cumulative incidence increases over time; presence of plateau can not be assessed	⊕⊕⊖⊖ LOW (6,8,34)
Modifying factors of cumulative incidence unknown	No studies
Risk <u>ACTHD</u> in CAYA CNS and non-CNS tumor survivors	**Quality of evidence**
• Overall average latency time ranges from 2.5 to 7.0 years, ranging from minimal 0.01 to at least 8.7 years • Average latency time *after tumor diagnosis* ranges from 2.5 to 6.6 years, ranging from minimal 0.01 to at least 8.7 years • Average latency time *after the end of treatment* ranges from 2.9 to 7.0 years, ranging from minimal 0.75 to at least 7.5 years	⊕⊕⊖⊖ LOW (6,35,47,51,52)
Modifying factors of latency time unknown	No studies
Cumulative incidence increases over time; presence of plateau can not be assessed	⊕⊕⊖⊖ LOW (6,8,28,34,49,51-54)
Modifying factors of cumulative incidence unknown	No studies

Risk CPP in childhood CNS and non-CNS tumor survivors	**Quality of evidence**
Average latency time *after tumor diagnosis* ranges from 3.1 to 3.8 years, ranging from minimal 0.1 to at least 8.8 years	⊕⊕⊖⊖ LOW (6,47)
Modifying factors of latency time unknown	No studies
Cumulative incidence increases over time; plateau is not applicable	⊕⊕⊖⊖ LOW (6,34,53)
Modifying factors of cumulative incidence unknown	No studies
Order of occurrence of HP dysfunction in general	**Quality of evidence**
Order of occurrence HP dysfunction CAYA CNS and non-CNS tumor survivors	See Figure 1
Order of occurrence of HP dysfunction in CAYA CNS tumor survivors with a tumor in the sellar and suprasellar region versus brain tumors elsewhere in the brain unknown	No studies
Order of occurrence HP dysfunction in CAYA non-CNS tumor survivors after brain injury unknown	No studies
What surveillance modality should be used?	
Diagnostic value of testing modalities to detect GHD in CAYA CNS and non-CNS tumor survivors	**Quality of evidence**
Diagnostic value of IGF- I compared to GH dynamic testing to detect GHD in cancer survivors of pediatric age is moderate (sensitivity ranged from 47% to 80%, specificity ranged from 77% to 100%)	⊕⊖⊖⊖ VERY LOW (55-58)
Diagnostic value IGFBP-3 compared to GH dynamic testing to detect GHD in cancer survivors of pediatric age is moderate (sensitivity is 20%, specificity is 100%, AUC 0.617)	⊕⊖⊖⊖ VERY LOW (55,56,58)
Unknown diagnostic value of height plotted in a growth chart compared to GH dynamic testing in cancer survivors of pediatric age	No studies
Unknown diagnostic value IGF-I or IGFBP-3 to detect GHD in adult cancer survivors	No studies
Diagnostic value of testing modalities to detect TSHD in CAYA CNS and non-CNS tumor survivors	**Quality of evidence**
Correlation between nocturnal TSH surge and FT4 concentrations to detect TSHD is low	⊕⊖⊖⊖ VERY LOW (59,60)
Correlation between TSH peak after TRH test and FT4 concentrations to detect TSHD is low	⊕⊖⊖⊖ VERY LOW (59,60)
Correlation between TSH decline after TRH test and FT4 concentrations to detect TSHD is low	⊕⊖⊖⊖ VERY LOW (59,60)
Diagnostic value of testing modalities to detect LH/FSHD in CAYA CNS and non-CNS tumor survivors	**Quality of evidence**
Unknown diagnostic value of pubertal stage (according to Tanner stage), bone age, LH, FSH and sex steroids measurements to detect LH/FSHD	No studies
Unknown interobserver variability and likelihood performance for defining pubertal stages (according to Tanner stage) among health care providers from different specialities	No studies

Diagnostic value of testing modalities to detect ACTHD in CAYA CNS and non-CNS tumor survivors	**Quality of evidence**
The agreement between morning cortisol and low dose-ACTH test to detect ACTHD in cancer survivors of pediatric age is poor (Agreement 63%, kappa 0.25)	⊕⊖⊖⊖ VERY LOW (61)
Diagnostic value of morning plasma cortisol versus dynamic testing (preferably ITT) for detecting ACTHD in adult cancer survivors	Existing guidelines
Influence of steroid use on the testing results of the hypothalamic-pituitary-adrenal axis	No studies
Confounders which bias the testing results of the hypothalamic-pituitary-adrenal axis	Expert opinion
Diagnostic value of testing modalities to detect CPP in childhood CNS and non-CNS tumor survivors	**Quality of evidence**
Unknown diagnostic value of pubertal stage and/or height velocity compared to LH, FSH, sex steroids, LHRH/GnRH testing, pelvic ultrasound and/or bone age	No studies
Unknown diagnostic value of testes volume in boys treated with gonadotoxic therapy	No studies
What should be done when abnormalities are identified?	
Potential harms of treatment of HP dysfunction in CAYA cancer survivors	**Quality of evidence**
Suggestion for possible significant effect of GH therapy on the occurrence of secondary neoplasms	⊕⊖⊖⊖ VERY LOW (62-69)
No significant effect of GH therapy on the occurrence of tumor recurrence	⊕⊕⊕⊖ MODERATE (62,65,66,68,70-73)
Potential benefits of treatment of HP dysfunction in CAYA cancer survivors	**Quality of evidence**
Improvement of final adult height, bone mineral density and cardiovascular and metabolic health, and quality of life (including fatigue) after treatment of GHD	Expert opinion, existing guidelines (74-79)
Improvement of final adult height, metabolic health and quality of life (including fatigue) after treatment of TSHD	Expert opinion, existing guidelines (75,80)
Adequate pubertal development and maintenance of secondary sex characteristics, fertility, bone mineral density, final adult height, psychological well-being (including sexual health) / quality of life after treatment of LH/FSHD	Expert opinion, existing guidelines (75,81,82)
Prevention of adrenal crisis, and possibly mortality, improvement of fatigue and quality of life after treatment of ACTHD	Expert opinion, existing guidelines (75)
Improvement of final adult height and psychological well-being/quality of life after treatment of CPP	Expert opinion, existing guidelines (83)

Abbreviations: ACTHD= adrenocorticotropic hormone deficiency, CAYA= childhood and young adult, CCP= central precocious puberty, CNS= central nervous system, FT4= free thyroxine, FSH= follicle stimulating hormone, GHD= growth hormone deficiency, HP= hypothalamic-pituitary, IGF-I= insulin-like growth factor, LH= luteinizing hormone, SDS= standard deviation score, LH/FSHD= luteinizing hormone/follicle-stimulating hormone deficiency, TRH= thyrotropin releasing hormone, TSH= thyroid stimulating hormone, TSHD= thyroid stimulating hormone deficiency.