Evidence tables hypothalamic-pituitary dysfunction

WG1; Who needs surveillance?

WG1: Who needs screening for hypothalamic-pituitary dysfunction?				
GT Armstrong, Survival and long-term health and cognitive outcomes after low-grade glioma, Neuro-Oncology (2011)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort study Treatment era: Between 1985-2007 Patients were stratified by treatment eras (1985-1996, 1997-2007) Follow-up: Mean follow-up (from diagnosis) in n=240 5-year survivors: 10 ys (range 5-21.5)	Study population: n=361 (≤21 ys at diagnosis) Endocrine outcomes reported for a subpopulation of n=240 5-year survivors Male n=137 (57.1%) Female n=103 (42.9%) Primary cancer diagnosis: Low-grade glioma (grade 1+2 astrocytoma, incl. optic pathway glioma) Age at primary cancer diagnosis: 5-year survivors: 0-4 ys: n=82 (34.2%) 5-9 ys: n=80 (33.3%) 10-20 ys: n=78 (32.5%) Age at follow-up: 5-year survivors: median age at last follow-up 18.3 ys (range 5.6-29.9)	5-year survivors (n=240) Observation only: n=4 (1.7%) Surgery only: n=110 (45.8%) RT only: n=6 (2.5%) Chemotherapy only: n=4 (1.7%) Any surgery + RT: n=67 (27.9%) Any surgery + chemotherapy: n=11 (4.6%) RT + Chemotherapy: n=7 (2.9% Any surgery + RT + Chemotherapy: n=31 (12.9%) *RT details*	Definitions • Endocrine diagnoses were based on random or dynamic testing including spontaneous overnight secretion of TSH, TRH stimulation test, overnight metyrapone, ITT, low-dose ACTH test, GH stimulation test; no details on definitions or cut-off values • Unclear, if "Hypothyroidism" refers to central or peripheral hypothyroidism Prevalence survivors with HP dysfunction: *At diagnosis* Not reported *At (last) follow-up* Cumulative incidences at 15yrs from diagnosis (%): GHD 29.0%, ACTH deficiency 25.7% Hazard ratios for HP-dysfunction, adjustments not reported (Cox's proportional hazards model): **GHD:** Chemotherapy (yes vs. no) HR 0.8 (95% CI 0.4-1.4) Radiotherapy (yes vs. no) HR 3.9 (95% CI 1.9-8.2)* Surgery (GTR vs no GTR) HR 0.2 (95% CI 0.1-0.6)*	Strengths Large cohort, long follow-up period, calculation of hazard ratios according to various risk factors/ predictor variables Limitations Endocrine outcomes not rigorously defined. No information of hypothyroidism refers to primary or secondary origin, and therefore excluded as result. Radiotherapy defined as yes/no instead of specific dose. Risk of bias A. Selection bias: unclear how many patients were included in the original cohort of survivors (240 of 361=66.5%) were 5-yr survivors). B. Attrition bias: unclear for how many survivors follow-up data was complete. 'not all patients

		All had conventional focal RT	Tumor location (Diencephalon vs. other) HR 3.5 (1.6-7.7)* NF-1 (yes vs. no) HR 1.1 (95% CI 0.5-2.1) **ACTHD:** Sex (Male vs. female) HR 1.6 (95% CI 0.9-3.0) Chemotherapy (yes vs. no) HR 0.8 (95% CI 0.4-1.5) Radiotherapy (yes vs. no) HR 4.6 (95% CI 2.1-10.0)* Surgery (GTR vs. no GTR) HR 0.4 (95% CI 0.2-1.2) Tumor location (Diencephalon vs. other) HR 3.4 (95% CI 1.6-7.3)* Treatment era (1985-1996 vs. 1997-2007) HR 0.5 (95% CI 0.3-0.9)	received the same screening and detection measures.' C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. D. Confounding: low risk, analyses were adjusted for important confounding factors.
Conclusion • In a study of **240 5-year low grade glioma (LGG)** survivors (mean follow-up time of 10 years), treated with several modalities, **diecenphalic tumor location** and **radiotherapy** were significantly associated with an increased risk for the development of GHD and ACTHD compared to survivors who had other tumor location or did not receive radiotherapy, in multiple regression analysis. **Gross total resection (GTR)** was a protective factor for the development of GHD, compared to patients who had no GTR. • Chemotherapy and presence of NF-1 were not significantly associated with the development of GHD in LGG survivors, in multiple regression analysis. • Sex, chemotherapy, surgery and treatment era were not significantly associated with the development of ACTHD in LGG survivors, in multiple regression analysis. • The outcomes on hypothyroidism are not reported, because no clear distinction between central or primary origin of hypothyroidism was stated.				

WG1: Who needs screening for hypothalamic-pituitary dysfunction?				
BMD Brennan, Growth hormone status in adults treated for acute lymphoblastic leukaemia in childhood, Clinical Endocrinology (1998)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Patient series including a healthy control group (medical students) with cross-sectional, one time measurement of GH deficiency Treatment era: Not reported Follow-up: Not reported	Study population: 32 adult survivors of ALL who underwent CRT Male n=16 (50.0%) Female n=16 (50.0%) Control population: N=35 healthy controls, medical students Primary cancer diagnosis: ALL Age at primary cancer diagnosis: median 6.9 ys (range 1.7-16.0) Age at follow-up: ALL survivors: Median 23 ys (range 18.8-33) Controls Median 21.6 ys (range 21-25 y)	All survivors received cranial RT and varying chemotherapy regimens RT details: - 18 Gy (n=11, 34.4%) - 19-25 Gy (n=21, 65.6%) N=4 also received 24 Gy spinal RT All had conventional RT	Definitions Growth hormone status was defined using two agents (Insulin and Arginine) administered on two different mornings. Survivors were categorized into three groups: -GH status group 1 (n=9): peak GH to both tests <9 mU/l -GH status group 2 (n=12): peak GH both tests <20 mU/l and one or both >9 mU/l -GH status group 3 (n=11); peak GH to one or both tests >20 mU/l Group 1 was labelled as severely 'GH deficient', group 2 as 'GH insufficient' (although this was not clearly defined in methods section). Prevalence cancer survivors with GH deficiency: *At diagnosis:* none had received any hormone replacement therapy *At follow-up/evaluation:* 9 (28.1%) survivors were labelled as 'GH deficient' and 12 (37.5%) survivors as 'GH insufficient' Risk factor analysis for GH peak response to ITT, adjustments not reported (multivariable linear regression model after log_{10} transformation of the GH peak response): Age at RT, RR not reported, p=0.41 RT dose (18 Gy vs. 24/25 Gy), RR not reported, p=0.11	Strengths Healthy control group Limitations -Criteria to determine eligibility of ALL patients from underlying treated cohort of ALL patients not reported (selection bias) -Control group is younger than the ALL group of interest even though it is labelled as being "age matched" in the abstract. This is not reported in the Methods section -Small dose range (18-25 Gy) in small sample so not surprising that CRT dose is not showing up in a multivariable model. -Outcomes of multivariable analyses inadequately reported Risk of bias A. Selection bias: unclear how many patients were included in the original cohort of survivors B. Attrition bias: low risk, all survivors underwent dynamic GH testing C. Detection bias: unclear if the outcome assessors were blinded

			Time since RT, RR not reported, p=<0.01*	for important determinants related to the outcome. D. Confounding: high risk, no adjustment of follow-up in analysis.
Conclusion • In a study of **32 ALL survivors** (mean follow-up time unknown), treated with cranial radiotherapy and varying chemotherapy regimens, **time since cranial radiotherapy** was significantly associated with an increased risk for low peak GH response to ITT, in multivariable linear regression analysis. • Age at cranial radiotherapy and radiotherapy dose were not significantly associated with an increased risk for low peak GH response to ITT in ALL survivors, in multivariable linear regression analysis.				

WG1: Who needs screening for hypothalamic-pituitary dysfunction?				
W. Chemaitilly, Anterior Hypopituitarism in Adult Survivors of Childhood Cancers Treated With Cranial Radiotherapy: A Report From the St Jude Lifetime Cohort Study, JCO (2015)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort-study (with prospective follow-up) Treatment era: Unknown Follow-up: Mean 27.3 ys (range 10.8-47.7)	Study population: 748 childhood cancer survivors treated with cranial radiotherapy, age ≥18yrs, without direct mass effect of tumor on hypothalamus or pituitary. Male n=394 (52.7%) Female n=354 (47.3%) Primary cancer diagnosis: Leukemia,n=543 (72.6%) Lymphoma, n=33 (4.4%) CNS tumor, n=90 (12.0%) Embryonal, n=30 (4.0%) Bone and soft tissue sarcoma, n=38 (5.1%) Carcinoma, n=11 (1.5%) Other, n=3 (0.4%) Age at treatment: Mean 7.6 ys (range 0.1-26.0 ys) at start CRT Age at follow-up: 34.2 yrs (range 19.4-59.6 ys)	CRT: n=748 (total study cohort) RT details 1-14.9 Gy, n=40 (5.3%) 15-21.9 Gy, n=208 (27.8%) 22-29.9 Gy, n=316 (42.3%) 30-39.9 Gy, n=31 (4.1%) ≥40 Gy, n=153 (20.5%) All had conventional RT Unknown (but likely that) other tumor treatments were given.	Definitions: GHD: previously diagnosed or IGF-1 z-scores <-2 LH/FSHD: previously diagnosed or total testosterone <200ng/dL 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 TSHD: previously diagnosed or FT4 <0.9 ng/dL coincided with TSH <4 mIU/L ACTHD: previously diagnosed or 08.00 AM cortisol <5µg/dL Prevalence cancer survivors with HP dysfunction: *At diagnosis:* not reported *Point prevalence at (last) follow-up:* GHD (assessed in n=748): n=348 (46.5%) LH/FSHD (assessed in n=731): n=79 (10.8%) TSHD (assessed in n=743): n=56 (7.5%) ACTHD (assessed in n=743): n=30 (4.0%) Risk factor analysis for HP dysfunction, adjustments not reported (multivariable logistic regression model): *GHD:* Ethnicity (nonwhite vs. white) OR 0.66 (95% CI 04-1.1) Age at CRT (5-9yrs vs. <5yrs) OR 0.73 (95% CI 0.5-1.0) Age at CRT (10-14yrs vs. <5yrs) OR 0.63 (95% CI 0.4-0.9)* Age at CRT (≥15yrs vs. <5yrs) OR 0.43 (95% CI 0.2-0.7)* Age at SJLIFE (≥26-35yrs vs. <26yrs) OR 0.51 (95% CI 0.6-13) Age at SJLIFE (≥36 vs. <26yrs) OR 0.51 (95% CI 0.3-0.9)*	Strengths Large cohort with systematic screening and long follow-up. Study uncovers many previously undetected HP dysfunction. Limitations No dynamic testing to establish diagnosis of GHD and ACTHD Dose cranial radiotherapy based on maximum tumor prescribed dose to the brain Risk of bias A. Selection bias: high risk, 748 out of 1175 (63.7%) eligible survivors were included in the study. B. Attrition bias: low risk, almost all survivors (97.7%) underwent endocrine testing for all four HP-axes C. Detection bias: unclear if the outcome assessors were blinded for

			CRT dose (22-29.9 Gy vs. ≤21.9 Gy) OR 1.99 (95% CI 1.4-2.9)* CRT dose (≥30 Gy vs. ≤21.9 Gy) OR 0.91 (95% CI 0.6-1.4) Adjusted BMI (25-29.9 kg/m^2 vs <25 kg/m^2) OR 0.69 (95% CI 0.5-1.0) Adjusted BMI (≥30 kg/m^2 vs. <25 kg/m^2) OR 1.00 (95% CI 0.7-1.5) *LH/FSHD:* Sex (female vs. male) OR 0.58 (95% CI 0.3-0.97)* Ethnicity (nonwhite vs. white) OR 0.28 (95% CI 0.1-0.8)* Time since CRT (15-19yrs vs. <15yrs) OR 0.38 (95% CI 0.1-1.1) Time since CRT (20-24yrs vs. <15yrs) OR 0.77 (95% CI 0.3-2.0) Time since CRT (≥25yrs vs. <15yrs) OR 0.67 (95% CI 0.3-1.7) CRT dose (22-29.9 Gy vs. ≤21.9 Gy) OR 3.02 (95% CI 1.3-7.0)* CRT dose (≥30 Gy vs. ≤21.9 Gy) OR 9.71 (95% CI 4.2-22.3)* Adjusted BMI (25-29.9 kg/m^2 vs. BMI <25 kg/m^2) OR 0.54, 95% CI 0.2-1.2, p=0.14) Adjusted BMI (≥30 kg/m^2 vs. BMI <25 kg/m^2) OR 2.03, (95% CI 1.1-3.9)* *TSHD:* Ethnicity (nonwhite vs. white) OR 0.16 (95% CI 0.04-0.7)* Age at SJLIFE (26-35yrs vs. <26yrs) OR 0.37, 95% CI 0.2-0.8)* Age at SJLIFE (≥36yrs vs. <26yrs) OR 0.20 (95% CI 0.1-0.6)* Time since CRT (15-19yrs vs. <15yrs) OR 0.70 (95% CI 0.2-2.0) Time since CRT (20-24yrs vs. <15yrs) OR 0.94 (95% CI 0.3-2.7) Time since CRT (≥25yrs vs. <15yrs) OR 0.88 (95% CI 0.3-2.9) CRT dose (22-29.9 Gy vs. ≤21.9 Gy) OR 1.57 (95% CI 0.7-3.7) CRT dose (≥30 Gy vs. ≤21.9 Gy) OR 4.46 (95% CI 2.1-9.7)* Adjusted BMI (25-29.9 kg/m^2 vs. BMI <25 kg/m^2) OR 0.53 (95% CI 0.2-1.3) Adjusted BMI (≥30 kg/m^2 vs. BMI <25 kg/m^2) OR 1.35 (95% CI 0.7-2.7) *ACTHD:* Time since CRT (15-19yrs vs. <15yrs) OR 0.53 (95% CI 0.2-1.5) Time since CRT (20-24yrs vs. <15yrs) OR 0.41 (95% CI 0.1-1.2)	important determinants related to the outcome. D. Confounding: low risk, analyses were adjusted for important confounding factors.

			Time since CRT (≥25 yrs vs. <15 yrs) OR 0.11 (95% CI 0.03-0.4)* CRT dose (≥22-29.9 Gy vs ≤ 21.9 Gy) OR 2.93 (95% CI 0.7-12.5) CRT dose (≥30 Gy vs ≤ 21.9 Gy) OR 8.81 (95% CI 2.5-30.9)*	

Conclusion

- In a study of **748 childhood cancer survivors** (mean follow-up time of 27.3 years), treated with cranial radiotherapy:
  - **Age <10 yrs at CRT, age <36yrs at SJLIFE evaluation and CRT dose ≥22 Gy** were significantly associated with an increased risk for the development of GHD in multiple regression analysis. Ethnicity, time since CRT and adjusted BMI were not significantly associated with the development of GHD in survivors treated with CRT, in multiple regression analysis.
  - **Male sex, white race, CRT dose ≥22 Gy and adjusted BMI ≥30kg/m^2** were significantly associated with an increased risk for the development of LH/FSHD in multiple regression analysis. Time since CRT was not significantly associated with the development of LH/FSHD in survivors treated with CRT, in multiple regression analysis.
  - **White race, age <26yrs at SJLIFE evaluation and CRT dose ≥30 Gy** were significantly associated with an increased risk for the development of TSHD in multiple regression analysis. Time since CRT and adjusted BMI were not significantly associated with the development of TSHD in survivors treated with CRT, in multiple regression analysis.
  - **Time since CRT <15 years and CRT dose ≥30 Gy** were significantly associated with an increased risk for the development of ACTHD in multiple regression analysis.

WG1: Who needs screening for hypothalamic-pituitary dysfunction?				
PE Clayton, Dose dependency of time of onset radiation-induced growth hormone deficiency, The Journal of Pediatrics (1991)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort study, single center; cross sectional follow-up data Treatment era: Not reported Follow-up: Median 4.3 yrs (0.2-18.9 yrs)	Study population: 82 survivors of childhood malignancy who received cranial/craniospinal RT for a childhood brain tumor or leukemia/other tumor (prophylactic RT) Male n=52 (63.4%) Female n=30 (36%.6) Primary cancer diagnosis: Brain tumor not involving the HPA, n=66 (80.5%) Leukemia, n=16 (19.5%) Age at treatment: Median 6.2 yrs (range 1-16.6 yrs) Age at follow-up: Not reported. (median can be estimated from median age at RT and median follow-up time to be 6.2+4.3=10.5 yrs	CRT n=24 (29.3%) CSI n=58 (70.7%) RT details CRT for brain tumor (n=66): doses of 27 to 45 Gy Prophylactic cranio(spinal) RT for CNS leukemia (n=16): 16 at doses of 24 or 25 Gy in 10-12 fractions (n=12 had CRT, n=4 had CSI) Hypothalamic pituitary RT dose Range 27-47.5 Gy <30 Gy, n=46 (56.1%) ≥30 Gy, n=36 (43.9%) All had conventional RT Surgery, TBI and/or chemotherapy regimens are not reported	Definitions ITT showing peak GH concentration of >15 mU/L during insulin-induced hypoglycemia was defined as normal, (after logarithmic transformation). For multivariable analysis, GH concentrations as continuous variables (log peak GH concentration) were used. Prevalence cancer survivors with GH deficiency: *At diagnosis:* not reported *At (last) follow-up (Cave number of abnormal tests reported, not patients having GHD)* GHD: incidence 74% of all tests *During interval 3-5 yrs post-cancer diagnosis:* *Cave number of abnormal tests reported, not patients having GHD* <30 Gy: 63.2% (24/38) ≥30 Gy: 100% (16/16) *During interval >5 yrs post-cancer diagnosis:* <30 Gy: 85% (22/26) ≥30 Gy: 84% (21/25) -subgroup >35Gy: 100% Risk factor analysis for GHD, adjustments not reported (stepwise multivariable linear regression model): Age at irradiation: RR not reported, NS	Strengths -Original GH testing results retrieved and used for analysis -Hypothalamic pituitary dose calculated Limitations -Calendar period not reported -Surgery, chemotherapy, TBI not reported/analyzed -Protocol for testing ITT and methods to ensure adequate follow-up/tracing not reported -Not clear why some patients had 1 test and others had >1 -Not clear how follow-up time, loss to follow-up, and vital status are distributed by radiation dose -Not clear which and how many patients had recurrences nor on treatment or survival characteristics -Multivariable model parameters not shown, except for p-values Additional remarks -1 of 38 patients with >1 test and who showed abnormal response

			Time since radiotherapy: RR not reported, p=0.0007* Hypothalamic pituitary axis dose: RR not reported, p=0.03*	later had a borderline normal GH response -74% of all ITT tests showed GH deficiency <u>Risk of bias</u> A. Selection bias: unclear how many patients were included in the original cohort of survivors B. Attrition bias: high risk, one ITT performed in 44 patients, >1 ITT performed in 38 patients C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. D. Confounding: high risk, limited multivariable analysis performed, limited information on outcomes of multivariable analysis (only p-value known)
<u>Conclusion</u> • In a study of **82 brain tumor or leukemia survivors** (median follow-up time of 4.3 yrs), treated with cranial radiotherapy and/or craniospinal radiotherapy, **time since cranial radiotherapy** and **hypothalamic pituitary RT dose** were significantly associated with an increased risk for <u>low peak GH response to ITT</u>, in multivariable linear regression analysis. • Age at cranial radiotherapy was <u>not</u> significantly associated with an increased risk for low peak GH response to ITT, in multivariable linear regression analysis.				

WG1: Who needs screening for hypothalamic-pituitary dysfunction?				
NL Davis, Growth hormone deficiency after childhood bone marrow transplantation with total body irradiation: interaction with adiposity and age, Clinical Endocrinology (2015)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Single center Cross sectional case control study Treatment era: 1988-2004 Follow-up: Median 8.8 yr (range 1.4 – 19.2)	Study population: 22 survivors of hematological malignancy, treated with BMT/TBI Male n=12 (54.5%) Female n=10 (45.5%) 19 healthy controls with short stature (age range 7.8-20.1 yrs) Primary cancer diagnosis: AML, n=16 (72.7%) ALL, n=4 (18.2%) CML, n=2 (9.1%) Age at primary cancer diagnosis: Not reported Age at follow-up: Males range 6-24.5yrs Females range 1.4-19.2 yrs All patients had a clinical indication for GH testing (poor height velocity (n=8), end of growth testing in	All received conditioning with chemotherapy and TBI. TBI 14.4 Gy in eight fractions, n=20 10 Gy in single fraction, n=2 Additional CNS boost of 6 Gy, n=2, additional CNS prophylactic RT, 12-18 Gy, n=2 All had conventional RT Chemotherapy: Cyclophosphamide 60mg/kg and Campath (1mg/kg) Matched related donor n=11 Matched unrelated donor 10 Stem cell unrelated donor n=1 Other treatment: Oral prednisolone for graft versus host disease (n=10) topical steroids (n=3)	Definition of GHD: ITT peak GH cut off adult: 3μg/l, child 7μg/l For multivariable analysis, GH concentrations were analyzed as GH concentration area under the curve. Prevalence cancer survivors with HP dysfunction: *At diagnosis:* GHD: not reported, n=8 previously treated with GH *At last follow-up:* 18 of 22 (81.8%) had GHD according to criteria. At the end of growth (using adult cut off 3μg/l) 7 of 11 survivors and 1 of 9 with short stature had persistent GHD on retesting. (p=0.025) Risk factor analysis for GH area under the curve concentrations, adjustments not reported (multiple linear regression): Fat mass index, RR not reported, p<0.001* BMT/TBI, RR not reported, p<0.001* Age at study, RR not reported, NS Pubertal status, RR not reported, NS Time since BMT, RR not reported, NS	Strengths -Comprehensive measurement of GH profiles and levels -One of the few studies that assess GH secretion after BMT/TBI Limitations -Small number in some groups -Lack of information about time of surveillance after BMT/TBI -Lack of information on chemotherapy given at disease diagnosis as well as variations in conditioning treatment. Additional remarks -Methods refer to CNS boost, results to CRT (CNS includes the spine, CRT brain only) -Five participants were on thyroxine replacement therapy for primary hypothyroidism -All pubertal/postpubertal female took estrogen, and four of eight male on testosterone -Loss of pituitary reserves over time means need for ongoing surveillance

	those previously treated with GH (n=11), and symptoms of GHD (n=3))			Risk of bias A. Selection bias: high risk, 22 out of 32 (68.8%) eligible survivors were included in the study. B. Attrition bias: low risk, all survivors underwent dynamic GH testing C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. / high, clinical indication for GH testing D. Confounding: high risk, limited multivariable analysis performed, not only survivors included in analysis
Conclusion • In a study of **22 survivors of hematological malignancies** (median follow-up time of 8.8 yrs), treated with BMT/TBI and **short stature control patients**, **fat mass index and BMT/TBI** were significantly associated with GH AUC concentrations in multivariable logistic regression analysis. • Age, pubertal status and time since BMT were not significantly associated with GH AUC concentrations in multivariable logistic regression analysis.				

WG1: Who needs screening for hypothalamic-pituitary dysfunction?				
HW Gan, Neuroendocrine Morbidity After Pediatric Optic Gliomas: A Longitudinal Analysis of 166 Children Over 30 Years, JCEM 2015				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort study, single center Treatment era: Between 1980-2010 Patients were stratified by treatment eras (1980-1996, 1997-2004, 2005-2010) Follow-up: Median follow-up 8.3yr (range 0.04-26.8)	General 166 survivors <16yrs at primary diagnosis Male n=76 (45.8%) Female n=90 (54.2%) Primary cancer diagnosis: All had low grade glioma affecting the optic pathway, hypothalamus or suprasellar area (OP/HSGs) Juvenile pilocytic astrocytoma, n=40 (24.1%) Subependymal giant cell astrocytoma, n=2 (1.2%) Diffuse fibrillary astrocytoma, n=6 (3.6%) Pilomyxoid astrocytoma, n=3 (1.8%) Grade 1 not otherwise specified, n=9 (5.4%) Grade 2 not otherwise specified, n=3 (1.8%) No biopsy/histology, n=103 (62.0%) Age at primary cancer diagnosis:	Observation only: N=38 (22.9%) Surgery only: N=21 (12.7%) RT only N=15 (9.0%) Chemotherapy only N=20 (12.0%) Any surgery + RT N=31 (18.7%) Any surgery + chemotherapy N=18 (10.8%) RT + Chemotherapy N=6 (3.6%) Any surgery + RT + Chemotherapy N=17 (10.2%)	Definitions -GHD: serum GH peak concentration <7 ng/ml on an insulin tolerance or glucagon stimulation test -ACTHD: serum cortisol peak concentration <500nmol/L on an ITT OR short synacthen or low-dose synacthen test -TSHD: Low serum free thyroxine (fT4) concentrations in the presence of an inappropriately normal/ low TSH, based on age-appropriate reference ranges -LH/FSHD: Boys: Testicular volume <4mL at age 14 years OR failure to progress through puberty after normal onset (pubertal arrest) Girls: Tanner breast stage B1 at age 13 years OR pubertal arrest OR primary amenorrhea at age 16 years with Delayed bone age, undetectable serum concentrations of gonadal steroids (testosterone/ oestradiol) AND/OR poor or absent serum gonadotropin responses to GnRH stimulation testing -CPP: Boys: Testicular volume ≥4 ml prior to age 9 years Girls: Tanner breast stage B2 prior to age 8 years and advanced bone age, pubertal serum concentrations of gonadal steroids (testosterone/ oestradiol) AND/OR pubertal serum gonadotropin responses to GnRH stimulation testing (2.5 µg/kg GnRH) Prevalence cancer survivors with HP dysfunction: *At diagnosis* GHD: n=1 (0.6%) TSHD: n=2 (1.2%) ACTHD: n=1 (0.6%) LH/FSHD (assessed in 7): n=1 (14.3%) CPP (assessed in 123): n=14 (11.4%) *At last follow-up*	Strengths -Large cohort with long-follow up period. Complete and thorough endocrine evaluations. Limitations -Authors assumed normal endocrine function without clinical or biochemical evidence to the contrary. -No subanalysis performed on individual treatment risks (e.g. radiotherapy dose or degree of surgical resection). Risk of bias A. Selection bias: low risk, 166 out of 203 (81.8%) eligible survivors were included in the study. B. Attrition bias: unclear for how many survivors follow-up data was complete. 'Normal endocrine function was assumed without clinical or biochemical evidence to the contrary." C. Detection bias: unclear if the outcome assessors were

	Median 4.9yr (range 0.2-15.4 yrs) <u>Age at follow-up:</u> Median 15.5yr (range 2.4-37.4 yrs)	*RT details:* Focal RT to total dose 48-55 Gy (25-30 fractions) All had conventional RT	GHD: n=67 (40.3%) TSHD: n=22 (13.3%) ACTHD: n=22 (13.3%) LH/FSHD (assessed in 103): n=21/103 (20.4%) CPP (assessed in 123): n=32 (26.0%) <u>Risk factor analysis for HP dysfunction, adjustments not reported (multivariable Cox regression model):</u> *GHD:* Any radiation therapy (yes vs. no), HR 5.76 (95% CI 2.93-11.23)* Treatment era (1997-2004 vs. 1980-1996), HR 0.89 (95% CI 0.50-1.58) Treatment era (2005-2010 vs. 1980-1996), HR 2.48 (95% CI 1.29-4.79)* Primary radiotherapy (yes vs. no), HR 2.48 (95% CI 1.36-4.52)* Number of surgeries, HR 1.09 (95% CI 1.04-1.14)* *TSHD:* Hypothalamic involvement (yes vs. no), HR 7.18 (95% CI 2.41-21.38)* *ACTHD:* Diencephalic syndrome (yes vs. no), HR 15.72 (95% CI 4.38-56.39)* Primary radiotherapy (yes vs. no), HR 5.16 (95% CI 2.12-12.57)* Sex (female vs. male), HR 0.30 (95% CI 0.12-0.74)* Any chemotherapy (yes vs. no), HR 0.30 (0.10-0.92)* *LH/FSHD:* Hypothalamic involvement (yes vs. no) HR 5.09 (95% CI 1.95-13.31)* Primary radiotherapy (yes vs. no), HR 3.27 (95% CI 1.35-7.94)* *CPP* Hypothalamic involvement (yes vs. no), HR 4.42 (95% CI 1.97-9.92)* Sex (female vs. male), HR 0.43 (95% CI 0.21-0.90)* Any chemotherapy (yes vs. no), HR 0.42 (95% CI 0.20-0.90)*	blinded for important determinants related to the outcome. D. Confounding: low risk, extended multivariable analysis
<u>Conclusion</u> • In a study of **166 low grade glioma survivors** (median follow-up time of 8.3 years), ○ **Any radiation therapy, treatment era after 2005, primary radiotherapy and number of surgeries** were significantly associated with an increased risk for the development of <u>GHD</u> in multivariable cox regression analysis. ○ **Hypothalamic involvement** was significantly associated with an increased risk for the development of <u>TSHD</u> in multivariable cox regression analysis. ○ **Diencephalic syndrome primary radiotherapy, male sex** and **no chemotherapy** were significantly associated with an increased risk for the development of <u>ACTHD</u> in multivariable cox regression analysis.				

- **Hypothalamic involvement** and **primary radiotherapy** were significantly associated with an increased risk for the development of LH/FSHD in multivariable cox regression analysis.
- **Hypothalamic involvement, male sex** and **no chemotherapy**, were significantly associated with an increased risk for the development of CPP in multivariable cox regression analysis.

WG1: Who needs screening for hypothalamic-pituitary disorders?				
JG Gurney, Metabolic Syndrome and Growth Hormone Deficiency in Adult Survivors of Childhood Acute Lymphoblastic Leukemia, Cancer (2006)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Cross sectional study design Treatment era: 1970-1986 Follow-up: Mean 24.6 yrs (SD 4.8)	Study population: 75 childhood ALL survivors of CCSS cohort Male n=31 (41.3%) Female n=44 (58.7%) 132 controls from population based group (age 20-45 years), NHANES study Primary cancer diagnosis: All had ALL, n=75 (100%) Age at primary cancer diagnosis: Mean 5.6 yrs (SD 4.3) Age at follow-up: Mean 30.2 (SD 7.1)	Radiotherapy N=50 (66.7%) RT details *RT dose* <24 Gy, n=25 (33.3%) >24 Gy, n=25 (33.3%) *Radiation field* Brain, n=50 (66.7%) Spine, n=17 (22.7%) Pelvis or testes, n=11 (14.7%) Total body, n=5 (6.7%) All had conventional RT Chemotherapy N=75 (100%) Actinomycin, n=1 (1.3%) Cytoxan, n=33 (44.0%) Ara-C, n=33 (44.0%) Daunorubicin, n=21 (28.0%) Dexamethasone, n=11 (14.7%) Doxorubicin, n=21 (28.0%) Isofosfomide, n=1 (1.3%) L-aspariginase, n=72(96.0%) 6-mercaptopurine, n=69 (92.0%) Methotrexate, n=75 (100%) Prednisone, n=74 (98.7%)	Definition of GHD: GH peak after GHRH/arginine dynamic testing: -Normal GH: GH peak >16.5 µg/L -GH-insufficient: GH peak 9-16.5 µg/L -GH-deficient: GH peak <9 µg/L For multivariable analysis, mean peak GH was used. Prevalence cancer survivors with HP disorders: *At diagnosis:* Not reported *At (last) follow-up:* Hypogonadism: n=2 (2.7%, unknown if central/gonadal origin), 15 females on estrogen (all birth control), 1 male on testosterone. GHD (evaluated in 72): n=33 (46%) GH-insufficiency (evaluated in 72): n=13 (18.1%) 5 patients without CRT, had GHD Risk factor analysis for mean peak GH concentrations, adjusted for BMI, sex, age at diagnosis and age at study date (multivariable linear regression model): Cranial radiotherapy (yes vs. no), RR unknown, 95% CI -31.5 to -64.8)* BMI, RR 0.62 (95% CI -0.16 to -1.08)* No data reported on parameters sex, age at diagnosis and age at study.	Strengths -Control group included Limitations -Different RT doses are not analyzed separately Additional remarks -T4 and TSH are determined but data are not shown Risk of bias A. Selection bias: high risk, 75 out of 207 (36.2%) eligible survivors were included in the study. B. Attrition bias: low risk, 72 of 75 (96%) subjects completed GHRH/arginine testing C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: low risk, adjustments for important co-variates.

		6-thioguanine, n=18 (24.0%) Vincristine, n=75 (100%) Teniposide, n=2 (2.7%) Allopurinol, n=2 (2.7%) Anthracycline dose None, n=46 (61.3%) 1-100 mg/m^2, n=10 (13.3%) 101-300 mg/m^2, n=11 (14.7%) >300 mg/m^2, n=8 (10.7%)		
Conclusion • In a study of **75 ALL survivors** (mean follow-up time 24.6 yrs), potentially treated with chemotherapy and/or cranial RT, **cranial radiotherapy** and **BMI** were significantly associated with GH peak hormone levels after dynamic testing in multivariable linear regression.				

WG1: Who needs screening for hypothalamic-pituitary dysfunction?				
W Leung, A Prospective Cohort Study of Late Sequelae of Pediatric Allogeneic Hematopoietic Stem Cell Transplantation, Medicine (2007)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Prospective cohort study Treatment era: 1990-2003 Follow-up: Median 9 yrs (range 3.1-15.9)	Study population: 155 patients who survived >1yr after HSCT Male n=82 (53%) Female n=73 (47%) Primary cancer diagnosis: Myeloid malignancy, n=84 (54%) Lymphoid malignancy, n=40 (26%) Nonmalignant, n=31 (20%) Age at primary cancer diagnosis: Median 9.7 yrs (range 0.5-21.4) at time of HSCT Age at follow-up: Median 18.5 yrs (range 4.6-36.1)	All patients received myeloablative conditioning Bone marrow transplant, n=145 (94%) Blood stem cell transplant, n=10 (6%) Conditioning regimens: Total body irradiation, n=123 (79%) Alkylator based, n=32 (21%) Dose of TBI: 14.4 Gy, n=59 (38%) 8-12 Gy, n=64 (41%) None, n=32 (21%) All had conventional RT	Definitions Central hypothyroidism: FT4 below the lower limit of normal without TSH elevation or FT4 in the lowest third of the normal range with a blunted TSH surge (<50% rise). Precocious puberty: onset of secondary sexual development before age 8 yrs in girls or 9 yrs in boys. Delayed puberty: no breast development by age 13 yrs or no menses by 14 yrs, no testis growth >3ml by age 14yrs in boys. ACTHD: peak cortisol ≤18 µg/dL to low-dose ACTH test or 11-deoxcortisol response to metyrapone was <7ng/dL with serum cortisol <5µg/L. GHD: peak serum GH concentration in response to arginine and L-dopa stimulation <10ng/mL. Dynamic endocrine evaluation was performed if initial endocrine screening suggested abnormality. Prevalence cancer survivors with HP dysfunction: *At diagnosis:* Not reported *At (last) follow-up:* Central hypothyroidism: n=5 (+4 mixed hypothyroidism) Precocious puberty: n=3 (of 136 who have attained pubertal normal age) Delayed puberty, unknown ACTHD, n=7 (5%) GHD, n=39 (25%)	Strengths -Prospective cohort study with annual follow-up of HP function after stem cell transplantation Limitations -Limited number of events for risk factor analysis -Delayed puberty defined, but not reported. No distinction between primary or secondary cause of delayed puberty -Non-significant factors included in multivariable model, were not listed in the result section -Hypogonadism defined as elevated LH/FSH, central and primary hypothyroidism analyzed as 'hypothyroidism' in multivariable analysis, and thus excluded. Additional remarks x Risk of bias A. Selection bias: low risk, 155 out of 204 (76.0%) eligible survivors were included in the study.

			<u>Risk factor analysis for GHD, adjustments not reported (multivariable Cox regression model):</u> Age at HSCT (per yr), HR 0.83 (95% CI 0.76-0.89)* Radiation dose (per Gy), HR 1.54 (95% CI 1.13-2.09)*	B. Attrition bias: low risk, each patient had annual follow-up, regardless of signs and symptoms. C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: unclear which non-significant variables were included in the multivariable model
<u>Conclusion</u> • In a study of **155 survivors who underwent allogeneic hematopoietic stem cell transplantation** (median follow-up time 9 yrs), **younger age** and **higher radiation** dose were significantly associated with an increased risk <u>GHD</u> in multivariable cox analysis.				

WG1: Who needs screening for hypothalamic-pituitary dysfunction?				
TE. Merchant, Growth Hormone Secretion After Conformal Radiation Therapy in Pediatric Patients With Localized Brain Tumors, JCO (2011)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Prospective cohort study Treatment era: 1997-2008 Follow-up: Serial endocrine testing for GHD before CRT, and at 6, 12, 36, and 60 months follow-up	Study population: n=192 pediatric patients with localized brain tumors Gender unknown Primary cancer diagnosis: Ependymoma, n=88 (45.8%) LGG, n=51 (26.6%) Craniopharyngioma, n=28 (14.6%) High-grade glioma, n=23 (12%) Others, n=2 (1.0%) Age at primary cancer diagnosis: Not reported Age at follow-up: Not reported	All received conformal radiotherapy or intensity-modulated radiation therapy Information on RT dose or additional treatments not reported in study. Authors refer to previously published work: Ependymoma: CRT dose 59.4 Gy, n=73 CRT dose 54.0 Gy, n=15 Low grade glioma: CRT dose 54 Gy, n=unknown	Definitions Arginine tolerance/L-dopa test at baseline, 6, 12, 36 and 60 months after initiation of CRT GHD: peak GH response to arginine/L-dopa test <7ng/mL Prevalence cancer survivors with HP dysfunction: *At diagnosis:* 39 of 170 patients (22.9%) had pre-irradiation GHD. *At (last) follow-up:* not reported Associations with longitudinal trend of peak GH level (mixed effects model): Five variables included (time after start CRT, mean RT dose to hypothalamus, CSF shunting, baseline peak GH, tumor location) Significant associations between: -mean dose and CSF shunt, p=0.0253 -mean dose and tumor location, p=<0.001 -mean dose and time interval, p=0.0025 Significant exponential decline: -peak GH levels after start of irradiation, as function of time Paired interactions in model including time and mean RT dose as predictors: -time after CRT and mean dose (p<0.001) -time after CRT and CSF shunt (p<0.0022) -time after CRT and basal GH (p=0.0484)	Strengths -Large data set, high number of included endocrine function tests, -Prospective study design; -Informative and relevant statistical approach Limitations Important information missing on basic population characteristics and important, potentially confounding variables (surgery etc.) Additional remarks x Risk of bias A. Selection bias: unclear how many patients were included in the original cohort of survivors B. Attrition bias: unclear, n=118 patients (without GHD at baseline) underwent GH testing at t=0 and n=56 had t=60 months measurements. Unclear how many of these patients developed GHD and were not further tested.

			Best model: Interaction between time and radiation dose, p<0.001 Interaction between time and basal GH, p=0.0029 Interaction between time and CSF shunt, p=0.0350 Prediction model: -Development of GHD, follow-up 12 months, CRT>60 Gy -Development of GHD, follow-up 36 months, CRT 25-30 Gy -Development of GHD, follow-up 60 months, CRT 15-20 Gy <u>Additional Comments:</u> -TD5/5 and TD50/5 are calculated for radiation dose tolerance estimated at 60 months follow-up revealing a maximum dose of 16.1 Gy over a 6 weeks-course for patients to have a less than 50% risk of peak GH <7ng/ml at 5 years. -Greater risk baseline GHD in black patients, craniopharyngioma, supratentorial tumors; and in those with previous CSF shunts for hydrocephalus	C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: high risk, limited demographic factors included (e.g. gender, age etc).
<u>Conclusion</u> • In a study of **192 survivors who received cranial radiotherapy** (follow-up at start CRT, and 6,12, 36 and 60 months after CRT), **time after cranial radiotherapy**, **radiation dose**, **basal GH** and **CSF shunt** were associated with peak GH levels in mixed effects model.				

WG1: Who needs screening for hypothalamic-pituitary dysfunction?				
M Schmiegelow, Assessment of the Hypothalamo-Pituitary-Adrenal Axis in Patients Treated with Radiotherapy and Chemotherapy for Childhood Brain Tumor, JCEM (2003)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Cross-sectional study Treatment era: 1970-1997 Follow-up: Median 15 yrs (range 2-29)	Study population: 73 childhood brain tumor survivors (not involving HP region), <15yrs at diagnosis Male n=46 (63.0%) Female n=27 (37.0%) 17 controls from healthy hospital staff (median age 31 yrs) Primary cancer diagnosis: Astrocytoma, n=31 (42.5%) Medulloblastoma, n=23 (31.5%) Ependymoma, n=5 (6.8%) Germ cell tumor, n=3 (4.1%) Glioma, n=3 (4.1%) Pinealoma, n=1 (1.4%) Hemangiopericytoma, n=1 (1.4%) Primitive neuroectodermal tumor, n=1 (1.4%) Nonhistological diagnosis; chiasma glioma, n=4 (5.5%) medulloblastoma, n=1 (1.4%) Age at start RT:	Radiotherapy All patients received RT treatment *RT details* CSI, n=30 (41.1%) Whole brain RT, n=14 (19.2%) Focal brain RT, n=29 (39.7%) Median BED to HP region 73 Gy (range 0-94) Median BED to spine 55 Gy (range 27-78) Cobalt-60 RT, n=15 Conventional RT, n=58 Surgery n=68 (93.2%) had biopsy, partial or total resection Chemotherapy: N=30 (41.1%), of patients with surgery received pre- or post-surgery chemotherapy (consisting of lomustine and/or vincristine and/or methotrexate in the early nineties, cisplatin and/or bleomycin and/or etoposide and/or vincristine and/or	Definitions - Basal cortisol measurements <500 nmol/L with peak cortisol response to ACTHD test or insulin tolerance test <500nmol/liter Prevalence cancer survivors with HP dysfunction: *At diagnosis* Probably none as two patients were excluded due to hypofunction of the HPA axis at time of diagnosis. *At (last) follow-up* Hydrocortisone Tx, n=4 (5.5%) GH Tx, n=20 (27.4%) T4 Tx, n=20 (27.4%) E2 Tx, n=8 (11.0%) Testosterone Tx, n=2 (2.7%) ACTHD according to either ACTH test or ITT, n=14 (19%) + GHD in n=13 and/or hypothyroidism in n=5 (origin unknown) Peak cortisol (basal and stimulated) in the patients were significantly lower compared to the controls. Risk factor analysis for peak cortisol after ITT, adjustments not reported (stepwise backward multiple regression analysis): BED, β -0.53, p=0.04 Length of follow-up, β -0.49, p=0.06 BED to the spine, β 0.32, p=0.21	Strengths -Population based -BED to HP region calculated Limitations -Not all tested with ITT -Different dose RT eras -Small numbers Additional remarks Results important as there are abnormalities of HPA axis correlated best with BED and length of follow-up Risk of bias A. Selection bias: low risk, 73 out of 91 (80.2%) eligible survivors were included in the study B. Attrition bias: high risk, ACTH testing in all patients, but ITT only performed in 33 or 73 patients. Controls had only ACTH test performed. C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome

	Median 8.4 yrs (range 0.8-14.9) <u>Age at follow-up:</u> Median 21.6 yrs (range 6.2-43.5)	carboplatin and/or endoxan and/or etoposide).	Chemotherapy, β 0.31, p=0.21 Age at irradiation, β 0.01, p=0.40 Gender, β 0.00, p=1.00	D. Confounding: low risk, important variables included in models
<u>Conclusion</u> • In a study of **73 childhood brain tumor survivors who received cranial radiotherapy** (median follow-up time 15 yrs), peak cortisol levels after ITT was associated with **biological effective dose.** • Length of follow-up, biological effective dose to the spine, chemotherapy, age at irradiation and gender were <u>not</u> significantly associated with peak cortisol levels after ITT in multivariable regression analysis.				

WG1: Who needs screening for hypothalamic-pituitary dysfunction?				
M Schmiegelow, Cranial radiotherapy of childhood brain tumours: Growth hormone deficiency and its relation to the biological effective dose of irradiation in a large population based study, Clinical endocrinology (2000)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Cross-sectional study Treatment era: 1970-1997 Follow-up: Median 15 yrs (range 2-28)	Study population: 73 childhood brain tumor survivors (not involving HP region), <15yrs at diagnosis Male n=47 (64.4%) Female n=26 (35.6%) Primary cancer diagnosis: Astrocytoma, n=31 (42.5%) Medulloblastoma, n=22 (30.1%) Ependymoma, n=6 (8.2%) Germ cell tumor, n=3 (4.1%) Glioma, n=3 (4.1%) Pinealoma, n=1 (1.4%) Hemangiopericytoma, n=1 (1.4%) Primitive neuroectodermal tumor, n=1 (1.4%) Nonhistological diagnosis; chiasma glioma, n=4 (5.5%) medulloblastoma, n=1 (1.4%) Age at start RT: Median 8.7 yrs (range 0.8-14.9) Age at follow-up:	Radiotherapy All patients received RT treatment *RT details* CSI, 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) Cobalt-60 RT, n=15 Conventional RT, n=58 Surgery n=68 (93.2%) had biopsy, partial or total resection Chemotherapy: N=29 (39.7%), of patients with surgery received pre- or post-surgery chemotherapy (consisting of lomustine and/or vincristine and/or methotrexate in the early nineties, cisplatin and/or bleomycin and/or etoposide and/or vincristine and/or carboplatin and/or endoxan and/or etoposide).	Definitions IGF-1, IGFBP-3, dynamic GH testing (≥18 yrs ITT (n=34) or arginine (n=39)) GHD: peak GH response <9mU/L in patients ≥18 yrs and peak GH response <15mU/L in patients <18 yrs Prevalence cancer survivors with HP dysfunction: *At diagnosis* Not reported *At (last) follow-up* GH Tx, n=20 (27.4%) Levothyroxine Tx, n=19 (26.0%) Hydrocortisone Tx, n=4 (5.5%) E2 Tx, n=8 (11.0%) Testosterone Tx, n=3 (4.1%) GHD, n=58 (80%) Risk factor analysis for stimulated log peak GH following ITT or arginine, adjustments not reported (stepwise backward multiple regression analysis): Biological effective dose, β -0.47, p<0.0001* Length of follow-up, β -0.20, p=0.05 Age at irradiation, β 0.06, p=0.60 Gender, β -0.07, p=0.52 Chemotherapy, β 0.02, p=0.86	Strengths -Population based -BED to HP region calculated Limitations -Different RT types used -Peak GH responses used of two different GH stimulation tests -No control population included Additional remarks Patients >18 used ITT to assess; If had seizures of < 18 used arginine test Risk of bias A. Selection bias: low risk, 73 out of 91 (80.2%) eligible survivors were included in the study B. Attrition bias: low risk, all patients underwent dynamic GH testing (although two different GH testing modalities used, according to age) C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome

	Not reported			D. Confounding: low risk, important variables included in models

Conclusion

- In a study of **73 childhood brain tumor survivors who received cranial radiotherapy** (median follow-up time 15 yrs), peak GH levels after ITT or arginine testing were associated with **biological effective dose** and **length of follow-up** in multivariable regression analysis.
- Age at irradiation, chemotherapy and gender were not significantly associated with peak GH levels in multivariable regression analysis.

WG1: Who needs screening for hypothalamic-pituitary dysfunction?				
S Shalitin, Endocrine Outcome in Long-Term Survivors of Childhood Brain Tumors, Hormone research in Paediatrics (2011)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort study Treatment era: 1986-2005 Follow-up: Mean 12.8 ± 6.25 yrs (range 3.7-28.7)	Study population: 114 childhood brain tumor survivors (excluding craniopharyngioma or pituitary adenoma) with a follow-up >2yr and age <30yr at follow-up Male n=68 (59.6%) Female n=46 (40.4%) Primary cancer diagnosis: Optic glioma, n=30 (26.3%) Medulloblastoma, n=29 (25.4%) Astrocytoma, n=26 (22.8%) Ependymoma, n=9 (7.9%) Germinoma, n=6 (5.3%) Other, n=14 (12.3%) Age at primary cancer diagnosis: Mean 7.07 ± 5.42 yrs (range 0.1-23.9 yrs) Age at follow-up: Mean 15.57 ± 5.93 yrs (range 3.8-30)	Neurosurgery + CT + RT N=52 (45.6%) Neurosurgery + CT N=23 (20.2%) Neurosurgery + RT N=9 (7.9%) CT + RT N=3 (2.6%) Neurosurgery only N=15 (13.2%) No therapy N=12 (10.5%) *RT details* -Cranial RT, n=55 (48.2%), RT dose 35-56 Gy -Spinal RT, n=27 (23.7%), RT dose 30-54 Gy Cave: not mutually exclusive All had conventional RT	Definitions GHD: GH peak <10 ng/ml to stimulation with clonidine or glucagon Hypogonadotropic hypogonadism: lack of LH increase after GnRH stimulation and prepubertal sex hormones (estradiol <20 pmol/L in females, testosterone <0.7 nmol/L in males) ACTHD: peak cortisol <540 nmol/L after Synacthen test (250 µg) TSHD: subnormal FT4 level (<10.5 pmol/ml) with a low, normal or mildly raised TSH level Early puberty: not defined in methods section Prevalence cancer survivors with HP dysfunction: *At diagnosis* Not reported *At (last) follow-up* GHD: n=40 (35.1%) LH/FSHD: n=9 (11%) ACTHD: n=9 (7.9%) TSHD: n=17 (14.9%) Early puberty: n=19 (16.7%) Risk factor analysis for GHD, adjustments not reported (multiple logistic regression model): Age at tumor diagnosis, OR 0.88 (95% CI 0.79-0.97)* Cranial radiation, OR 10.3 (95% CI 3.48-31.25)* Spinal radiation, OR 3.49 (95% CI 0.83-14.9)	Strengths -Fairly large cohort and long follow-up time -Detailed information on endocrine sequelae -Annual screening for HP dysfunction Limitations -Limited multivariable analysis possible -No detailed information on radiation dose as risk factor for HP dysfunction Additional remarks x Risk of bias A. Selection bias: low risk, all 114 eligible patients included in study B. Attrition bias, low risk, annual physical examinations and laboratory assessments. C. Detection bias, unclear if the outcome assessors were blinded for important determinants related to the outcome

			AUC for these parameters was 0.805 For other HP dysfunction, no multivariable analysis was performed	D. Confounding, high risk, limited multivariable analysis performed

Conclusion

- In a study of **114 childhood brain tumor survivors** (median follow-up time 12.8 yrs), **age at tumor diagnosis** and **cranial radiotherapy** were significantly associated with GHD, in multivariable logistic regression analysis.
- Spinal radiation was not associated with GHD in multivariable analysis.

WG1: Who needs screening for hypothalamic-pituitary dysfunction?				
S Shalitin, Endocrine dysfunction and parameters of the metabolic syndrome after bone marrow transplantation during childhood and adolescence, Bone Marrow Transplantation (2006)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort study Treatment era: 1987-2003 Follow-up: Mean 6.2 ± 3.5 yrs from BMT (range 1-22.5)	Study population: 91 allogeneic or autologous BMT survivors Male n=52 (57.1%) Female n=39 (42.9%) Primary cancer diagnosis: ALL, n=10 (11%) AML, n=22 (24.2%) CML, n=4 (4.4%) Hodgkin's lymphoma, n=8 (8.8%) Neuroblastoma, n=16 (17.6%) Sarcoma, n=4 (4.4%) Medulloblastoma, n=2 (2.2%) Wilms tumor, n=1 (1.1%) Germ cell tumor, n=1 (1.1%) Hepatoblastoma, n=1 (1.1%) Aplastic anemia, n=5 (5.5%) Fanconi anemia, n=4 (4.4%) B-thalassemia major, n=9 (9.9%) Wiskott-Aldrich syndrome, n=2 (2.2%) Hemophagocytic syndrome, n=2 (2.2%)	All patients received BMT Allogeneic BMT, n=45 (49.5%) Autologous BMT, n=46 (50.5%) *Pre-BMT treatment* Pre- BMT chemotherapy: n=60 (65.9%) Pre-BMT RT + Chemotherapy: n=10 (11.0%) *RT details* CRT, n=5 (5.5%) Neck/mediastinal RT, n=5 (5.5%) *Conditioning regimens:* Conditioning chemotherapy Alkylating agents, n=81 (89%) Other, n=10 (11%) Chemotherapy (consisting of cyclophosphamide and/or busulfan and/or melphalan and/or thiotepa and/or VP-16 or antithymocotyic globulin) or antithymocytic globulin Radiotherapy as part of conditioning (cyclophosphamide and/or busulfan and/or melphalan and/or VP-16 or antithymocotyic globulin) No irradiation, n=73 (80.2%)	Definitions GHD: GH peak level <10ng/ml in response to clonidine or glucagon. GH dynamic testing only performed in patients with short stature or reduced growth rate with marked growth deceleration -Failure of spontaneous puberty: absence of breast development in girls >13yrs or testicular enlargement in boys >14yrs -Arrested puberty: lack of advancement of puberty for >1year with no advancement to Tanner stage 4-5 after age 16 yrs -Secondary amenorrhea: absence of menses for 12 months or longer after menarche Prevalence cancer survivors with HP dysfunction: *At diagnosis* Not reported *At (last) follow-up* GHD, n=10 (11%) Risk factor analysis for GHD, adjustments not reported (multiple logistic regression model): Conditioning with TBI, OR 37 (95% CI 5.94-231)* Other factors in model not reported.	Strengths -Very well-defined treatment regimen Limitations -Retrospective chart review with a small number of patients -Outcomes on gonadal and thyroid axis only assessed for primary gland damage -Weight confidence intervals limits validity of data -Heterogeneous population undergoing BMT (allo or auto) for various dysfunction. -Methodology and results of multivariable analysis not clearly described -Inclusion of Fanconia anemia and beta thalassemia major patients where underlying disease significant contribution to short stature -GH testing only completed in patients with short stature or reduced growth rate/growth deceleration; real prevalence of GHD not assessed Additional remarks

	<u>Age at diagnosis:</u> Mean 5.6 ± 5.1 yrs (range 0.1-18.5) <u>Age at BMT:</u> Mean 7.4 ± 5.2 yrs (range 0.6 – 21.5) <u>Age at follow-up:</u> Mean 13.6 ± 5.9 yrs (range 4.3-32.5)	TBI (12Gy), n=14 (15.4%) CRT (7 Gy) + TBI, n=1 (1.1%) Thoraco-abdominal RT (4-5 Gy), n=3 (3.3%) All had conventional RT <u>Other treatments</u> -n=27 received corticosteroid therapy >4 weeks as part of pretransplant regimen. -most patients received a short course of methotrexate together with cyclosporine for GVHD prophylaxis		Relatively small number of patients who achieved final adult height at last evaluation <u>Risk of bias</u> A. Selection bias: low risk, all 91 eligible patients included in study B. Attrition bias, high risk, GH testing only performed in patients with short stature or reduced growth rate/growth deceleration. C. Detection bias, unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding, high risk, limited multivariable analysis performed
<u>Conclusion</u> • In a study of **91 survivors who underwent allogeneic or autologous BMT** for diverse indications (median follow-up time 6.2 yrs), **conditioning with total body irradiation** was significantly associated with GHD, in multivariable logistic regression analysis.				

WG1: Who needs screening for hypothalamic-pituitary dysfunction?				
SC Clement, Prevalence and Risk Factors of Early Endocrine Dysfunction in Childhood Brain Tumor Survivors: A Nationwide, Multicenter Study, JCO (2016)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort-study Treatment era: Diagnosis between 2002-2012 Follow-up: Median 6.6 ys (range 2.0-13.4)	Study population: 718 childhood brain tumor survivors, ≤18yrs at diagnosis, excluding craniopharyngioma and pituitary tumors and survived at least ≥2 years after diagnosis Male n=389 (54.2%) Female n=329 (45.8%) Primary cancer diagnosis: Low-grade glioma, n=358 (49.9%) DNET, n=17 (2.4%) High-grade glioma, n=18 (2.5%) Medulloblastoma, n=97 (13.5%) sPNET, n=13 (1.8%) Ependymoma, n=50 (7.0%) Choroid plexus tumors, n=20 (2.8%) Germ-cell tumor, n=26 (3.6%) ATRT, n=7 (1.0%) Other, n=23 (3.2%) Without histology, n=89 (12.4%) Age at treatment:	Wait and see N=52 (7.2%) Neurosurgery only N=328 (45.7%) Chemotherapy only N=26 (3.6%) Radiotherapy only N=6 (0.8%) Neurosurgery + chemotherapy N=54 (7.5%) Neurosurgery + radiotherapy N=91 (12.7%) Chemotherapy + radiotherapy N=2 (0.3%) Neurosurgery + chemotherapy + radiotherapy N=159 (22.1%) *RT details* Cranial RT dose, median 54.0 Gy (range 12.5-60.0) Craniospinal RT dose, median 24.0 Gy (range 18.0-39.7)	Definitions: GHD: insufficient peak response (<20 to 30 mU/L) after GH stimulation test with low IGF-1, or diagnosis by an endocrinologist ACTHD: use of hydrocortisone maintenance or substitution under suspicion of central hypocortisolism TSHD: FT4 below the age-specific reference range, in combination with low, normal or mildly raised (<10mU/L) TSH level, or use of LT4 for documented TSHD LH/FSHD: low LH and/or FSH in the absence of pubertal development, or use of estrogens or testosterone for the diagnosis LH/FSHD CPP: early onset of puberty (if Tanner B2 in girls <8 years, testes >4 mL in boys <9 years) Prevalence cancer survivors with HP dysfunction: *At diagnosis (assessed in n=206, but reported of the total cohort):* GHD: n=2 (0.3%) TSHD: n=7 (1.0%) ACTHD: n=7 (1.0%) CPP (evaluable in n=394): n=10 (1.4%) LH/FSHD (evaluable in n=481): n=1 (0.1%) *At (last) follow-up:* GHD: n=90 (12.5%) TSHD: n=66 (9.1%) ACTHD: n=31 (4.3%) CPP (evaluable in n=394): n=48 (12.2%)	Strengths -Large and relatively young cohort Limitations -Large proportion of the cohort did not receive endocrine screening -Large proportion of the cohort did not receive endocrine screening in a timely manner Risk of bias A. Selection bias: unclear how many patients were included in the original cohort of survivors B. Attrition bias: high risk, only 459 of 718 survivors (63.9%) underwent endocrine testing C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. D. Confounding: low risk, analyses were adjusted for

	Mean 7.7 ys (range 0-17.7 ys) at diagnosis <u>Age at follow-up:</u> 15.1 yrs (range 3.0-29.3 ys)		LH/FSHD (evaluable in n=481): n=20 (4.2%) <u>Risk factor analysis for HP dysfunction (multivariable logistic regression model):</u> *GHD:* Sex (male vs. female) OR 1.66 (95% CI 0.93-2.98) Younger age at diagnosis (years), OR 1.06 (95% CI 1.00-1.13) Follow-up time (years), OR 1.17 (95% CI 1.07-1.28)* Hydrocephalus (yes vs. no) OR 1.33 (95% CI 0.71-2.49) Tumor location (suprasellar vs. supratentorial) OR 10.15 (95% CI 3.48-29.56)* Tumor location (infratentorial vs. supratentorial) OR 5.64 (95% CI 2.66-11.94)* Neurosurgery (yes vs. no) OR 8.52 (95% CI 0.84-86.35) Radiotherapy (yes vs. no) OR 79.39 (95% CI 24.21-260.37)* *TSHD:* Sex (male vs. female) OR 2.02 (95% CI 1.10-3.70)* Younger age at diagnosis (years), OR 1.00 (95% CI 0.93-1.06) Follow-up time (years), OR 1.08 (95% CI 0.99-1.18) Hydrocephalus (yes vs. no) OR 1.59 (95% CI 0.86-2.92) Tumor location (suprasellar vs. supratentorial) OR 13.04 (95% CI 5.04-33.76)* Tumor location (infratentorial vs. supratentorial) OR 2.46 (95% CI 1.17-5.19)* Neurosurgery (yes vs. no) OR 2.39 (95% CI 0.59-9.75) Radiotherapy (yes vs. no) OR 11.48 (95% CI 5.51-23.92)* *CPP:* Sex (male vs. female) OR 0.88 (95% CI 0.41-1.87) Younger age at diagnosis (years), OR 0.86 (95% CI 0.77-1.03) Follow-up time (years), OR 1.03 (95% CI 0.92-1.17) Hydrocephalus (yes vs. no) OR 3.73 (95% CI 1.56-8.89)*	important confounding factors.

			Tumor location (suprasellar vs. supratentorial) OR 110.45 (95% CI 23.90-510.35)* Tumor location (infratentorial vs. supratentorial) OR 1.96 (95% CI 0.52-7.46) Neurosurgery (yes vs. no) OR 1.68 (95% CI 0.61-4.63) Radiotherapy (yes vs. no) OR 2.97 (95% CI 1.20-7.32)*	

Conclusion

- In a study of **718 childhood brain tumor survivors** (mean follow-up time of 6.6 years):
  - **Longer follow-up time, suprasellar and infratentorial tumor location and exposure to radiotherapy** were significantly associated with an increased risk for the development of GHD in multiple regression analysis. Gender, age at diagnosis, presence of hydrocephalus and neurosurgery were not significantly associated with the development of GHD in childhood brain tumor survivors, in multiple regression analysis.
  - **Male sex, suprasellar and infratentorial tumor location and exposure to radiotherapy** were significantly associated with an increased risk for the development of TSHD in multiple regression analysis. Age at diagnosis, follow-up time, presence of hydrocephalus and neurosurgery were not significantly associated with the development of TSHD in childhood brain tumor survivors, in multiple regression analysis.
  - **Presence of hydrocephalus, suprasellar tumor location and exposure to radiotherapy** were significantly associated with an increased risk for the development of CPP in multiple regression analysis. Gender, age at diagnosis, follow-up time, infratentorial tumor location and neurosurgery were not significantly associated with the development of CPP in childhood brain tumor survivors, in multiple regression analysis.

WG1: Who needs screening for hypothalamic-pituitary dysfunction?				
BR Eaton, Endocrine outcomes with proton and photon radiotherapy for standard risk medulloblastoma, Neuro-Oncology (2016)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective multi-institutional cohort-study (with routine follow-up) Treatment era: 2000-2009 Follow-up: For photon cohort: median 7.0 ys (range 3.5-13.5) For proton cohort: median 5.8 ys (range 3.4-9.9)	Study population: 77 survivors of childhood standard-risk medulloblastoma treated with photon or proton RT, with at least ≥3 yrs routine endocrine screening and without disease progression or receipt of salvage therapy. Male n=45 (58.4%) Female n=32 (41.6%) Primary cancer diagnosis: All had standard-risk medulloblastoma Age at diagnosis: Photon cohort: median 8.3 yrs (range 3.4-19.5) Proton cohort: median 6.2 yrs (range 3.3-21.9) Age at follow-up: Not reported	All patients underwent primary tumor resection, followed by craniospinal RT and RT involved field or posterior fossa boost and chemotherapy (vincristine, cisplatin, cyclophosphamide and/or lomustine) *RT details* Craniospinal RT dose -Photon cohort: n=37 (48.1%) median 23.4 Gy, (range 18-26.4) -Proton cohort: n=40 (51.9%) median 23.4 Gy, (range 18-27) Total RT dose -Photon cohort: 54-55.8 Gy, n=36 (97.3%), >55.8 Gy, n=1 (2.7%) -Proton cohort: 54-55.8 Gy, n=40 (100%)	Definitions Patients were considered to have an endocrinopathy when the clinical diagnosis was made and documented in the medical record by the endocrinologist or treating oncologist or when medical management for the endocrinopathy was initiated. CPP: puberty at an abnormal early age (<8 yr in girls and <9yr in boys) Sex steroid deficiency: clinically significant lack of production of sex steroids requiring exogenous replacement. Routine endocrine screening included height, TSH, FT4, IGF-1, IGF-BP3, estrogen, testosterone, FSH, LH and cortisol. Dynamic adrenal testing was performed if abnormal morning cortisol. GH stimulation testing was recommended in patients with a clinical suspicion (growth rate, IGF-1 levels) Prevalence cancer survivors with HP dysfunction: *At diagnosis* Not reported *At (last) follow-up:* GHD: n=42 (54.5%), n=21 (56.8%) after photon, n=21 after proton (52.5%) ACTHD: n=5 (6.5%), n=3 (8.1%) after photon, n=2 after proton (5.0%)	Strengths -First study that assesses the risk after photon vs. proton radiation therapy Limitations -Unable to distinguish primary from central forms of hypothyroidism -Unable to distinguish primary from central forms of hypogonadism -Endocrine testing and data collection differed between the photon and proton cohort Additional remarks X Risk of bias A. Selection bias: low risk, 77 of 88 (87.5%) patients were included in the study B. Attrition bias: high risk, screenings protocols differed between photon and proton cohorts. Also, the photon cohort data was collected retrospectively, while the proton cohort data was collected prospectively.

			CPP: n=13 (16.9%), n=6 after photon (16.2%), n=7 after proton (17.5%) <u>Risk factor analysis for HP dysfunction (multivariable logistic regression model):</u> *GHD:* Proton vs. photon, OR 0.81 (95% CI 0.26-2.59) Gender (male vs. female), OR 3.80 (95% CI 1.29-11.17)* Classic histology vs. others, OR 7.07 (95% CI 1.66-30.19)* Age at diagnosis (years), OR 0.83 (95% CI 0.71-0.97)*	C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: low risk, analyses were adjusted for important confounding factors.
<u>Conclusion</u> • In a study of **77 childhood medulloblastoma survivors** (mean follow-up time of 7.0 years after photon RT, 5.8 years after proton RT): ○ **Male gender, classic histology and younger age at diagnosis** were significantly associated with an increased risk for the development of <u>GHD</u> in multiple regression analysis. Type of radiation therapy (proton vs. photon) was <u>not</u> significantly associated with the development of <u>GHD</u> in childhood medulloblastoma survivors, in multiple regression analysis.				

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

WG2: When should screening be initiated and for how long should screening be continued? How frequently should we screen?				
GT. Armstrong, Survival and long-term health and cognitive outcomes after low-grade glioma, Neuro-oncology (2011)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment &** **Screenings protocol**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort study, with prospective follow-up Treatment period: 1985-2007 Patients were stratified by treatment eras (1985-1996, 1997-2007) Follow-up: Mean follow-up (from diagnosis) in n=240 5-year survivors: 10 ys (range 5-21.5)	Study population: 361 (≤21 ys at diagnosis) survivors of low-grade glioma Endocrine outcomes reported for a subpopulation of n=240 5-year survivors Male n=137 (57.1%) Female n=103 (42.9%) Primary cancer diagnosis: All had low-grade glioma (grade 1 astrocytoma (pilocytic) or grade 2 astrocytoma (incl pilomyxoid fibrillary astrocytoma, oligoastrocytoma, oligodendroglioma or low-grade astrocytic tumors nor otherwise specified)) Optic pathway glioma (n=27)	5-year survivors (n=240) Observation only: n=4 (1.7%) Surgery only: n=110 (45.8%) RT (CRT/CSI) only: n=6 (2.5%) Chemotherapy only: n=4 (1.7%) Any surgery + RT: n=67 (27.9%) Any surgery + chemotherapy: n=11 (4.6%) RT + Chemotherapy: n=7 (2.9% Any surgery + RT + Chemotherapy: n=31 (12.9%) *RT details* All had conventional focal RT Start screening Follow-up in the after completion of therapy clinic (ACT), at least two years after completion of	Definitions • Endocrine diagnoses were based on random or dynamic testing including spontaneous overnight secretion of TSH, TRH stimulation test, overnight metyrapone, ITT, low-dose ACTH test, GH stimulation test; no details on definitions or cut-off values • Unclear, if “Hypothyroidism” refers to central or peripheral hypothyroidism Prevalence survivors with HP dysfunction: *At diagnosis* Not reported *At (last) follow-up* Not reported Latency time from treatment to HP disorder Not assessed Cumulative incidence Cumulative incidence at 5 years:	Strengths -Length of follow-up and annual assessment able to demonstrate cumulative incidence increases over time Limitations -Didn’t assess effect of RT dose; used multiple different modalities to make diagnoses -No information of hypothyroidism refers to primary or secondary origin, and therefore excluded as result. Additional remarks x Risk of bias A. Selection bias: unclear how many patients were included in the original cohort of survivors (240 of 361=66.5%) were 5-yr survivors). B. Attrition bias: unclear for how many survivors follow-up data was complete. ‘not all patients received

	<u>Age at primary cancer diagnosis:</u> 5-year survivors: 0-4 ys: n=82 (34.2%) 5-9 ys: n=80 (33.3%) 10-20 ys: n=78 (32.5%) <u>Age at follow-up:</u> 5-year survivors: median age at last follow-up 18.3 ys (range 5.6-29.9)	antineoplastic therapy and no tumor progression. <u>Frequency of screening</u> Annual <u>Screenings protocol</u> Random or dynamic testing, including spontaneous overnight secretion of TSH, TRH, metyrapone testing, ITT, low-dose ACTH test, GH testing (arginine, L-dopa, clonidine or hypoglycemia).	GHD: 13% (95% CI unknown) ACTHD: 12% (95% CI unknown) Cumulative incidence at 10 years: GHD: 27% (95% CI unknown) ACTHD: 22% (95% CI unknown) Cumulative incidence at 15 years: GHD: 29% (95% CI 22.2-32.5%) ACTHD: 26% (95% CI 18.9-32.5%) The cumulative incidence continued to increase, even at 15 years from diagnosis Kaplan meier curve included	the same screening and detection measures.' C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. D. Confounding: not applicable
<u>Conclusion</u> • In a study of **240 5-year low grade glioma (LGG)** survivors (mean follow-up time of 10 years), treated with several modalities the cumulative incidence at 15 years was 33% for GHD and 26% for ACTHD.				

WG2: When should screening be initiated and for how long should screening be continued? How frequently should we screen?				
R. Brauner, Growth and endocrine dysfunction in optic glioma, Eur. J. Pediatrics (1990)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment &** **Screenings protocol**	**Main outcomes**	**Additional remarks**
Study design Retrospective case series Treatment period: 1971-1983 Follow-up: Mean follow-up (from irradiation) 5.1 ± 0.8 yrs (range 1-14.3)	Study population 21 survivors of optic glioma Male n=13 (61.9%) Female n=8 (38.1%) Primary cancer diagnosis All had optic glioma Age at radiotherapy: Mean age 5.4 ± 0.7 yrs (range 1.5-10.3) Age at follow-up: Not reported	Treatment All received cranial radiotherapy *RT details* 45-55 Gy over 5-6 wks All had conventional RT Surgery Partial resection, n=5 (23.8%) Biopsy, n=1 (4.8%) Chemotherapy: No patient received chemotherapy Start screening: Endocrine evaluation before radiotherapy, n=10 (of whom 2 were also evaluated after surgery) All had endocrine evaluation after radiotherapy Frequency of screening At least 2 yearly growth measurements at different intervals after RT. Frequency	Definitions GHD: GH peak response to arginine-insulin tolerance test <8µg/L, and confirmed by a second test Gonadal axis: basal and stimulated (LHRH test) LH and FSH, and plasma testosterone and estradiol, no cut-off values defined. Adrenal axis: basal and stimulated cortisol levels, no cut-off values defined. Thyroidal axis: basal and stimulated (TRH test) FT4 concentrations. TSH response <10mU/l after TRH test considered as abnormal (independent of FT4 concentrations). Precocious puberty: breast and pubic hair development before age of 8yrs in girls, increase in testicular volume and testosterone secretion (>3.5nmol/L) before age of 10yrs in boys. Prevalence of HP dysfunction *At diagnosis:* GHD: n=1 TSHD: n=0 (FT4 levels normal in all ten patients, TRH test normal in two patients tested) ACTHD: n=0 (basal and stimulated cortisol normal in all ten patients) CPP: n=5 (23.8%)	Strengths GHD diagnosed by GH<8 mcg/L on AITT & confirmed by 2nd test; supports early onset of GHD after high dose RT Limitations Not clear how many tumors may have involved the hypothalamus; contribution of RT to development of precocious puberty difficult in population that is at high risk for precocious puberty Additional remarks Diagnosis of central hypothyroidism based on poor response to TRH, but T4 levels were normal Used mean when likely should have been median Risk of bias A. Selection bias: unclear how many patients were included in the original cohort of survivors B. Attrition bias: high risk, not all patients received pre-irradiation testing and patients were tested at

		of endocrine testing not reported. <u>Screenings protocol</u> -GH secretion evaluated by GH peak response to arginine-insulin tolerance test. Patients were tested at different time-intervals after RT (mean 2.5 ± 0.6 yrs, range 1-9 yrs) -HP-gonadal axis by basal and stimulated (LHRH test) LH and FSH, and testosterone in boys and estradiol in girls. -FT4 levels, TRH testing -Basal and stimulated cortisol levels	*At (last) follow-up* GHD: n=21 (100%) TSHD: n=11 (52.4%, TSH response <10mU/l) to TRH test in eleven, none had low FT4 levels) ACTHD: n=1 (4.8%) CPP: n=7 (33.3%) <u>Latency time from treatment to HP disorder</u> GHD: occurred within 2 yrs of RT GH testing at ± 0.6 yrs, range 1-9 yrs Mean interval between RT & first test showing GHD was 1.5 ± 0.2 yrs (range 1-2.3) <u>Cumulative incidence</u> Not reported No Kaplan meier included	different time intervals during follow-up. C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. D. Confounding: not applicable
<u>Conclusion</u> • In a study of **21 survivors of optic glioma** (mean follow-up time of 5.1 years), treated with radiotherapy, GHD occurred within 2 years of radiotherapy.				

WG2: When should screening be initiated and for how long should screening be continued? How frequently should we screen?				
W. Chemaitilly, Anterior Hypopituitarism in Adult Survivors of Childhood Cancers Treated With Cranial Radiotherapy: A Report From the St Jude Lifetime Cohort Study, JCO (2015)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment &** **Screenings protocol**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort-study (with prospective follow-up) Treatment era: Unknown Follow-up: Mean 27.3 yrs (range 10.8-47.7)	Study population: 748 childhood cancer survivors treated with cranial radiotherapy, age ≥18yrs, without direct mass effect of tumor on hypothalamus or pituitary. Male n=394 (52.7%) Female n=354 (47.3%) Primary cancer diagnosis: Leukemia,n=543 (72.6%) Lymphoma, n=33 (4.4%) CNS tumor, n=90 (12.0%) Embryonal, n=30 (4.0%) Bone and soft tissue sarcoma, n=38 (5.1%) Carcinoma, n=11 (1.5%) Other, n=3 (0.4%) Age at treatment: Mean 7.6 yrs (range 0.1-26.0 ys) at start CRT Age at follow-up: 34.2 yrs (range 19.4-59.6 ys)	CRT: n=748 (total study cohort) RT details 1-14.9 Gy, n=40 (5.3%) 15-21.9 Gy, n=208 (27.8%) 22-29.9 Gy, n=316 (42.3%) 30-39.9 Gy, n=31 (4.1%) ≥40 Gy, n=153 (20.5%) All had conventional RT Unknown (but likely that) other tumor treatments were given. Start screening Clinical surveillance St Jude until alumni status. SJLIFE screening start 2007. Frequency of screening Not reported Screenings protocol SJLIFE evaluations were performed between 2007-2012 according to the COG guidelines.	Definitions: GHD: previously diagnosed or IGF-1 z-scores <-2 LH/FSHD: previously diagnosed or total testosterone <200ng/dL 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 TSHD: previously diagnosed or FT4 <0.9 ng/dL coincided with TSH <4 mIU/L ACTHD: previously diagnosed or 08.00 AM cortisol <5µg/dL Prevalence cancer survivors with HP dysfunction: *At diagnosis:* not reported *Point prevalence at (last) follow-up:* GHD (assessed in n=748): n=348 (46.5%, 95% CI 42.9% to 50.2%) -CRT dose ≥18 Gy, 47.5% (95% CI 43.8% to 51.3%) -CRT dose <18 Gy, 30.2% (95% CI 17.2% to 46.1 LH/FSHD (assessed in n=731): n=79 (10.8%, 95% CI 8.6% to 13.3%) -CRT dose ≥40 Gy, 22.7% (95% CI 16.2% to 30.2%) -CRT dose <40 Gy, 7.8% (95% CI 5.7% to 10.2%) TSHD (assessed in n=743): n=56 (7.5%, 95% CI 5.7% to 9.7%)	Strengths Large cohort with systematic screening and long follow-up. Study uncovers many previously undetected HP dysfunction. Limitations No dynamic testing to establish diagnosis of GHD and ACTHD Dose cranial radiotherapy based on maximum tumor prescribed dose to the brain Risk of bias A. Selection bias: high risk, 748 out of 1175 (63.7%) eligible survivors were included in the study. B. Attrition bias: low risk, almost all survivors (97.7%) underwent endocrine testing for all four HP-axes

		Fasting morning (08.00 AM) blood sample of IGF-1, LH, FSH, total testosterone (males), estradiol (females), TSH, FT4, cortisol. Dynamic testing was not available for GHD and ACTHD. Before SJLIFE, patients were followed in St Jude Children's research hospital until alumni status was reached. Previously diagnosed pituitary deficiencies were extracted from the medical record, and clinically verified if not on hormone replacement therapy.	-CRT dose ≥40 Gy, 18.2% (95% CI 12.4% to 25.4%) -CRT dose <40 Gy, 4.9% (95% CI 3.3 to 6.9%) ACTHD (assessed in n=743): n=30 (4.0%, 95% CI 2.7% to 5.7%) -CRT dose ≥40 Gy, 13.3% (95% CI 2.7 to 5.7%) -CRT dose <40 Gy, 1.7% (95% CI 0.8 to 3.1%) <u>Latency time from treatment to HP disorder</u> Not reported <u>Cumulative incidence</u> Estimated cumulative incidence at 40 yrs GHD: 72.4% (95% CI 66.8% to 77.8%) LH/FSHD: 24.4% (95% CI 18.1% to 32.3%) TSHD: 11.6% (95% CI 8.1% to 16.4%) ACTHD: 5.2% (95% CI 3.3% to 8.0%) Kaplan meier included	C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. D. Confounding: not applicable
<u>Conclusion</u> • In a study of **748 childhood cancer survivors** (mean follow-up time of 27.3 years), treated with cranial radiotherapy, the estimated cumulative incidence at 40 years was 72.4% for GHD, 24.4% for LH/FSHD, 11.6% at TSHD and 5.2% for ACTHD.				

WG2: When should screening be initiated and for how long should screening be continued? How frequently should we screen?				
PE Clayton, Dose dependency of time of onset radiation-induced growth hormone deficiency, The Journal of Pediatrics (1991)				
Study design Treatment era Years of follow-up	**Participants**	**Treatment & screenings protocol**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort study, single center Treatment era: Not reported Follow-up: Median 4.3 yrs (0.2-18.9 yrs)	Study population: 82 survivors of childhood malignancy who received cranial/craniospinal RT for a childhood brain tumor or leukemia/other tumor (prophylactic RT) Male n=52 (63.4%) Female n=30 (36%.6) Primary cancer diagnosis: Brain tumor not involving the HPA, n=66 (80.5%) Leukemia, n=16 (19.5%) Age at treatment: Median 6.2 yrs (range 1-16.6 yrs) Age at follow-up:	CRT n=24 (29.3%) CSI n=58 (70.7%) RT details CRT for brain tumor (n=66): doses of 27 to 45 Gy Prophylactic cranio(spinal) RT for CNS leukemia (n=16): 16 at doses of 24 or 25 Gy in 10-12 fractions (n=12 had CRT, n=4 had CSI) Hypothalamic pituitary RT dose Range 27-47.5 Gy <30 Gy, n=46 (56.1%) ≥30 Gy, n=36 (43.9%)	Definitions ITT showing peak GH concentration of >15 mU/L during insulin-induced hypoglycemia was defined as normal, (after logarithmic transformation). For multivariable analysis, GH concentrations as continuous variables (log peak GH concentration) were used. Prevalence cancer survivors with GH deficiency: *At diagnosis:* not reported *At (last) follow-up (Cave number of abnormal tests reported, not patients having GHD)* GHD: incidence 74% of all tests *During interval 3-5 yrs post-cancer diagnosis:* *Cave number of abnormal tests reported, not patients having GHD* <30 Gy: 63.2% (24/38) ≥30 Gy: 100% (16/16) *During interval >5 yrs post-cancer diagnosis:*	Strengths -Original GH testing results retrieved and used for analysis -Hypothalamic pituitary dose calculated Limitations -Calendar period not reported -Surgery, chemotherapy, TBI not reported/analyzed -Protocol for testing ITT and methods to ensure adequate follow-up/tracing not reported -Not clear why some patients had 1 test and others had >1 -Not clear how follow-up time, loss to follow-up, and vital status are distributed by radiation dose -Not clear which and how many patients had recurrences nor on treatment or survival characteristics

	Not reported. (median can be estimated from median age at RT and median follow-up time to be 6.2+4.3=10.5 yrs	All had conventional RT Surgery, TBI and/or chemotherapy regimens are not reported <u>Start screening</u> Not reported <u>Frequency of screening</u> GH testing in all children by an insulin tolerance test on one (n=44) or more (n=38) occasions in the years after irradiation. <u>Screenings protocol</u> Not reported	<30 Gy: 85% (22/26) ≥30 Gy: 84% (21/25) -subgroup >35Gy: 100% GHD <5 years: 66.7% GHD >5 years: 84% <u>Latency time from treatment with radiotherapy to HP disorder</u> 55% of children became GH deficient within one year -Incidence of GHD varied from time from irradiation -GHD developed more rapidly in those who received the higher irradiation dose (≥30 Gy vs <30Gy, p<0.01) After five years, no difference in prevalence of GHD n the different RT groups (i.e. ≥30 Gy vs <30Gy) <u>Cumulative incidence</u> Not reported Kaplan meier included	-Multivariable model parameters not shown, except for p-values <u>Additional remarks</u> -1 of 38 patients with >1 test and who showed abnormal response later had a borderline normal GH response -74% of all ITT tests showed GH deficiency <u>Risk of bias</u> A. Selection bias: unclear how many patients were included in the original cohort of survivors B. Attrition bias: high risk, one ITT performed in 44 patients, >1 ITT performed in 38 patients. "On one or more occasions tested between 0.2-19.8 yrs after treatment) C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. D. Confounding: not applicable
<u>Conclusion</u> • In a study of **82 brain tumor or leukemia survivors** (median follow-up time of 4.3 yrs), treated with cranial radiotherapy and/or craniospinal radiotherapy, 55% of survivors had GHD within one year after irradiation. GHD developed more rapidly in those who received higher RT doses, but the incidence of GHD after >5yrs was not dependent on dose.				

WG2: When should screening be initiated and for how long should screening be continued? How frequently should we screen?				
SC Clement, Endocrine dysfunction among long-term survivors of childhood head and neck rhabdomyosarcoma, European Journal of Cancer (2015)				
Study design Treatment era Years of follow-up	**Participants**	**Treatment & screenings protocol**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort study three centers: GOSH, RMH, London and EKZ-AMC Amsterdam Treatment era: Jan 1990 – Dec 2010 Follow-up: Median 11.8 yrs (range 2.4 – 22.9 yrs)	Study population: 80 survivors < 18yrs at diagnosis Male n=52 (65%) Female n=28 (35%) Primary cancer diagnosis: Head and Neck Rhabdomyosarcoma, n=80 (100%) Histology -Embryonal rhabdomyosarcoma, n=67 (83.8%)	Initial Radiotherapy No RT, n=15 (18.8%) AMORE, n=25 (31.25%) EBRT, n=38 (47.5%) Proton, n=2 (2.5%) RT details Initial local RT dose median 45.0 Gy (range 36.0-57.8) First recurrence (n=17) local RT dose median 45.0 Gy (range 40.0-60.0 Gy) In total, n=74 (92.5%) received RT (initial or during follow-up), n=6 (7.5%) did not receive RT Chemotherapy	Definitions GHD: insufficient peak to GH stimulation test, in combination with low-IGF-1 TSHD: FT4 concentration below the reference range, in combination with inadequate low, normal or mildly raised TSH or use of thyroxine at for TSHD ACTHD: peak cortisol <550nmol/L in response ACTH stimulation test or peak 11-deoxycortisol <200nmol/L after Metyrapone or use of hydrocortisone at follow-up LH/FSHD: low FSH/LH concentration in the absence of pubertal development (girls > 12 years B1, boys > 13 years testes volume < 4) and decreased sex hormone levels. CPP: pubertal development in girls < 8 years Tanner stage B2, boys < 9 years testes volume > 4 ml) in	Strengths -Patients merged from three large centers to obtain large cohort of rhabdomyosarcoma patients Limitations -All had chemotherapy so any effect couldn't be analyzed -All had radiotherapy but given in a different way. -External beam treats a wider area -Brachytherapy is implanted and gives a very high dose to the tumor and close surrounding area only. -This retrospective study depended on chart review for timing and detection of endocrinopathies. -

	-Alveolar rhabdomyosarcoma, n=10 (12.5%) -Not specified, n=3 (3.8%) Location -Parameningeal, n=38 (47.5%) -Orbital, n=28 (35%) Head and neck non-parameningeal, n=10 (12.5%) Orbital and parameningeal, n=4 (5%) <u>Age at primary cancer diagnosis:</u> Median 5.2 yrs (range 0.0 - 13.6 yrs) <u>Age at follow-up:</u> Median 11.8 yrs (range 2.4 – 22.9 yrs)	All patients had multiagent chemo before local treatment no details given except 2-3 courses No details on initial surgery: Bx or resection <u>Start screening (e.g. after end of therapy)</u> Not reported <u>Frequency of screening</u> Endocrine function was routinely checked, usually annually, during oncologic follow-up, or at the multidisciplinary late-effects clinic in case endocrine function had not been assessed in the preceding year. All survivors had at least one endocrine evaluation between 2009-2012 <u>Screenings protocol</u> Survivors were evaluated in multidisciplinary late-effects clinics using a standard protocol, by evaluation of linear growth, TSH, FT4, IGF-1, IGFBP-3.	combination with a peak LH concentration of > 5 mU/L in response to GnRH stimulation test <u>Prevalence cancer survivors with HP dysfunction</u>: *At diagnosis:* None of the patients had been diagnosed with an endocrine disorder before cancer treatment. *At (last) follow-up:* Any pituitary deficiency: 24 (30%) GHD: n=22 (27.5%) TSHD: n=7 (9%) ACTHD: n=3 (4%) LH/FSHD: n=3 (4%) CPP: n=3 (4%) <u>Latency time from treatment to HP disorder</u> Any pituitary dysfunction: median 3.0 yrs (range 0.3-9.8) after cancer diagnosis GHD: median 3.2 yrs (range 2.0-11.1) after cancer diagnosis TSHD: median 4.5 yrs (range 0.3-11.9) after cancer diagnosis ACTHD: median 6.6 yrs (range 2.5-8.7) after cancer diagnosis LH/FSHD: 10.2 yrs (range 5.5-11.6) after cancer diagnosis CPP: 3.8 yrs (range 2.3-3.9) after cancer diagnosis <u>Cumulative incidence</u> Only demonstrated in Kaplan Meier curves	Gonadal function not routinely assessed. <u>Additional remarks</u> -I think this is an important paper for our purposes and future treatment options for patients in an attempt to reduce late effects. -when the multivariable model was adjusted for follow-up time, the estimates of the covariates were similar to described results <u>Risk of bias</u> A. Selection bias: high risk, 80 out of 112 (71.4%) eligible survivors were included in the study. B. Attrition bias: low, all survivors were evaluated at least once for HP-damage. Endocrine function was 'routinely' checked. C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. D. Confounding: not applicable
<u>Conclusion</u> • In a study of **80 rhabdomyosarcoma survivors** (median follow-up time of 11.8 yrs), treated according AMORE or EBRT protocol, GHD was diagnosed after median 3.2 yrs, TSHD after median 4.5 yrs, ACHTD after median 6.6 yrs, LH/FSHD after median 10.2 yrs and CPP after median 3.8 yrs after cancer diagnosis.				

WG2: When should screening be initiated and for how long should screening be continued? How frequently should we screen?				
HW Gan, Neuroendocrine Morbidity After Pediatric Optic Gliomas: A Longitudinal Analysis of 166 Children Over 30 Years, JCEM 2015				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment & screenings protocol**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort study, single center Treatment era: Between 1980-2010 Patients were stratified by treatment eras	General 166 survivors <16yrs at primary diagnosis Male n=76 (45.8%) Female n=90 (54.2%) Primary cancer diagnosis: All had low grade glioma affecting the optic pathway, hypothalamus or suprasellar area (OP/HSGs) Juvenile pilocytic astrocytoma, n=40 (24.1%)	Observation only: N=38 (22.9%) Surgery only: N=21 (12.7%) RT only N=15 (9.0%) Chemotherapy only N=20 (12.0%) Any surgery + RT	Definitions -GHD: serum GH peak concentration <7 ng/ml on an insulin tolerance or glucagon stimulation test -ACTHD: serum cortisol peak concentration <500nmol/L on an ITT OR short synacthen or low-dose synacthen test -TSHD: Low serum free thyroxine (fT4) concentrations in the presence of an inappropriately normal/ low TSH, based on age-appropriate reference ranges -LH/FSHD: Boys: Testicular volume <4mL at age 14 years OR failure to progress through puberty after normal onset (pubertal arrest) Girls: Tanner breast stage B1 at age 13 years OR pubertal arrest OR primary amenorrhea at age 16 years with Delayed bone age, undetectable serum concentrations of	Strengths -Large cohort with long-follow up period. Complete and thorough endocrine evaluations. Limitations -Authors assumed normal endocrine function without clinical or biochemical evidence to the contrary. -No subanalysis performed on individual treatment risks (e.g.

(1980-1996, 1997-2004, 2005-2010) <u>Follow-up:</u> Median follow-up 8.3yr (range 0.04-26.8)	Subependymal giant cell astrocytoma, n=2 (1.2%) Diffuse fibrillary astrocytoma, n=6 (3.6%) Pilomyxoid astrocytoma, n=3 (1.8%) Grade 1 not otherwise specified, n=9 (5.4%) Grade 2 not otherwise specified, n=3 (1.8%) No biopsy/histology, n=103 (62.0%) <u>Age at primary cancer diagnosis:</u> Median 4.9yr (range 0.2-15.4 yrs) <u>Age at follow-up:</u> Median 15.5yr (range 2.4-37.4 yrs)	N=31 (18.7%) <u>Any surgery + chemotherapy</u> N=18 (10.8%) <u>RT + Chemotherapy</u> N=6 (3.6%) <u>Any surgery + RT + Chemotherapy</u> N=17 (10.2%) *RT details:* Focal RT to total dose 48-55 Gy (25-30 fractions) All had conventional RT <u>Start screening</u> Not reported <u>Frequency of screening</u> Biochemical endocrine testing was performed in 75.4% between 1980-1996, 74.0% between 1997-2004, 82.4% between 2005-2010. <u>Screenings protocol</u> Unknown, follow-up in a single center	gonadal steroids (testosterone/ oestradiol) AND/OR poor or absent serum gonadotropin responses to GnRH stimulation testing -CPP: Boys: Testicular volume ≥4 ml prior to age 9 years Girls: Tanner breast stage B2 prior to age 8 years and advanced bone age, pubertal serum concentrations of gonadal steroids (testosterone/ oestradiol) AND/OR pubertal serum gonadotropin responses to GnRH stimulation testing (2.5 µg/kg GnRH) <u>Prevalence cancer survivors with HP dysfunction:</u> *At diagnosis* GHD: n=1 (0.6%) TSHD: n=2 (1.2%) ACTHD: n=1 (0.6%) LH/FSHD (assessed in 7): n=1 (14.3%) CPP (assessed in 123): n=14 (11.4%) *At last follow-up* GHD: n=67 (40.3%) TSHD: n=22 (13.3%) ACTHD: n=22 (13.3%) LH/FSHD (assessed in 103): n=21/103 (20.4%) CPP (assessed in 123): n=32 (26.0%) <u>Latency time from treatment to HP disorder</u> First endocrine event at a median of 0.8 yrs (range 0.0-14.2) from diagnosis. One patient developed isolated GHD 14.2 yrs postdiagnosis after chemotherapy alone. Multivariate cox proportional hazard ratios for EEFS -Hypothalamic involvement, adjusted HR 2.20 (95% CI 1.41-3.42)* -Primary radiotherapy, adjusted HR 1.98 (95% CI 1.16-3.39)* -Any radiotherapy, adjusted HR 1.67 (95% CI 0.95-2.94)	radiotherapy dose or degree of surgical resection). <u>Risk of bias</u> A. Selection bias: low risk, 166 out of 203 (81.8%) eligible survivors were included in the study. B. Attrition bias: unclear for how many survivors follow-up data was complete. 'Normal endocrine function was assumed without clinical or biochemical evidence to the contrary. C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. D. Confounding: not applicable

			Multivariate linear regression model with regression coefficient β for endocrine morbidity score (total number of hypothalamo-pituitary deficits at last follow up) -Any radiotherapy, β 1.27 (95% CI 0.88-1.65) -Diencephalic syndrome, β 0.93 (95% CI 0.23-1.63) -Number of surgeries, β 0.08 (95% CI 0.03-0.13) -Female sex, β -0.41 (95% CI -0.78-0.03) Cumulative incidence Only demonstrated in figures (Kaplan Meier included)	
Conclusion • In a study of **166 low grade glioma survivors** (median follow-up time of 8.3 years) the endocrine event-free survival was dependent on **hypothalamic involvement** and **primary radiotherapy**, and not on any radiotherapy.				

WG2: When should screening be initiated and for how long should screening be continued? How frequently should we screen?				
PM. Kanev, Growth hormone deficiency following radiation therapy of primary brain tumors in children, J. Neurosurgery (1991)				
Study design Treatment era Years of follow-up	**Participants**	**Treatment & Screenings protocol**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort study Treatment period: 1985-1987	Study population 123 children with a brain tumor, of whom 65 received radiotherapy and were alive at time of chart review (=study population) Male n=37 (56.9%) Female n=28 (43.1%)	Treatment of all children with a brain tumor (n=123) Radiotherapy n=95 (77.2%), of whom 30 deceased, remaining 65 are study population. *RT details* n=40 CSI field dosage	Definitions GHD: somatomedin-C levels, and if low, followed by provocative testing Criteria for GH replacement: fall off in stature and growth velocity, delayed bone age, depressed somatomedin-C levels and failure of GH testing <10ng/ml.	Strengths -Systematic clinical follow-up Limitations -Duration of FU not detailed but seems to be less than 48 months in most children -Endocrine evaluations are made only if growth velocity declined.

Follow-up: Not reported	Primary cancer diagnosis (n=65) Medulloblastoma, n=16 (24.6%) Astrocytoma, n=10 (15.4%) Oligodendroglioma, n=8 (12.3%) Brain stem, n=6 (9.2%) Optic pathway, n=6 (9.2%) Craniopharyngioma, n=5 (7.7%) Ependymoma, n=5 (7.7%) Germinoma, n=5 (7.7%) Pineoblastoma, n=2 (3.1%) Choroid plexus carcinoma, n=1 (1.5%) PNET, n=1 (1.5%) Age at diagnosis (n=65): Range 6 months to 18 years Age at follow-up: Not reported	Average whole brain exposure: 37.5 Gy, with posterior fossa boost 52.0 Gy, average spinal dose 35.0 Gy. n=31 supratentorial field average 51.0 Gy n=24 infratentorial field 53 Gy Chemotherapy only N=8 Observation only: N=5 (parents refused all treatments) Surgery only N=17 Start screening: Immediately Frequency of screening Every 3 months Screenings protocol Patient height (standing and sitting) and plotted in growth chart. Endocrinological evaluation and laboratory studies when growth velocity <4cm/yr in patients age>4yr or drop in height percentile <4yr. Endocrinological follow-up: bone age, T3, thyroxine, TSH, somatomedin-C, prolactin. Provocative GH testing if somatomedin-C levels were below age-specific values. -Serial assay of GH followed by L-dopa stimulation test and clonidine.	TSHD: T3, T4, TSH and serial TSH measurements during TRH testing. No cut-off values defined. Prevalence of HP dysfunction *At diagnosis* Not reported *At last follow-up* GHD: n=26 (40%) Panhypopituitarism: n=5 (7.7%) GHD was twice as common after focal infratentorial and CSI when adjuvant chemotherapy was involved. Latency time from tumor diagnosis to HP disorder GHD: mean 26 months in boys, and 17 months in girls. Range 6 months-42 months. Cumulative incidence: Not reported (No Kaplan Meier included)	-Hypothyroidism not divided into primary or central origin. Additional remarks Old study, few details Risk of bias A. Selection bias: unclear, 123 patients were treated for a brain tumor, but only 65 received radiotherapy and were alive, and thus included for the study on endocrinological outcomes. B. Attrition bias: high risk, endocrine evaluations only performed if growth velocity declined. C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. D. Confounding: not applicable

		-Serial TSH and prolactin assays followed by TRH testing -Oral metyrapone testing		
Conclusion • In a study of **65 brain tumor survivors** (median follow-up time unknown) treated with radiotherapy, GHD developed after 26 months in boys and after 17 months in girls.				

WG2: When should screening be initiated and for how long should screening be continued? How frequently should we screen?				
S. Laughton et al. Endocrine Outcomes for Children With Embryonal Brain Tumors After Risk-Adapted Craniospinal and Conformal Primary-Site Irradiation and High-Dose Chemotherapy With Stem-Cell Rescue on the SJMB-96 Trial, JCO 2008				
Study design Treatment era Years of follow-up	**Participants**	**Treatment & screenings protocol**	**Main outcomes**	**Additional remarks**
Study design Prospective cohort study Treatment era:	Study population 88 childhood cancer survivors diagnosed with a primary CNS embryonal tumor between the ages 3	Surgery, radiotherapy and chemotherapy followed by autologous stem cell support: All patients, n=88 (100%)	Definitions -GHD: serum GH peak concentration <10 µg/ml after an arginine tolerance or L-dopa test	Strengths -Prospective follow-up with solid measurements and definitions -Differences in hypothalamic RT dose considered

1996-2003 <u>Follow-up:</u> Entire cohort: Median 5.1 (range 2.1-9.6) years from date start radiation Average-risk patients: Median 5.1 (range 2.7-9.6) years from date start radiation High-risk patients: Median 4.7 (range 2.1-9.4) years from date start radiation	and 21 years, who were included in the SJMB-96 clinical trial and who had endocrine follow-up beyond 2 years from the start of RT <u>Primary cancer diagnosis:</u> *Supratentorial*, n=10 (11.4%): ATRT, n=5 (5.7%) Pineoblastoma, n=4 (4.5%) sPNET, n=1 (1.1%) *Infratentorial,* n=78 (88.6%)*:* ATRT, n=2 (2.3%) Medulloblastoma, n=75 (85.2%) PNET, n=1 (1.1%) <u>Age at primary cancer diagnosis:</u> Median 7.3 (range 3-20.1) years <u>Age at follow-up:</u> Not reported	Surgery and chemotherapy (including cisplatin, vincristine, cyclophosphamide) regimens were equal among both groups. Radiotherapy differed. *RT details* Average-risk patients (n=53): -Hypothalamus dose: median 38.6 Gy (range 26.3-50.1) -CSI dose: 23.4 Gy High-risk patients (n=35) hypothalamus: -Hypothalamus dose: median 50.5 Gy (range 39.3-56.9) -CSI dose: 39.6 Gy (range 36.0-40.5) All received conformal RT <u>Start screening:</u> Unknown <u>Frequency of screening</u> Regular intervals <u>Screenings protocol</u> Clinical evaluation for TSHD, GHD, ACTHD by primary neuro-oncology team and endocrinology specialists. Endocrine screening investigations were undertaken in all patients. When indicated by screening tests, stimulation tests were performed. Arginine and L-dopa tests, FT4, TSH, 1µg ACTH test and metyrapone test.	-TSHD: FT4 lower than the normal range, with a normal or low TSH level -ACTHD: cortisol level after 20 minutes <18µg/dL after 1µg ACTH test or 11-deoxycortisol level ≤7ng/dL after metyrapone test -LH/FSHD: not possible to assess due to young cohort <u>Prevalence of HP dysfunction</u> *At diagnosis* Not reported *At last follow-up* GHD (assessed in n=70): n=66 (94%) TSHD (assessed in n=87): n=9 (10%) ACTHD (assessed in n=76): n=33 (43%) <u>Latency time from initiation of RT to HP disorder</u> GHD (assessed in n=70): median 1.8 yrs (range 0.9-4.3) TSHD (assessed in n=87): median 1.8 yrs (range 1.1-3.7) ACTHD (assessed in n=76): not reported <u>Cumulative incidence</u> Cumulative incidence at 4 yrs GHD (assessed in n=70): 93% ± 4% -RT <42 Gy: 86.4 ± 7.0% -RT ≥42 Gy: 97.2% ± 3.5% TSHD (assessed in n=87): 23% ± 8% -RT <42 Gy: 10.6 ± 8.4% -RT ≥42 Gy: 44.4% ± 19.3% ACTHD (assessed in n=76): 38% ± 6% -RT <42 Gy: 36.3 ± 8.3%	<u>Limitations</u> -LH/FSHD could not be determined -Frequency of screening unknown <u>Additional remarks</u> x <u>Risk of bias</u> A. Selection bias: low risk, of 94 patients included in the study, 88 patients (93.6%) could be evaluated. B. Attrition bias: low risk, of the included 88 patients, in n=70 (79.5%) the GH axis could be evaluated C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. D. Confounding: not applicable

			-RT ≥42 Gy: 40.9% ± 8.7% There was a significant association between hypothalamus RT dose and the cumulative incidence of TSHD, but not for GHD and ACTHD. Kaplan Meier curve included	
Conclusion • In a study of **88 survivors of embryonal CNS tumors** (median follow-up time 5.1 yrs) treated with radiotherapy, the median latency time was 1.8 yrs for both GHD and THSD • The cumulative incidence at 4 yrs was 93% for GHD, 23% for TSHD and 38% for ACTHD.				

WG2: When should screening be initiated and for how long should screening be continued? How frequently should we screen?				
W. Leung, A Prospective Cohort Study of Late Sequelae of Pediatric Allogeneic Hematopoietic Stem Cell Transplantation, Medicine (2007)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment &** **Screenings protocol**	**Main outcomes**	**Additional remarks**

Study design Prospective cohort study Treatment period: 1990-2003 Follow-up: Median 9 yrs (range 3.1-15.9)	Study population 155 patients who survived >1yr after HSCT Male n=82 (53%) Female n=73 (47%) Primary cancer diagnosis Myeloid malignancy, n=84 (54%) Lymphoid malignancy, n=40 (26%) Nonmalignant, n=31 (20%) Age at diagnosis and/or treatment: Median 9.7 yrs (range 0.5-21.4) at time of HSCT Age at follow-up: Median 18.5 yrs (range 4.6-36.1)	All patients received myeloablative conditioning Bone marrow transplant, n=145 (94%) Blood stem cell transplant, n=10 (6%) Conditioning regimens: Total body irradiation, n=123 (79%) Alkylator based, n=32 (21%) Dose of TBI: 14.4 Gy, n=59 (38%) 8-12 Gy, n=64 (41%) None (=conditioning with chemotherapy), n=32 (21%) All had conventional RT Start screening 1 year Frequency of screening Every year until at least 10 yrs after HSCT and until at least 18 yrs of age. Screenings protocol Complete physical examination together with thyroid function tests (total T4, FT4, TSH), gonadotropins (FSH, LH), testosterone or estradiol, cortisol, prolactin, IGF-1, IGFBP-3, bone age.	Definitions Central hypothyroidism: FT4 below the lower limit of normal without TSH elevation or FT4 in the lowest third of the normal range with a blunted TSH surge (<50% rise). Precocious puberty: onset of secondary sexual development before age 8 yrs in girls or 9 yrs in boys. Delayed puberty: no breast development by age 13 yrs or no menses by 14 yrs, no testis growth >3ml by age 14yrs in boys. ACTHD: peak cortisol ≤18 µg/dL to low-dose ACTH test or 11-deoxcortisol response to metyrapone was <7ng/dL with serum cortisol <5µg/L. GHD: peak serum GH concentration in response to arginine and L-dopa stimulation <10ng/mL. Dynamic endocrine evaluation was performed if initial endocrine screening suggested abnormality. Prevalence of HP dysfunction *At diagnosis:* Not reported *At (last) follow-up:* GHD, n=39 (25%) TSHD, n=5 (+4 mixed hypothyroidism) ACTHD, n=7 (5%) Precocious puberty: n=3 (of 136 who have attained pubertal normal age) Delayed puberty, unknown	Strengths - Prospective cohort study with annual follow-up of HP function after stem cell transplantation Limitations -No details on the time interval to central hypothyroidism (only hypothyroidism in general) or ACTH deficiency -Delayed puberty defined, but not reported. No distinction between primary or secondary cause of delayed puberty - Hypogonadism defined as elevated LH/FSH (no central origin) Additional remarks On the curve, begins to appear at 1 year, last event at 11 years. (but the longest FU is 15.9) Risk of bias A. Selection bias: low risk, 155 out of 204 (76.0%) eligible survivors were included in the study. B. Attrition bias: low risk, each patient had annual follow-up, regardless of signs and symptoms. C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome

		Evaluations by specialists in endocrinology. A dynamic endocrine evaluation was performed if initial endocrine testing suggested an abnormality. -Growth axis: GH stimulation test if slow growth rate and IGF-1 and/or IGFBP-3 <1SD -Thyroid axis: nocturnal TSH surge and/or TRH test (if slow growth rate and FT4 in lower third normal range) -Gonadal axis: GHRH test if sign of puberty starting too early or had not occurred at normal age, or if elevated LH/FSH -Adrenal axis: ACTH test if 08.00AM cortisol <20µg/dL	<u>Latency time from HSCT to HP disorder</u> GHD: median 36 months (25th percentile: 24 months and 75th percentile 58 months) <u>Cumulative incidence</u> Cumulative incidence at 10 yrs: GHD: 31.2% (95% CI 23.0-41.4) The cumulative incidence for GHD differed significantly by doses of irradiation (0 Gy, vs 8-12 Gy, vs 14.4 Gy, p<0.001) Kaplan Meier included	D. Confounding: not applicable
<u>Conclusion</u> • In a study of **155 survivors who underwent allogeneic hematopoietic stem cell transplantation** (median follow-up time 9 yrs), GHD occurred after a median of 36 months. • The cumulative incidence at 10 years for GHD is 31.2%				

WG2: When should screening be initiated and for how long should screening be continued? How frequently should we screen?				
TE. Merchant, Late Effects of Conformal Radiation Therapy for Pediatric Patients With Low-Grade Glioma: Prospective Evaluation of Cognitive, Endocrine, and Hearing Deficits, JCO (2009)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment &** **Screenings protocol**	**Main outcomes**	**Additional remarks**
Study design Prospective cohort study Treatment period: Aug 1997- Aug 2006 Follow-up: Not reported. Data provided for 12 & 24 months after start radiotherapy	Study population 78 survivors of low grade glioma (First 50 only examined endocrinologically) Male n=39 (50%) Female n=39 (50%) Primary cancer diagnosis Low grade glioma Location: -Central or diencephalic/optic pathway, n= 58 (74.3%) -Cerebral hemisphere, n=3 (3.8%) -Cerebellum, n=17 (21.8%) 13 (16.7%) patients had NF-1 Age at diagnosis and/or treatment:	All patients received cranial radiotherapy *RT details* 54Gy in 6 weeks (1.8Gy fractions) All received conformal cranial radiotherapy or intensity-modulated radiation therapy (n=3) Prior chemotherapy n=25 (32.1%) Surgery *Number of surgeries* None, n=13 (16.7%) One, n=42 (53.8%) More than one, n=23 (29.5%) *Extent of surgery* No biopsy, n=13 (16.7%) Biopsy, n=30 (38.5%) Subtotal resection, n=35 (44.9%) Other treatment: Hydrocephalus present at diagnosis in n=31 (39.7%), VP shunt required in n=29 (37.2%) Start screening Before CRT provocative testing in 50 patients. Thereafter endocrinopathy defined by	Definitions GHD: response to ATT/l-dopa < 10 ng/mL (10 µg/L) TSHD: nocturnal TSH surge <50% or >300% of afternoon TSH nadir. Alternatively, abnormal TRH testing defined as either delayed peak or prolonged plateau of TSH (60-min postpeak TSH value >75% peak value) was indicative of TSH disturbance ACTHD: 1-µg ACTH test with 20-min post-ACTH cortisol level ≤18 µg/dL (500 nmol/L) or 11-deoxycortisol level ≤7 ng/dL metyrapone test LH/FSHD: GnRH stimulation test with rise in LH or FSH <5 mIU/mL for females >13 years and males >14 years CPP: diagnosis based on clinical and laboratory evidence of CPP, with abnormal GnRH stimulation test The incidence of hormone replacement therapy (HRT) was determined from a database. Prevalence of HP dysfunction *Before radiotherapy:* -Glucocorticoid: n=3 -GnRH analog: n=6 -GH peak <10 ng/mL: n=18/42 *At start radiotherapy (n=50 evaluated):* -Glucocorticoid: n=7 (14%) -GnRH analog: n=6 (12%) *At 12 months after radiotherapy:*	Strengths Well defined population and treatment. Limitations -Use of hormone prescriptions rather than results of endocrine testing. -No documentation of numbers of patients studied at time points, except baseline. -Given the study is based on prescription of hormones for replacement it is unclear why only the first 50 patients were studied. - XRT dose at HP axis unclear. -Use of thyroid hormone and sex hormone replacement excluded as it does not refer to primary or central origin. Additional remarks x Risk of bias A. Selection bias: low risk, all patients enrolled in the

	Mean 9.7 ± 4.4 yrs after start radiotherapy Median 8.9 yrs (range 2.2-19.8) after start radiotherapy <u>Age at follow-up:</u> Not reported	proportion of patients on hormone replacement therapy in database at 12 & 24 months. <u>Frequency of screening</u> Clinical examinations were performed every three months for the first 2 years, every 6 months through 5 years, and then yearly through 10 years. <u>Screenings protocol</u> The first 50 patients were subjected to a battery of provocative tests before and after CRT. Before CRT, arginine and L-dopa tests, TSH surge, TRH test, ACTH test, metyrapone test and GnRH test were used. The incidence of hormone replacement therapy (HRT) was determined from a database that records the initiation of HRT for each patient and accounts for those who were replacing hormones at the initiation of CRT.	-Glucocorticoid: n=9 (18%) -GnRH analog: n=8 (16%) *At 24 months after radiotherapy:* -Glucocorticoid: n=11 (22%) -GnRH analog: n=11 (22%) One patient required sex hormone replacement within 24 months of irradiation <u>Latency time from treatment to HP disorder</u> Not reported <u>Cumulative incidence at 5 years after RT (n=50)</u> GH replacement: 46% ± 7.2 Glucocorticoid replacement: 19.2% ± 5.8 GnRH analogue therapy: 31.8% ± 7.1 <u>Cumulative incidence at 10 years after RT</u> GH replacement: 48.9% ± 7.4 Glucocorticoid replacement: 19.2% ± 5.8 GnRH analog therapy: 34.2% ± 7.3 (two of the patients did not have CPP, but were treated with GnRH analog to increase time for growth promotion) <u>Cumulative incidence at 10 years after RT ≥40 Gy to hypothalamus (n=43)</u> GH replacement: 54.7% Glucocorticoid replacement: 20% GnRH analog therapy: 35.3% Kaplan Meier included	original study (phase 2 study of CRT study St Jude) were included. B. Attrition bias: high risk, 50 patients of 78 (64.1%) were subjected to a battery of provocative tests before and after radiotherapy. C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: not applicable
<u>Conclusion</u> • In a study of **78 survivors low grade glioma survivors who received radiotherapy** (median follow-up time unknown), the cumulative incidence was 49.8% for GH replacement, 64.0% for thyroid hormone replacement, 19.2 for glucocorticoid replacement, 14.1% for sex hormone replacement and 34.2% for GnRH analog therapy.				

WG2: When should screening be initiated and for how long should screening be continued? How frequently should we screen?				
TE. Merchant, Growth Hormone Secretion After Conformal Radiation Therapy in Pediatric Patients With Localized Brain Tumors, JCO (2011)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment &** **Screenings protocol**	**Main outcomes**	**Additional remarks**
<u>Study design</u> Prospective cohort study <u>Treatment period:</u> 1997-2008 <u>Follow-up:</u> Up to 60 months follow up. Mean follow-up not reported. Serial endocrine testing for GHD before CRT, and at 6, 12, 36, and 60 months follow-up.	<u>Study population</u> n=192 pediatric patients with localized brain tumors Gender unknown <u>Primary cancer diagnosis</u> Ependymoma, n=88 (45.8%) Low grade glioma, n=51 (26.6%) Craniopharyngioma, n=28 (14.6%) High grade glioma, n=23 (12.0%) Other tumours, n=2 (1.0%) <u>Age at diagnosis and/or treatment:</u> Not reported <u>Age at follow-up:</u> Not reported	All received cranial radiotherapy or intensity-modulated radiation therapy Information on RT dose or additional treatments not reported in study. Authors refer to previously published work: Ependymoma: CRT dose 59.4 Gy, n=73 CRT dose 54.0 Gy, n=15 Low grade glioma: CRT dose 54 Gy, n=unknown <u>Start screening</u> Baseline and then at 6 months post-XRT	<u>Definitions</u> Arginine tolerance/L-dopa test at baseline, 6, 12, 36 and 60 months after initiation of CRT GHD: peak GH response to arginine/L-dopa test <7ng/mL <u>Prevalence of HP dysfunction</u> *At diagnosis:* 39 of 170 patients (22.9%) had pre-irradiation GHD. *At (last) follow-up:* Not reported <u>Latency time from treatment to HP disorder, prediction model:</u> Average patient would develop GHD with the following combinations of time and dose to hypothalamus: 12 months and >60Gy; 36 months and 25-30Gy; 60 months and 15-20Gy.	<u>Strengths</u> -Relatively large cohort. -Data modelling into prediction models -Prospective study design; <u>Limitations</u> -Only GH axis reported. -GH stimulation tests used arginine/L-dopa test. -Unclear regarding absolute numbers that developed GHD as data modelled. - Important information missing on basic population characteristics <u>Additional remarks</u> x <u>Risk of bias</u> A. Selection bias: unclear how many patients were included in the original cohort of survivors B. Attrition bias: unclear, n=118 patients (without GHD at baseline) underwent GH

		<u>Frequency of screening</u> Screening performed at baseline (n=118), 6 (n=110), 12 (n=113), 36 (n=72), and 60 (n=56) months after initialization of XRT <u>Screenings protocol</u> The arginine tolerance/L-dopa test was performed at baseline, 6, 12, 36 and 60 months after initiation or radiotherapy.	<u>Cumulative incidence</u> Not reported Exponential decline in peak GH defined by time and XRT dose defined by "peak GH = exp(2.5947 + {time x [0.0019 –(0.00079 x mean dose) Kaplan Meier included	testing at t=0 and n=56 had t=60 months measurements. Unclear how many of these patients developed GHD and were not further tested. C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: not applicable
<u>Conclusion</u> • In a study of **192 survivors who received cranial radiotherapy** (follow-up at start CRT, and 6,12, 36 and 60 months after CRT), the peak of GH to stimulation testing was dependent on time and hypothalamic radiation dose.				

WG2: When should screening be initiated and for how long should screening be continued? How frequently should we screen?				
E. Ramanauskienė, Early development of endocrine and metabolic consequences after treatment of central nervous system tumors in children, Medicina (2014)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment &** **Screenings protocol**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort study Treatment period: January 2000- September 2011 Follow-up after: Median 21 months (range 0.25–10.6 years) after completion of cancer treatment	Study population 51 children treated for CNS tumors, excluding craniopharyngioma Male n=32 (62.7%) Female n=19 (37.3%) Primary cancer diagnosis WHO grade I–II glioma, n=17 (33.3%) WHO grade III–IV glioma, n=2 (3.9%) Medulloblastoma/PNET, n=13 (25.5%)	Surgery: Total excision, n=13 (25.5%) Partial/subtotal resection, n=19 (37.3%) Biopsy, n=10 (19.6%) Not applied, n=9 (17.6%) Radiotherapy: n=29 (56.9%) *RT details* -CRT, n=13 (25.5%) -CSI, n=16 (31.4%) Mean cumulative dose, 54.2 Gy (range 45.0–60.0) All had conventional RT Chemotherapy:	Definitions TSHD: low or normal TSH and a low level of FT4 ACTHD: morning (<10.00 AM) serum cortisol <138nmol/L For low IGF-1, no cut-off values were defined Prevalence of HP dysfunction *At diagnosis:* Not reported *At (last) follow-up:* Low IGF-1: n=unknown, 58.3% TSHD: n=unknown, 25.9% Cortisol deficiency: n=1 (4.2%) Latency time from end of treatment to HP disorder Low IGF-1: mean 30.7 months (95% CI 19.9–41.4)	Strengths -The paper underlines that endocrine/metabolic derangements are starting to be detectable as early as 12 months after the end of cancer therapy Limitations -Endocrinological data were available only in 51 out of 258 children treated for CNS tumors; no indications about this subgroup selection was specified -The start of follow up and how often screening was performed it is not mentioned -Low IGF-1 conditions were not investigated by GH stimulation test; no conclusions can be drawn on GHD

	WHO grade I–II ependymoma, n=2 (3.9%) WHO grade III–IV ependymoma, n=7 (13.7%) Intracranial germ cell tumor, n=1 (2.0%) Unidentified n=9 (17.6%) *Tumor location* Supratentorial, n=12 (23.5%) Midbrain/optic nerve, n=16 (31.4%) Subtentorial, n=18 (35.3%) Brainstem, n=3 (5.9%) Disseminated tumor, n=2 (3.9%) <u>Age at tumor diagnosis</u> Mean 7.9 yrs (range, 0.25–17.2)	n=26 (51%), of which n=3 chemotherapy alone (carboplatin/vincristine or carboplatin/etoposide or lomustine/cisplatin/vincristine and/or methotrexate/carboplatin/vincristine) <u>Chemotherapy and radiotherapy</u> n=14 (27.5%) <u>No treatment</u> n=9 (7.8% <u>Other treatments</u> The majority were given glucocorticoids in the preoperative or postoperative period and/or during radiotherapy <u>Start screening</u> At or later than 3 months after the completion of brain tumor treatment <u>Frequency of screening:</u> Not reported <u>Screenings protocol</u> Patients included who were tested for endocrinological consequences at least once at or later than 3 months after completion of brain tumor treatment. Data on endocrine consequences were collected from medical records. The status of the endocrine system was evaluated by measuring IGF-1, TSH, FT4, morning cortisol.	-Chemotherapy (yes): mean 20.2 months (95% CI 11.4-28.9) -Chemotherapy (no): 44.4 months (95% CI 25.7-63.1) Chemotherapy was associated with earlier decrease in IGF-1 levels (p=0.035) TSHD: mean 61.6 months (95% CI 44.7-77.4) Cortisol deficiency: 83.4 months (95% CI 7.1-95.5%) <u>Cumulative incidence</u> Cumulative incidence at 1 year after end of treatment -Low IGF-1: 32.4% ± 10.1% -TSHD: 4.8% ± 4.6% -Cortisol deficiency: 0% Cumulative incidence at 2 years after end of treatment -Low IGF-1: 52.1% ± 12.0% -TSHD: 33.7% ± 11.4% -Cortisol deficiency: 9.1% ± 8.7% Cumulative incidence at 3 years after end of treatment - Low IGF-1: 60.1% ± 12.4% - TSHD: 33.7% ± 11.4% - Cortisol deficiency: 9.1% ± 8.7% Cumulative incidence at 4 years after end of treatment - Low IGF-1: 84.0% ± 10.1% - TSHD: 33.7% ± 11.4% - Cortisol deficiency: 9.1% ± 8.7% Cumulative incidence at 5 years after end of treatment - Low IGF-1: 84.0% ± 10.1% - TSHD: 33.7% ± 11.4% - Cortisol deficiency: 9.1% ± 8.7% No Kaplan Meier included	- Numbers of patients for each hormone or metabolic defect are sporadically specified; it is difficult to understand if the complete screening was performed in all the patients. (e.g. thyroid deficiency was reported in 11 out of 27 pts; no numbers but only prevalence is reported for TSHD and Primary Hypothyroidism -In the Kaplan-Meyer analyses numbers of patients at risk/year are not shown (risk of over or under-estimation of endocrine defects) <u>Additional remarks</u> The paper bears many inaccuracies due to the aforementioned limitations <u>Risk of bias</u> A. Selection bias: high risk, of the 258 CNS brain tumor patients, 133 patients were in remission, but only 51 patients (38.3%) were included for the analysis. B. Attrition bias: high risk, endocrine screening not systematically performed in all patients and not clarified throughout the entire manuscript C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: not applicable

Conclusion

- In a study of **51 brain tumor survivors** (median follow-up after 21 months completion of cancer treatment), the latency time to develop low IGF-1 is 30.7 months, TSHD 61.6 months and cortisol deficiency 83.4 months. Chemotherapy was associated with earlier decrease in IGF-1 levels.
- The cumulative incidence at 5 years after end of treatment was 84% for low-IGF-1, 33.7% for TSHD and 9.1% for cortisol deficiency

WG2: When should screening be initiated and for how long should screening be continued? How frequently should we screen?

JE. Sanders, Final adult height of patients who received hematopoietic cell transplantation in childhood, Blood (2005)

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment &** **Screenings protocol**	**Main outcomes**	**Additional remarks**
Study design Prospective cohort study Treatment period: July 1978-July 2000 Follow-up: Total group, not reported	Study population 90 GH deficient survivors of hematopoietic cell transplantation (HCT) before the age of 18 yrs, who survived >2yrs and had reached >16yrs of age. Male n=55 (61.1%) Female n=35 (38.9%)	All patients received hematopoietic cell transplantation after fractionated TBI Radiotherapy: All received TBI, n=32 also preceding CNS irradiation (range 9-24 Gy) *RT details* TBI regimen 12 Gy, n=17 (18.9%) TBI regimen 14-15.75Gy, n=73 (81.1%) TBI dose: 12.0 Gy (2.0 Gy/d for 6 days, n=17) 14.0 Gy (2.0 Gy/d for 7 days, n=3)	Definitions GHD: two abnormal tests results to two tests that measured GH production: -spontaneous GH production by 12-hour sampling, every 20 minutes. Abnormal results ≤3 spontaneous GH peaks, and cumulative GH production >3 ng/dL -GH stimulation test (i.e. Clonidine) GH peak <8.6 ng/dL at 60 and 90 minutes. Prevalence of HP dysfunction *At diagnosis:* Not reported	Strengths: -The study design is robust and guaranties very clear pictures of the prevalence of thyroid and gonadal function (primary dysfunction) over time in the GHD cohort after HCT, underlining early endocrine derangement (GHD already after a median of 1,3 years after HCT). Limitations: -Having GHD was the main inclusion criterion and treatment risk factors were considered

GH treatment (n=42, yes): median 11.0 yrs (range 3.2-23) GH treatment (n=48, no): median 11.2 yrs (range 2.7-20.3)	<u>Primary cancer diagnosis</u> ALL, n=45 (50%) NHL, n=3 (3.3%) AML, n=23 (25.6%) MDS, n=4 (4.4%) CML, n=15 (16.7%) <u>Age at HCT:</u> Total group, not reported GH treatment (yes) median 7.9 yrs (range 1.0-14) GH treatment (no) median 11 yrs (range 2.9-15) <u>Age at follow-up:</u> Not reported	14.4 Gy (1.2 Gy 3 times a day for 4 days, n=33) 15.75 Gy (2.25 Gy/d for 7 days, n=37) All received Cobalt-60 RT <u>Type of HCT</u> Allogeneic identical sibling, n=41 (45.6%) Allogeneic unrelated donor, n=17 (18.9%) Allogeneic mismatched, family n=29 (32.2%) Autologous, n=3 (3.3%) <u>Chemotherapy</u> All received cyclophosphamide at 60 mg/kg per day for 2 days <u>Other treatment</u> Glucocorticoids, n=66 Cyclosporin or tacrolimus, n=69 for a median of 9.5 (range, 1.9-135.2) months <u>Start screening</u> One year after HCT <u>Frequency of screening</u> Annually until subjects were 17 or final height was achieved and gonadal maturity was reached, whichever occurred first <u>Screenings protocol</u> Serum was obtained for thyroid function, growth hormone and insulin-like growth factor and gonadotropin levels, also bone age, Tanner stage, height measurements. In general, all patients underwent two tests to measure GH production:	*At (last) follow-up:* Sex hormone replacement therapy, n=37 (41.1%) GHD: 90 of 107 patients tested (84.1%) <u>Latency time from HCT to HP disorder</u> GHD: median 1.3 years (range, 0.8-9.5) after HCT <u>Cumulative incidence:</u> Not reported (no Kaplan Meier included)	within height outcome and not overall endocrine outcomes. -Study evaluated only primary thyroid and gonadal failure. -Evaluation of glucocorticoid axis difficult due to active steroid use for graft versus host disease. <u>Additional remarks:</u> The paper shows that early treatment with GH (<10 years of age) and being females is associated to a better final height in GHD patients after HCT, also after correcting for CRT, steroid use and height at the time of HCT. ALL and NHL diagnosis were associated to a reduced final height compared to other diagnosis. <u>Risk of bias</u> A. Selection bias: high risk, of 183 patients who met protocol entry, 90 were included in the study (49.2%) B. Attrition bias: low risk, all patients underwent two tests to measure GH production, prospective follow-up. C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. D. Confounding: not applicable

		spontaneous GH secretion (12 hour sampling) and clonidine stimulation.		
Conclusion • In a study of **90 survivors who underwent hematopoietic cell transplantation** (median follow-up time 11 yrs), GHD occurred after a median of 1.3 years.				

WG2: When should screening be initiated and for how long should screening be continued? How frequently should we screen?				
S. Shalitin, Endocrine Outcome in Long-Term Survivors of Childhood Brain Tumors, Hormone Research in Paediatrics (2011)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment &** **Screenings protocol**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort study Treatment period: (diagnosed between) 1986-2005	Study population: 114 childhood brain tumor survivors (excluding craniopharyngioma or pituitary secreting adenoma) with a follow-up >2yr and age <30yr at follow-up Male n=68 (59.6%) Female n=46 (40.4%)	Neurosurgery + chemotherapy + radiotherapy N=52 (45.6%) Neurosurgery + chemotherapy N=23 (20.2%) Neurosurgery + radiotherapy N=9 (7.9%)	Definitions GHD: GH peak <10 ng/ml to stimulation with clonidine or glucagon Hypogonadotropic hypogonadism: lack of LH increase after GnRH stimulation and prepubertal sex hormones (estradiol <20 pmol/L in females, testosterone <0.7 nmol/L in males) ACTHD: peak cortisol <540 nmol/L after Synacthen test (250 µg)	Strengths -Long follow up -Detailed information on endocrine sequelae -Annual screening for HP dysfunction Limitations -Other tumors including pituitary adenomas (n=1)

Follow-up: Mean 12.8 ± 6.25 yrs (range 3.7-28.7)	Primary cancer diagnosis: Optic glioma, n=30 (26.3%) Medulloblastoma, n=29 (25.4%) Astrocytoma, n=26 (22.8%) Ependymoma, n=9 (7.9%) Germinoma, n=6 (5.3%) Other, n=14 (12.3%) including brain stem glioma, pineoblastoma, choroid plexus carcinoma, primitive neuroectodermal tumor, neurocytoma, lymphoma or the brain, medulloepithelioma, meningioma and nonsecreting pituitary adenoma. Age at diagnosis: Mean 7.07 ± 5.42 yrs (range 0.1-23.9 yrs) Age at follow-up: Mean 15.57 ± 5.93 yrs (range 3.8-30)	Chemotherapy + radiotherapy N=3 (2.6%) Neurosurgery only N=15 (13.2%) No therapy N=12 (10.5%) *RT details* -Cranial RT, n=55 (48.2%), RT dose 35-56 Gy -Spinal RT, n=27 (23.7%), RT dose 30-54 Gy Cave: not mutually exclusive All had conventional RT Start screening Not reported Frequency of screening Physical examinations were performed annually. Laboratory assessment for thyroid function performed annually. Screenings protocol Endocrine dysfunction was determined by the clinical manifestations and laboratory findings. Physical examinations included measurement of height, weight, and pubertal age (Tanner staging). Annual laboratory assessment including thyroid function.	TSHD: subnormal FT4 level (<10.5 pmol/ml) with a low, normal or mildly raised TSH level Early puberty: not defined in methods section Prevalence cancer survivors with HP dysfunction: *At diagnosis* Not reported *At (last) follow-up* GHD: n=40 (35.1%) LH/FSHD: n=9 (11%) ACTHD: n=9 (7.9%) TSHD: n=17 (14.9%) Early puberty: n=19 (16.7%) Latency time from diagnosis to HP disorder GHD: mean 4.43 ± 0.48 ACTHD: mean 3.94 ± 2.44 LH/FSHD: not possible to assess Latency time from chemotherapy to HP disorder GHD: mean 4.16 ± 0.58 ACTHD: mean 5.05 ± 2.91 LH/FSHD: not possible to assess Latency time from radiotherapy to HP disorder GHD: mean 3.96 ± 0.55 ACTHD: mean 4.78 ± 3.00 LH/FSHD: not possible to assess Cumulative incidence Not reported (no Kaplan Meier included)	-Study includes adolescence brain tumor survivors (max 23.9 yr at tumor diagnosis) -Latency time for hypothyroidism included both central and primary hypothyroidism Additional remarks x Risk of bias A. Selection bias: low risk, all 114 eligible patients included in study B. Attrition bias, low risk, annual physical examinations and laboratory assessments. C. Detection bias, unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: not applicable

		GH stimulation testing performed in patients with short stature (height <-2SD) or reduced growth velocity. Not stated when stimulation testing for the other HP axes was performed.		
Conclusion • In a study of **114 brain tumor survivors** (mean follow-up time 12.8 yrs), GHD occurred after a mean of 3.96 yrs after start radiotherapy, and ACTHD 4.78 yrs.				

WG2: When should screening be initiated and for how long should screening be continued? How frequently should we screen?				
S. Uday, Endocrine sequelae beyond 10 years in survivors of medulloblastoma, Clinical Endocrinology (2015)				
Study design Treatment era Years of follow-up	**Participants**	**Treatment Screenings protocol**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort study, single institution	Study population 35 survivors of medulloblastoma treated at	All patients received surgery and RT, and 27 (77%) chemotherapy. Radiotherapy *RT details*	Definitions Severe GHD: peak GH level <3 µg/L after glucagon stimulation test or ITT in adults. In pediatric patients cut-off value of peak GH level was <7 µg/L Partial GHD: peak GH level between 3 and 7 µg/L	Strengths Prolonged duration of follow-up; frequent assessment of endocrine function; use of stimulation assays

Treatment period: 1982-2002 Follow-up: Median 18 yrs (range 10-28)	single UK institution Male n=25 (71.4%) Female n=10 (28.6%) Primary cancer diagnosis Medulloblastoma--35 (100%) Age at diagnosis Median 8 yrs (range 2-14) Age at follow-up: Median 23 yrs (range 16-35)	CSI: n=32 (91.4%), median dose 35 Gy (range 23.4-36) and posterior fossa boost with median dose 55 Gy (range 54-55.8) Gy One patient received 35 Gy CSI + 12 Gy posterior fossa boost One patient received 35 Gy CSI + 28 Gy posterior fossa boost All received conventional photon RT without hyperfractionation Chemotherapy SIOP II (MTX/Procarb/ VCR/Pred), n=2 (6%) PNET3 (VCR/VP-16/ Cyclo/Cisplat), n=10 (29%) Packer (VCR/Cisplat/ CCNU), n=11 (31%) UK "Baby Brain" (VCR/ Cyclo/Cisplat/VP-16), n=3 (9%) One patient received ifosfamide based chemotherapy followed by high dose melphalan and an autologous transplant after relapse Eight patients did not receive chemotherapy Other treatment Eight patients developed hydrocephalus after surgery, requiring either VP shunt or external ventricular drain device. Start screening (e.g. after end of therapy) Not specifically reported Frequency of screening Thyroid function, cortisol, and gonadotropin levels checked annually, with stimulation tests every 2-3 years as clinically indicated Screenings protocol Investigations for assessment of endocrine dysfunction were carried out under the supervision of the pediatric and adult endocrinologists. Growth axis: 32 patients underwent glucagon stimulation testing, and three had an insulin stress	Complete ACTHD: peak cortisol 400 nmol/L after glucagon stimulation test or ITT Partial ACTHD: peak cortisol between 400 and 450 nmol/L after glucagon stimulation test or between 400 and 550 nmol/L after ITT TSHD: FT4 level <10 pmol/L in the presence of mildly elevated (TSH <10 miu/L) or normal or decreased TSH (patients with persistently suppressed TSH on LT4 were considered as have developed secondary hypothyroidism). Precocious puberty: thelarche in girls <8 yrs and testicular volume <4ml in boys <9yrs Delayed puberty: lack of thelarche in girls at 13 yrs and testicular volume <4mL in boys at 14 yrs Secondary hypogonadism: In the postpubertal age group, total testosterone <8 nmol/L in males and oestradiol <70 nmol/l in amenorrhoeic women, with inappropriately low gonadotropins. Prevalence cancer survivors with HP dysfunction: *At diagnosis* Not reported *At (last) follow-up* -Complete GHD: 28/35 (80%) -Partial GHD: 6/35 (17%) -Complete ACTHD: 13/35 (37%) -Partial ACTHD: 3 (8.5%) -Precocious puberty: 7/35 (20%) -Delayed puberty: 1/35 (2.8%) -Secondary hypogonadism: 2/35 (6%) -TSHD (possible, not confirmed 'suppressed levels of TSH on LT4'): 2/35 (6%) Latency time from end of treatment to HP disorder GHD: median 1.7 yrs (range 0.7-15) ACTHD: median 2.9 yrs (range 9 months -7.5)	Limitations No report of when screening initiated; single institution retrospective study; smaller sample size; no RT dose mapping to HPA available Additional remarks x Risk of bias A. Selection bias: high risk, of 109 medulloblastoma patients, 45 patients were alive, of whom 35 patients were included in the study (32.1%) B. Attrition bias: low risk, clear protocol; thyroid function, cortisol, and gonadotropin levels checked annually, with stimulation tests every 2-3 years as clinically indicated C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: not applicable

		test. Pediatric patients with a height velocity <25th percentile were considered to have clinical GHD and underwent dynamic tests. Gonadal axis: assessment according to Tanner method. Physical examination was carried out by a consultant pediatric endocrinologist.	Median time to other HP dysfunction not reported. <u>Cumulative incidence</u> Only demonstrated in figures (Kaplan Meier curves)	
<u>Conclusion</u> • In a study of **35 medulloblastoma survivors** (median follow-up time 18 yrs), GHD occurred after a median of 1.7 yrs after the end of treatment, and ACTHD after 2.9 yrs.				

WG2: When should screening be initiated and for how long should screening be continued? How frequently should we screen?				
TI. Yock, Long-term toxic effects of proton radiotherapy for paediatric medulloblastoma: a phase 2 single-arm study, Lancet Oncology (2016)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment** **Screenings protocol**	**Main outcomes**	**Additional remarks**

Study design Prospective, non-randomized, single center, phase 2 trial Treatment period: May 2003-December 2009 Follow-up: Median 7.0 yrs (IQR 5.2-8.6)	Study population 59 patients aged 3-21 years with newly diagnosed medulloblastoma or pineoblastoma Male n=33 (56%) Female n=26 (44%) Primary cancer diagnosis Medulloblastoma: 59/59 (100%) -Standard risk (i.e. minimal residual disease and not evidence of metastasis): 39/59 (66%) -Intermediate risk (i.e. minimal or no residual disease, no evidence of metastasis and have large cell or anaplastic histology): 6/59 (10%) -High risk: 14/59 (24%) Pineoblastoma: 0/59 (0%) Age at diagnosis Median 6.6 yrs (IQR 5.1-9.9)	Surgery: n=58/59 (98%) had resection of primary tumor attempted -Near GTR or GTR: 55/59 (93%) Chemotherapy All patients (59/59, 100%) received CT -52/59 (88%) received CT concurrent with radiotherapy *Chemotherapy details* Agents: vincristine, etoposide, carboplatin, cisplatin, cyclophosphamide, etoposide (in different combinations) -Median cisplatin dose: 348 mg/m2 (IQR 275-429) Radiotherapy (=proton therapy) All received radiotherapy (6/59 (10%) received <20% of RT as photons) *RT details* Median CSI dose: 23.4 GyRBE (IQR 23.4-27.0) -57/59 received 54 GyRBE boost -2/59 received >54 GyRBE boost Median hypothalamus dose: 28.4 GyRBE (IQR 24.2-42.8) -37/59 received <40 GyRBE hypothalamus dose -22/59 received ≥40 GyRBE hypothalamus dose Other treatment Twelve patients (20%) received a ventriculoperitoneal shunt Start screening At baseline and then yearly	Definitions Neuroendocrine assessment with IGF-1, IGFBP-3, TSH, FT4, estrogen, testosterone and morning cortisol. No cut-off values reported. Prevalence cancer survivors with HP dysfunction: *At diagnosis* Not reported *At (last) follow-up* GHD: 31/59 (52.5%) Latency time for HP dysfunction Not reported Cumulative incidence Cumulative incidence at 3 years after RT -Any neuroendocrine deficit: 27% (95% CI 16-39%) -GHD: 22% (95% CI 12-33%) -Cortisol deficit: 5% (95% CI 1-13%) Cumulative incidence at 5 years after RT -Any neuroendocrine deficit: 55% (95% CI 41-67%) -GHD: 46% (95% CI 33-59%) -Cortisol deficit: 9% (95% CI 3-17%) Cumulative incidence at 7 years after RT -Any neuroendocrine deficit: 63% (95% CI 48-75%) -GHD: 55% (95% CI 40-68%) -Cortisol deficit: 9% (95% CI 3-17%) No differences noted with sex, age at treatment, CSI or boost field *Subgroup analysis (cumulative incidence at 7 years of any neuroendocrine deficit)* -Hypothalamic mean dose (D50) (p= 0.054)	Strengths Prospective data; larger sample size than other proton studies; longer follow-up than other proton studies Limitations Does not differentiate primary vs secondary endocrinopathies for hypothyroidism and hypogonadism; uses IGF-1 and IGFBP-3 for assessment of GHD; uses AM cortisol for assessment of cortisol deficiency; does not measure gonadotropins Additional remarks 13 patients died during trial Risk of bias A. Selection bias: high risk, 60 patients were enrolled in the study, of whom one was ineligible and 13 patients died during the trial (unknown at what time points) B. Attrition bias: low risk, yearly endocrine measurements in total cohort. C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: not applicable

		<u>Frequency of screening</u> Yearly <u>Screenings protocol</u> Neuroendocrine assessment included height, weight, IGF-1, IGFBP-3, TSH, FT4, estrogen, testosterone, SHBG, morning cortisol, bone age)	-<40 GyRBE: 58% (37-74%) -≥40 GyRBE: 73% (47-88%) -Sex (p=0.592) -Male: 64% (41-79%) -Female: 62% (38-79%) -Age (p=0.499) -<8 years: 69% (48-83%) -≥8 years: 54% (28-74%) -Craniospinal irradiation dose (p=0.471) -18-27 GyRBE: 62% (44-76%) -36 GyRBE: 64% (31-84%) -Boost field (p=0.292) -Involved field: 58% (37-75%) -Whole posterior fossa: 70% (45-85%) No Kaplan Meier included	
<u>Conclusion</u> • In a study of **59 pediatric medulloblastoma patients** (median follow-up time 7.0 yrs), the cumulative incidence of any neuroendocrine deficit at 7 years was 63% and for GHD 55%. • The cumulative incidence was not dependent on hypothalamic radiotherapy dose, sex, age, craniospinal irradiation dose or boost field.				

WG2: When should screening be initiated and for how long should screening be continued? How frequently should we screen?				
SC Clement, Prevalence and Risk Factors of Early Endocrine Dysfunction in Childhood Brain Tumor Survivors: A Nationwide, Multicenter Study, JCO (2016)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort-study Treatment era: Diagnosis between 2002-2012 Follow-up: Median 6.6 ys (range 2.0-13.4)	Study population: 718 childhood brain tumor survivors, ≤18yrs at diagnosis, excluding craniopharyngioma and pituitary tumors and survived at least ≥2 years after diagnosis Male n=389 (54.2%) Female n=329 (45.8%) Primary cancer diagnosis: Low-grade glioma, n=358 (49.9%) DNET, n=17 (2.4%) High-grade glioma, n=18 (2.5%) Medulloblastoma, n=97 (13.5%) sPNET, n=13 (1.8%) Ependymoma, n=50 (7.0%) Choroid plexus tumors, n=20 (2.8%) Germ-cell tumor, n=26 (3.6%) ATRT, n=7 (1.0%) Other, n=23 (3.2%) Without histology, n=89 (12.4%) Age at treatment:	Wait and see N=52 (7.2%) Neurosurgery only N=328 (45.7%) Chemotherapy only N=26 (3.6%) Radiotherapy only N=6 (0.8%) Neurosurgery + chemotherapy N=54 (7.5%) Neurosurgery + radiotherapy N=91 (12.7%) Chemotherapy + radiotherapy N=2 (0.3%) Neurosurgery + chemotherapy + radiotherapy N=159 (22.1%) *RT details* Cranial RT dose, median 54.0 Gy (range 12.5-60.0) Craniospinal RT dose, median 24.0 Gy (range 18.0-39.7)	Definitions: GHD: insufficient peak response (<20 to 30 mU/L) after GH stimulation test with low IGF-1, or diagnosis by an endocrinologist ACTHD: use of hydrocortisone maintenance or substitution under suspicion of central hypocortisolism TSHD: FT4 below the age-specific reference range, in combination with low, normal or mildly raised (<10mU/L) TSH level, or use of LT4 for documented TSHD LH/FSHD: low LH and/or FSH in the absence of pubertal development, or use of estrogens or testosterone for the diagnosis LH/FSHD CPP: early onset of puberty (if Tanner B2 in girls <8 years, testes >4 mL in boys <9 years) Prevalence cancer survivors with HP dysfunction: *At diagnosis (assessed in n=206, but reported of the total cohort):* GHD: n=2 (0.3%) TSHD: n=7 (1.0%) ACTHD: n=7 (1.0%) CPP (evaluable in n=394): n=10 (1.4%) LH/FSHD (evaluable in n=481): n=1 (0.1%) *At (last) follow-up:* GHD: n=90 (12.5%) TSHD: n=66 (9.1%) ACTHD: n=31 (4.3%) CPP (evaluable in n=394): n=48 (12.2%)	Strengths -Large and relatively young cohort Limitations -Large proportion of the cohort did not receive endocrine screening -Large proportion of the cohort did not receive endocrine screening in a timely manner Risk of bias A. Selection bias: unclear how many patients were included in the original cohort of survivors B. Attrition bias: high risk, only 459 of 718 survivors (63.9%) underwent endocrine testing C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. D. Confounding: not applicable

	Mean 7.7 ys (range 0-17.7 ys) at diagnosis <u>Age at follow-up:</u> 15.1 yrs (range 3.0-29.3 ys)	<u>Start screening</u> Not reported <u>Frequency of screening</u> Not reported <u>Screenings protocol</u> Local screenings protocol, not further defined	LH/FSHD (evaluable in n=481): n=20 (4.2%) <u>Latency time for HP dysfunction after brain tumor diagnosis</u> GHD: median 2.5 yrs (range 0.05-8.4) TSHD: median 2.8 yrs (range 0.02-10.3) ACTHD: median 2.5 yrs (range 0.01-7.0) CPP: median 3.1 yrs (range 0.1-8.8) LH/FSHD: median 4.5 yrs (range 0.2-9.5) <u>Cumulative incidence at 5 years</u> -GHD: 11.1% (95% CI 6.2-17.4) -TSHD: 7.2% (95% CI 3.0-13.9) -ACTHD: 2.9% (95% CI 0.4-10.6) -CPP: 4.0% (95% CI 0.9-11.1) -LH/FSHD: 1.7% (95% 0.0-11.1)	
<u>Conclusion</u> • In a study of **718 childhood brain tumor survivors** (mean follow-up time of 6.6 years), GHD was diagnosed after median 2.5 yrs, TSHD after median 2.8 yrs, ACHTD after median 2.5 yrs, LH/FSHD after median 4.5 yrs and CPP after median 3.1 yrs after brain tumor diagnosis. • The cumulative incidence at 5 years was 11.1% for GHD, 7.2% for TSHD, 2.9% for ACTHD, 4.0% for CPP and 1.7% for LH/FSHD.				

WG3; What surveillance modality should be used?

WG3: What surveillance modality should be used?					
K.H. Darzy, S.M. Shalet, Circadian and Stimulated Thyrotropin Secretion in Cranially Irradiated Adult Cancer Survivors, JCEM (2005)					
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Diagnostic tests**	**Main outcomes**	**Additional remarks**
Study design Cross-sectional cohort study Treatment period: Not reported Follow-up: Median 11.5 yrs (range 2-29)	Study population 37 adult irradiated cancer survivors of nonpituitary brain tumors or leukemia, who were euthyroid (FT4 in reference range, without receiving LT4) Male n=26 (70.3%) Female n=11 (29.7%) Comparison population: 33 age-, gender-, and BMI matched controls Diagnosis Medulloblastoma, n=17 (45.9%) Germinoma, n=3 (8.1%) Ependymoma, n=2 (5.4%) Pinealoma, n=2 (5.4%) Astrocytoma, n=3 (8.1%)	Radiotherapy All had a history of whole brain irradiation and/or focal irradiation (18–64 Gy), n=27 patients had also received spinal irradiation. *RT details* Biological effective dose to the HP-axis median, 58.3 Gy (range 23–106.4 Gy) Cranial radiotherapy: n=10 (27.0%) Craniospinal radiotherapy: n=27 (73%), of whom n=2 TBI (5.4%)	Diagnostic test: 24-h TSH profiles, TRH test Reference test: Free T4 Cut-off levels to define presence of HP disorder: Not reported, as all were euthyroid TSH surge: >50% maximum TSH surge Analysis: Comparison between control group and whole	Only descriptive outcomes (all were euthyroid) Prevalence of HP dysfunction: GHD (partial or severe): n=21 (56.8%) LH/FSHD: n=0 ACTHD: n=0 TSH surge -Essentially normal -The maximum TSH surge calculated from the highest peak (average of the highest three sequential samples) and the smallest nadir (average of the smallest three sequential samples) in the whole 24-h profile period was above the cut off value of 50% in all except one control subject and two patients. -The nocturnal TSH surge was greatly reduced or absent in eight normal subjects (24%) and six patients (16%), not due to a genuine loss of diurnal rhythm, but due to a shift in the timing of the peak TSH and/or the nadir TSH to outside the recommended sampling times (for the nocturnal surge) of 2200–0400 and 1400–1800 h, respectively; (thereby	Strengths -Comprehensive investigation in a well characterized cohort including 24 hour profiles which enabled them to identify delayed TSH surge -Comparison with normal controls Long duration of follow up Limitations Small mixed cohort treated at different ages with different doses and followed for different period of time Additional remarks x Risk of bias A. Selection bias: unclear how many patients were eligible for the study

	Optic nerve meningioma, n=1 (2.7%) Spinal neuroectodermal tumor, n=1 (2.7%) Nasopharyngeal carcinoma, n=1 (2.7%) B-cell lymphoma, n=1 (2.7%) Choroid plexus carcinoma, n=1 (2.7%) ALL, n=3 (8.1%) AML, n=2 (5.4%) <u>Age at radiotherapy:</u> Childhood (n=28): 7.5 yrs (range 1.3-14) Adult (n=9): 26.8 yrs (range 17-49) <u>Age at test</u> Median 21.5 yrs (range 17–53.7)		group and those that have had craniospinal and those with GHD	potentially leading to an erroneous diagnosis of hidden central hypothyroidism) -Overall, the maximum TSH surge was significantly reduced only in the GH-deficient patients (compared with normal subjects <u>TRH test response</u> -None of the patients had a blunted response (subnormal TSH peak at 20min) -Six patients (16%) had a hypothalamic TSH response to TRH. Those with hypothalamic TRH test had a lower (NS) free T4 and TSH surge but all were still normal -FT4 did not correlate with any basal or stimulated TSH measurement, TSH decline, TSH surge, BED, age at irradiation or post-irradiation interval -Patients with FT4 in the lowest third of the reference range (n=16) had similar mean profile TSH, TSH responses to TRH test, maximum and nocturnal TSH surges, compared to patients with higher FT4 (n=21) -Patients with lower TSH surge (<50%) had similar FT4 distribution -CSI and GHD affected basal and stimulated TSH levels, but not FT4 concentrations	B. Verification bias: low risk, all patients underwent both testing modalities at the same time C. I/R test bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. D. Confounding: not applicable
<u>Conclusion</u> • In a cohort of **37 irradiated tumor survivors**, FT4 concentrations did not correlate with any basal or stimulated TSH measurement, TSH decline, TSH surge, BED, age at irradiation or post-irradiation interval. • Patients with FT4 concentrations in the lowest third of the reference range, had similar basal or stimulated TSH measurements compared to patients with higher FT4 levels. The nocturnal TSH surge was reduced or absent in a proportion of both patients and controls, due to a shift in timing of the peak TSH.					

WG3: What surveillance modality should be used?					
C. Hua et al., Predicting the Probability of Abnormal Stimulated Growth Hormone Response in Children After Radiotherapy for Brain Tumors, Int J Radiation Oncol Biol Phys (2012)					
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Diagnostic tests**	**Main outcomes**	**Additional remarks**
Study design Prospective single center cohort study Treatment period: 1997-2008 Follow-up: Median 3 yrs (range 0.4-5.8)	Study population 106 brain tumor survivors, with normal GH level pre-radiotherapy and ≤17.5 yrs in males, ≤14.5 yrs in females at time of testing Male n=59 (55.7%) Female n=47 (44.3%) Diagnosis Low grade glioma, n=28 (26.4%) Ependymoma, n=72 (67.9%) Craniopharyngioma, n=6 (5.7%) Supratentorial, n=41 (38.7%) Infratentorial, n=65 (61.3%) Age at start radiotherapy	All received cranial radiotherapy *RT details* Low grade glioma, 54 Gy Craniopharyngioma, 54-55.8 Gy Ependymoma, 54-59.4 Gy	Diagnostic test IGF-1, IGFBP3 (standardized in z-scores) Reference test GH stimulation test; arginine and L-dopa test Testing at start radiotherapy, and 6, 12, 36 and 60 months after therapy Other measurements obtained: Height, weight, growth velocity and BMI Cut-off levels GHD: <7 ng/ml	Correlation/association Univariable analysis: IGF-1 z-score (p=0.0005), IGFBP-3 z-score (p=0.0066), weight z-score (p<0.0001), BMI z-score (p<0.0001), pituitary dose (p<0.0001), hypothalamus dose (p<0.0001) and tumor location (p=0.0002) Multivariable logistic regression analysis for stimulated GH peak <7 ng/mL: IGF-1 z score, OR 0.421 (95% CI 0.280-0.633) Weight z score, OR 2.668 (95% CI 1.838-3.873)	Strengths -Prospective study -All patients were consistently treated per protocol -All patients were tested for GH secretion throughout follow-up Limitations -Cutoff of 10 ng/ml identified same predicting variables -Need external validation using independent data set Risk of bias A. Selection bias: unknown how many patients were eligible for the study

	Median 5.6 yrs (range 1.1-16.6) <u>Age at testing:</u> Median 5.6 years (range 1.1-16.6, testing started at start radiotherapy)		<u>Analysis:</u> -Univariable logistic regression analysis to assess the association between stimulated GH peak levels and basal levels of growth factors. -Peak GH levels log transformed and used as dependent variable in backward logistic regression model. -Model performance by evaluating the receiver operating characteristic against the original test data	Hypothalamic dose, OR 1.056 (95% CI 1.034-1.078) <u>Are under the curve of model:</u> 0.883 If model with only IGF-1 used, AUC 0.651 If model with only IGFBP-3 used, AUC 0.671 <u>Sensitivity of model</u> 80% <u>Specificity of model</u> 78% <u>Negative or positive predictive value of model</u> Not reported -Patients who received <20 Gy to hypothalamus and maintained normal body weight are highly likely to have a normal GH stimulation test. -In patients who received >20 Gy, the GH stimulation test is likely to be abnormal if they are obese or have low IGF-1 level.	B. Verification bias: high risk, GH testing at five different time points, but only 191 tests in 106 children performed. IGF-1 or IGFBP-3 values were included if they were measured no more than 1 week before or after the stimulation test. C. I/R test bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. D. Confounding: not applicable
<u>Conclusion</u> • In a cohort of **106 irradiated brain tumor survivors**, GH stimulated peak was best predicted by a model including **IGF-1 z score**, **BMI** and **hypothalamic dose** (AUC 0.883). A model including only IGF-1 or IGFBP-3 decreased the AUC to 0.651 and 0.671 respectively.					

WG3: What surveillance modality should be used?					
B. Patterson et al., Adrenal Function Testing in Pediatric Cancer Survivors, Pediatr Blood Cancer (2009)					
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Diagnostic tests**	**Main outcomes**	**Additional remarks**
Study design Single center retrospective chart review Treatment period: Not reported (adrenal testing between 2003-2007) Follow-up: Mean 5.8 yrs ± 4.0 since cancer diagnosis	Study population 78 childhood cancer survivors with or without HP involvement, referred for adrenal function testing at a childhood cancer treatment center Male n=44 (56.4%) Female n=34 (43.6%) Diagnosis Medulloblastoma, n=15 (19.2%)	Radiotherapy N=53 (67.9%) *RT details* 10-19.9 Gy, n=12 20-29.9 Gy, n=17 30-39.9 Gy, n=8 40 Gy or more, n=12 Dose unknown, n=4 Surgery Primary tumor or surgery of	Diagnostic test 08.00 AM cortisol or Low dose ACTH test (LDCT, <1mcg) Reference test Low dose ACTH test (<1mcg) or standard dose ACTH test (SDCT, 225 mcg) Cut-off levels: ACTHD: Basal cortisol ≤365 nmol/L	Presence of HP disorder ACTHD: 75% after 08.00 AM cortisol ACTHD: 69% after random cortisol ACTHD: 35% after LDCT ACTHD: 11% after SDCT GHD, n=45 Hypothyroidism (primary/central), n=48 CPP, n=20 Hypogonadism (primary/central), n=37	Strengths -Study illustrates why there is controversy around the best testing modalities for AI as different modalities do not give the same results, but it does demonstrate that random cortisol is not useful. Limitations -Convenience sample. -No gold standard.

	Leukemia/lymphoma, n=14 (17.9%) Craniopharyngioma, n=9 (11.5%) Neuroblastoma, n=7 (9.0%) Nasopharyngeal rhabdomyosarcoma, n=6 (7.7%) Other brain tumor, n=5 (6.4%) Pineal tumor, n=5 (6.4%) Pituitary adenoma, n=4 (5.1%) Other solid tumor, n=4 (5.1%) Histiocytosis, n=3 (3.8%) Juvenile pilocytic astrocytoma, n=3 (3.8%) Optic nerve glioma, n=2 (2.6%) Hematological disorder, n=1 (1.3%) <u>Age at diagnosis:</u> Mean 6.5 yrs ± 4.4 <u>Age at testing:</u> Not reported	hypothalamus/pituitary, n=23 (29.5%)	ACTHD: cortisol <500 nmol/L after LDCT or SDCT <u>Analysis:</u> Agreement between basal cortisol levels, LDCT and SDCT was evaluation by kappa calculation	<u>According to RT dose</u> >40 Gy: ACTHD 83% after LDCT 30-39.9 Gy: ACTHD 50% after LDCT 20-29.9 Gy: ACTHD 12% after LDCT <20 Gy: ACTHD 8% after LDCT <u>Correlation/association</u> -Between 08.00 cortisol and LDCT, Kappa=0.25, agreement 63%, P=NS - Between random cortisol and LDCT, Kappa=0.03, agreement 51%, P=NS -Between LDCT and SDCT, Kappa=0.39, P<0.05), 68% of patients who failed LDCT, passed SDCT <u>Sensitivity, specificity, negative predictive value, positive predictive value and area under the curve</u> Not reported	-No correlation to symptoms or outcomes. -Unclear clinical significance of the biochemical findings <u>Additional remarks</u> X <u>Risk of bias</u> A. Selection bias: unknown how many patients were eligible for the study. B. Verification bias: high risk, retrospective study, testing performed between 2003 and 2007. Baseline and stimulation testing occurred at the same time. C. I/R test bias: Unclear if the outcome assessors were blinded for important determinants related to the outcome. D. Confounding: not applicable
<u>Conclusion</u> • In a cohort of **78 childhood cancer survivors**, the agreement between 08.00 cortisol and LDCT was 63%, and between random cortisol and LDCT 51%. There was a fair agreement between LDCT and SDCT (Kappa 0.39).					

WG3: What surveillance modality should be used?					
S.R. Rose et al., Diagnosis of Hidden Central Hypothyroidism in Survivors of Childhood Cancer, JCEM (1999)					
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Diagnostic tests**	**Main outcomes**	**Additional remarks**
Study design Cross-sectional design Treatment period: Not reported (TRH testing between 1995-1997)	Study population 208 childhood cancer survivors. Patients with unambiguous TSHD (FT4<reference range without TSH elevation) within 6 months after surgery for hypothalamic or pituitary tumors, or patients	Radiotherapy n=unknown, mean total RT dose 31 Gy ± 23 'Prior treatment had included surgical excision, chemotherapy,	Patients were included if they had declining FT4 or FT4 in the lowest third of the normal range, mild TSH elevation, slow growth velocity, impaired stamina, or altered timing of puberty	Presence of HP disorder FT4 levels in lower portion reference range, n=160 of whom -n=51 blunted TSH surge -n=40 low or late TSH peak or delayed decline after TRH TSHD: n=55 (34%) Mixed hypothyroidism: n=15	Strengths -Study illustrates that there is considerable variability in the performance characteristics of various tests that could be used to assess for H-P-T dysfunction Limitations

Follow-up: Mean 6.1 yrs ± 4.1 (range 1-16) after cancer diagnosis	with obvious primary hypothyroidism (TSH>15mU/L) were excluded. Male n=140 (67.3%) Female n=68 (32.7%) Diagnosis Cranial solid tumors, n=110 (52.9%) -Posterior fossa, n=59 (28.4%) -Suprasellar, n=26 (12.5%) -Supratentorial, n=25 (12.0%) Head and neck tumors, n=14 (6.7%) Noncranial solid tumors, n=11 (5.3%) Leukemia, n=73 (35.1%) Age at diagnosis and/or treatment: Mean 6.1 yrs ± 4.2 Age at testing: Not reported	and radiation therapy' Other treatment BMT in leukemia patients, n=17 (8.2%)	Diagnostic test Nocturnal TSH surge or TRH test Reference test FT4 concentrations, total T4, FT4 concentration in lower reference range Cut-off levels: Nocturnal TSH surge <95%CI (=50-300% above nadir) FT4 in lower portion of reference interval (0.71-1.2 ng/dL) FT4 in upper portion of reference interval (1.2-1.85 ng/dL) TSHD: or blunted TSH surge, or delayed TSH peak after TRH or delayed TSH decline after TRH Mixed hypothyroidism: evidence of TSHD and mildly elevated basal TSH level or elevated peak TSH response to TRH Analysis: Not reported	FT4 levels in upper portion reference range, n=48 of whom -n=2 had blunted TSH surge -n=5 had low or late TSH peak or delayed decline after TRH TSHD: n=7 (14%) In whole group TSHD: n=62 of whom -40% had only blunted TSH surge -29% had only low or late TSH peak or delayed decline after TRH -n=41 had GHD -n=6 only ACTH or CPP -31% abnormalities of both tests Mixed hypothyroidism: n=15 -60% elevated basal TSH -34% elevated peak TSH after TRH -6% had both elevated basal TSH and elevated peak TSH after TRH -54% had blunted TSH surge -40% had low or late TSH peak or delayed decline after TRH -6% had both blunted TSH surge and elevated basal TSH and elevated peak TSH after TRH Correlation/association Of 62 patients with TSHD: -n=5 had FT4 below reference range -n=57 (92%) of TSHD would have been missed using FT4 reference range Of 15 patients with mixed hypothyroidism:	-Study report cumulative incidence, but study design does not allow for determining the timing of onset of TSHD. -Study design uses the index modalities in the definition of the diagnosis (no independent gold standard), so while sensitivities are given, they are not true sensitivities -No attempt at assessment of specificity in the CCS population could be made with this data Additional remarks -Authors discuss the use of growth rate in clinical decision making as a screening tool for TSH-D (even for patients with normal basal TSH/free T4) but do not report any data related to growth rate to validate this suggestion. -Testing strategy proposed (overnight TSH surge PLUS TRH test) is potentially cumbersome and not widely available outside of endocrine subspeciality care, and thus would not make a good screening modality -No correlation to symptoms or outcomes. Unclear clinical significance of the biochemical findings Risk of bias A. Selection bias: unknown how many patients were eligible for the study. B. Verification bias: high risk, all patients underwent thyroid function tests, but between 1995 and 1997. C. I/R test bias: unclear if the outcome assessors were blinded for important

				-n=0 had had FT4 below reference range <u>Sensitivity</u> Blunted TSH surge 71% Delayed peak after TRH 21% Delayed decline after TRH 42% Blunted peak after TRH 17%	determinants related to the outcome. D. Confounding: not applicable
<u>Conclusion</u> • In a cohort of **208 childhood cancer survivors**, of the 62 patients with TSHD according to a blunted TSH surge or low or late TSH peak or delayed decline after TRH testing, 57 patients would have been missed using FT4 reference ranges alone.					

WG3: What surveillance modality should be used?					
C. Sklar et al. Efficacy of insulin-like growth factor binding protein 3 in predicting the growth hormone response to provocative testing in children treated with cranial irradiation, Acta Endocrinologica (1993)					
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Diagnostic tests**	**Main outcomes**	**Additional remarks**
<u>Study design</u> Cross-sectional cohort study <u>Treatment period:</u>	<u>Study population</u> 20 childhood cancer survivors with tumors distant from the hypothalamus and pituitary, in complete remission and	All patients had cranial or craniospinal irradiation *RT details* CSI, n=9	<u>Diagnostic test</u> IGFBP-3 (in n=20), IGF-1 (n=8), interpreted with age-specific normal ranges	<u>Presence of HP disorder</u> -Hypothyroidism & T4 Tx, n=4 (n=1 central, n=3 primary) -CPP, n=2 -GHD, n=15	<u>Strengths</u> -Determination of IGFBP-3 compared with well-defined peak GH tests

Not reported Follow-up: Median 2.7 yrs (range 2-7)	referred for evaluation of poor linear growth or short stature Male n=12 (60.0%) Female n=8 (40.0%) Diagnosis Ependymoma, n=1 (5%) Rhabdomyosarcoma, n=4 (20%) Medulloblastoma, n=8 (40%) Glioblastoma, n=1 (5%) ALL, n=5 (25%) AML, n=1 (5%) Age at diagnosis and/or treatment: Not reported Age at testing: Mean 9.4 yrs (range 5.6-16)	TBI, n=3 Estimated RT dose 18 to >60 Gy hypothalamus/pituitary Chemotherapy n=14 also received chemotherapy	Reference test: GH testing with both clonidine and L-dopa in all patients Cut-off levels to define presence of HP disorder: GHD: peak GH response of < 10 µg/l in at least two provocative tests Analysis: -Linear regression -Sensitivity and specificity calculation	Correlation/association -Significant positive correlation IGFBP-3 and IGF-1 (r=0.88, p=0.002) -Significant positive correlation IGFBP-3 and height velocity (r=0.56, p=0.010) -No significant positive correlation IGFBP-3 and height (r=0.40, p=0.080) -No significant positive correlation IGFBP-3 and peak GH (r=0.22, p=0.36) -No significant positive correlation IGFBP-3 and BMI (r=0.03, p=0.473) Sensitivity IGFBP3: 20% IGF-1: 66% Specificity IGFBP3: 100% IGF-1: 100% Negative predictive value, positive predictive value and area under the curve Not reported Additional outcomes -Adjusting the IGFBP-3 values for the patient's bone age or stage of puberty failed to improve the sensitivity of IGFBP-3 levels.	-Corrected for most important confounders Limitations -Small study population -High prevalence of GHD in small cohort; influences reliability of testing results -Pre-selected study population (patients at high risk for GHD) Additional remarks A. Selection bias: unknown how many patients were eligible for the study. B. Verification bias: unclear risk, patients had IGFBP3 measurements and GH testing at the same time, but timespan unknown (although only eight had IGF-1 measurement) C. I/R test bias: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: not applicable

				-IGF-1 concentration had a sensitivity of 66% and specificity of 100% to predict GHD	
Conclusion • In a cohort of **20 irradiated childhood cancer survivors**, the sensitivity of IGFBP-3 was low (20%) to predict GHD (using GH testing with both L-dopa and clonidine). However, the specificity was 100%.					

WG3: What surveillance modality should be used?					
V. Tillmann et al. Serum Insulin-Like Growth Factor-I, IGF Binding Protein-3 and IGFBP-3 Protease Activity after Cranial Irradiation, Hormone Research (1998)					
Study design Treatment era Years of follow-up	**Participants**	**Diagnostic tests**	**Diagnostic tests**	**Main outcomes**	**Additional remarks**

Study design Retrospective cohort study Treatment period: Not reported Follow-up: Total cohort: range 0.4-14.2 yrs CNS tumors: mean 4.2 yrs ± 4.0 (range 0.4-14.2) ALL: mean 6.7 yrs ± 3.2 (range 1.3-10.9)	Study population 28 childhood cancer survivors with tumors distant from the hypothalamus and pituitary region Male n=14 (50.0%) Female n=14 (50.0%) Diagnosis Medulloblastoma, n=7 (25%) Rhabdomyosarcoma, n=3 (10.7%) Glioma, n=3 (10.7%) Astrocytoma, n=2 (7.1%) Pineal teratoma, n=1 (3.6%) ALL, n=12 (42.9%) Age at diagnosis: Not reported Age at testing: CNS tumors: mean 12.4 yrs ± 5.5 (range 7.0-24.3) ALL: mean 11.8 yrs ± 2.5 (range 7.8-17.4)	All received radiotherapy *RT details* All received CRT of whom CSI: n=7 TBI: n=2 Estimated RT dose to HP-region -CRT (n=21): mean 33.5 ± 8.8 (range 20.0-55.0) -CSI (n=7): mean 19.3 ± 7.3 (range 14.0-42.0), additional 13-30 Gy to the spine -TBI (n=2): 14 Gy Chemotherapy n=20 (all 12 ALL patients and n=8 CNS tumors)	Diagnostic test IGF-1 (dichotomized <-2 SDS and >-2 SDS) IGFBP-3 (dichotomized in respectively <-1.5 SDS and >-1.5 SDS) Measured in all patients Reference test: Peak GH stimulation tests; arginine (n=20), glucagon (n=12), insulin (n=10), clonidine (n=6) Cut-off levels: GHD: Peak GH response of <7.5 ng/l (if a child had two GH tests (N=20) the result of the highest peak GH concentration was used in analysis). Analysis: -Linear and stepwise regression analysis was used to define bi- and multivariate relationships. -Sensitivity was defined as the	Presence of HP disorder GHD: n=15 Sensitivity IGF-1: 47% IGFBP-3: not reported Specificity IGF-1: 77% IGFBP-3: not reported Negative predictive value and positive predictive value and area under the ROC curve of IGF-1 and IGFBP-3 Not reported Multivariable linear and stepwise regression analysis for peak GH, not adjusted: -BMI sds, RR not reported (p=0.005) -Radiation dose, RR not reported (p=0.01) Not associated with age, height and time after radiation Multivariable linear and stepwise regression analysis for IGF-1, adjustments unknown: -peak GH, RR not reported (p=0.01) -IGFBP-3 (p=0.01) -BMI sds (p=0.02) Multivariable linear and stepwise regression analysis for IGFBP-3: -Age, RR not reported ('positively correlated') Not associated with height, BMI radiation dose, time after radiation or peak GH. Additional outcomes	Strengths -Determination of IGF-1 and IGFBP-3 compared with well-defined peak GH tests -Corrected for most important confounders Limitations -Small study population -Pre-selected study population (patients at high risk for GHD) -Includes both screening for GHD and GH retesting at end of growth Additional remarks A. Selection bias: unknown how many patients were eligible for the study. B. Verification bias: high risk, all patients had IGF-1/IGFBP-3 measurements and GH stimulation test, although different number and types of GH stimulation tests used C. I/R test bias: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: not applicable

			percentage of subjects with an IGF-I or IGFBP-3 < –2 SDS in the GHD group. -Specificity was defined as the percentage of subjects with an IGF-I or IGFBP-3 > –2 SDS in the non-GHD group.	-Mean serum IGF-I concentrations were reduced compared with a normal population in both the GHD and non-GHD groups but with nonsignificant difference between the groups. -Patients with CNS tumors who received chemotherapy (n= 8) had a significantly lower IGF-I SDS than those without chemotherapy (–2.1 ± 0.8 vs. –0.7 ± 1.3; $p < 0.05$). -There was a positive correlation between IGFBP-3 and IGF-I concentrations ($r = +0.78$; $p < 0.0001$), and between IGFBP-3 SDS and IGF-I SDS ($r = +0.47$; $p = 0.001$).	
Conclusion • In a cohort of **28 irradiated childhood cancer survivors**, the sensitivity of IGF-1 was low (47%) to predict GHD, but the specificity was 77%. • None of the 15 patients with GHD, had IGFBP-3 concentrations <-1.5 SDS.					

WG4; What should be done when abnormalities are identified?

WG4: What should be done when abnormalities are identified?				
B Bakker, *Growth hormone (GH) secretion and response to GH therapy after total body irradiation and haematopoietic stem cell transplantation during childhood,* Clinical Endocrinology (2007)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Prospective cohort study Treatment era: 1997-2005 Follow-up: 7.7 yrs (2.0-17.0)	Study population 66 (<14 yrs at diagnosis) survivors of hematological malignancy Male n=48 (72.7%) Female n=18 (27.3%) Primary cancer diagnosis: ALL, first remission, n=10 (15.2%) ALL, second remission, n=27 (40.9%) AML, first remission, n=11 (16.7%) AML, second remission, n=4 (6.1%) MDS, n=8 (12.1%) CML, n=4 (6.1%) NHL, second remission, n=2 (3.0%) Age at primary cancer diagnosis: Median 7.7 ys (range 1.7-14.3) Age at follow-up: Median 16.6 ys (range 8.8-22.4)	Tumor treatment: All patients received hematopoietic stem cell transplantation with conditioning consisting out of TBI and cyclophosphamide, with additionally cytarabine in n=19 and etoposide in n=37 TBI details: -5.0 Gy, n=1 (1.5%) -7.0 Gy, n=9 (13.6%) -7.5 Gy, n=37 (56.1%) -8.0 Gy, n=2 (3.0%) -2 x 6.0 Gy, n=17 (25.8%) -Testicular booster, n=6 (9.1%) Type of graft -Allogeneic, n=60 (90.9%) -Autologous, n=6 (9.1%) Treatment for HP disorder: Treatment type: GH, starting dose 34 µg/kg/day (range 27-39) in n=21, starting dose 0.67 mg/m^2 in n=2 GH tested in 29 of 66 survivors (43.9%) GHD in 8 of 29 GH tested survivors GH Tx in 23 of 29 tested survivors (79.3%)	Adult height (SDS) GH treatment, males n=6, -1.8 range -4.0 to 0.4 No GH treatment, males n=21, -1.8 range -3.7 to 0.1 GH treatment, females n=5, -1.7 range -3.2 to -0.1 No GH treatment, females n=11, -1.6 range -3.1 to 0.5 Final height – predicted height (SDS) GH treatment, males n=6, +1.1 range 0.3 to 2.7 No GH treatment, males n=21, -0.02 range -0.29 to 0.15 GH treatment, females n=5, 1.3 range 0.4 to 2.3 No GH treatment, females n=11, -0.02 range -0.13 to 0.13 Other outcomes -GH treatment, first year +0.35 SDS/year change in height -Estimated net effect after 5 years of therapy is 1.14 SDS (CI 0.88-1.41) -Mean GH concentration, IGF-1 and IGFBP3 had no effect on loss of height after SCT or increase in height after GH treatment	Strengths -Prospective follow-up -Fairly large cohort Limitations -Many patients received GH treatment without having GHD Other remarks -The response to GH treatment was similar in the non-GHD group vs. the GHD group Risk of bias A. Selection bias: unclear how many patients were included in the original cohort of survivors B. Attrition bias: high risk, of the 66 eligible patients, only 29 were tested for GHD (43.9%) C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. D. Confounding: high risk, only descriptive analysis

		GHD defined by GH peak <13.8mU/L, corresponding with <20mU/L of national assay in two occasions or decreased maximum peak GH or mean GH concentration in a 12-hour GH secretion profile) Duration of treatment: mean 3.2 ys, range 0.1-7.3	<u>Adverse effects GH treatment</u> GH treated (n=23) -Urticaria and angioedema, n=1 -Exostoses, n=6 -Growth in pre-existing exostoses, n=1 - Relapse, n=1 -Second malignancy; osteosarcoma, n=1, papillary thyroid carcinoma, n=1 Not GH treated (n=43) -Exostoses, n=2 -Relapse, n=6 -Schwannoma, n=1	
<u>Conclusion</u> • In a study of **66** survivors of **hematological malignancies** (mean follow-up time of 7.7 years), treated with hematopoietic stem cell transplantation with a TBI conditioning regimen, **height SDS** increased after treatment with GH. No differences were seen in height SDS in GH treated GH deficient and GH treated non-GH deficient survivors.				

WG4: What should be done when abnormalities are identified?				
E Brignardello et al., *GH replacement therapy and second neoplasms in adult survivors of childhood cancer: a retrospective study from a single institution*, Journal of Clinical Endocrinological Investigation (2015)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort study Treatment era: Before 1990: 19/49 1990-1999: 26/49 After 2000: 4/49 Follow-up: Not reported, but at least ≥ 5 years after primary cancer diagnosis	Study population 49 survivors (< 18 yrs at diagnosis) of childhood cancer, ≥ 5 years of survival after first cancer diagnosis ≥ 1 visit after the 18th birthday Male n=30 (61.2%) Female n=19 (38.8%) Primary cancer diagnosis: ALL, n=10 (20.4%) AML, n=5 (10.2%) Brain tumor, n=34 (69.4%) Age at primary cancer diagnosis: 0-4 yrs, n=17 (34.7%) 5-9 yrs, n=17 (34.7%) ≥ 15 yrs, n=15 (30.6%) Age at follow-up: Not reported	Tumor treatment: CRT, n=45 (91.8%) Surgery: not reported Chemotherapy: not reported RT details CRT, n=32 (65.3%; prophylactic in case of ALL 18-24Gy; curative in brain tumors 24-64 Gy) TBI, n=10 (20.4%; 12-14 Gy) Both CRT and TBI, n=3 (6.1%) Treatment for HP disorder: Treatment type: GH, dose 0.14-0.28 mg/kg/week GHD in all 49 survivors GH Tx in 26 of 49 survivors (53.1%) GHD diagnosed by standard provocative tests, specific definition unknown Duration of treatment: mean 42.5 months, range 12.0-96.1	Survivors with subsequent neoplasm GH treated patients: - Meningioma: n=5 (50%) - Basal cell carcinoma: n=3 (30%) - Thoracic spinal neurinoma: n=1 (10%) - Papillary thyroid carcinoma: n=1 (10%) Non-GH treated patients: - Meningioma: n= 5 (55.6%) - Basal cell carcinoma: n=3 (33.3%) - Melanoma skin cancer: n=1 (11.1%) Hazard ratio for second neoplasms in multivariable Cox regression analysis -Sex male vs. female: 0.39 (95% CI 0.11-1.43) -Age at primary cancer (every 5 years): 146 (95% CI 0.72-2.96) -Cancer type (brain tumors vs. hematologic malignancies): 0.26 (95% CI 0.05-1.33) -GH replacement therapy: 3.74 (95% CI 0.85-16.43) Incidence neoplasms over time: -Cumulative incidence of second neoplasms did not differ between GH treated and GH untreated survivors (p=0.331)	Strengths -Patients with genetic predisposition syndromes excluded Limitations -Small number of patients. -Different cancer diagnoses included. -Lack of data regarding patient characteristics - Not all received CRT -Presence of meningioma was suspected on the basis of neurological symptoms (i.e. headache or seizures) in three survivors Other remarks -Cumulative dose of GH was similar in patients who developed a second neoplasm, compared to patients who did not. Risk of bias A. Selection bias: low risk, all eligible patients with GHD were included B. Attrition bias: low risk, all patients were seen at the transition unit, and followed according to COG

				guidelines depending cancer diagnosis and previous cancer treatment. C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. D. Confounding: high risk, analyses were not adjusted for RT dose, but only tumor type (brain tumor vs. hematological malignancies)
Conclusion • In a study of **49** survivors of **hematologic malignancies** and **brain tumors** (mean follow-up time not reported), GH treatment did **not increase** the risk for development of **second neoplasms**.				

WG4: What should be done when abnormalities are identified?				
B Ergun-Longmire, *Growth Hormone Treatment and Risk of Second Neoplasms in the Childhood Cancer Survivor*, JCEM (2006)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective multicenter study Treatment era: Diagnosed between 1970-1986 Follow-up: Not reported	Study population 14,108 5-year childhood cancer survivors (≤21 yrs at diagnosis); 361 CCS with GH treatment 13,747 without GH treatment Male n=7554 (53.5%) Female n=6554 (46.5%) Primary cancer diagnosis: GH-treated CNS tumor, n=172 (47.6%) Acute leukemia, n=119 (33.0%) Soft tissue sarcoma, n=43 (11.9%) Neuroblastoma, n=17 (4.7%) Other, n=10 (2.8%) Non-GH treated CNS tumor, n=1601 (11.6%) Acute leukemia, n=4825 (35.1%) Soft tissue sarcoma, n=772 (5.6%) Neuroblastoma, n=698 (5.1%)	Tumor treatment: Not reported Treatment for HP disorder: Treatment type: GH, dose not reported. Various GH preparations, including human pituitary only (n=43, 11.9%), recombinant only (n=279, 77.3%), both (n=27, 7.5%) and unknown (n=12, 3.3%) GH Tx in 361 of 14,108 survivors (2.6%) Age start treatment: 11 yr (range 1-20.8) Duration of treatment:	Survivors with subsequent CNS neoplasm GH treated patients: -Meningioma: 9 (45%) -Osteosarcoma: 3 (15%) -Glioma: 2 (10%) -Astrocytoma: 1 (5%) -Mucoepidermoid carcinoma: 1 (5%) -Adenocarcinoma: 1 (5%) -Spindle cell sarcoma: 1 (5%) -Sarcoma: 1 (5%) -Papillary carcinoma thyroid: 1 (5%) Non-GH treated patients: - Meningioma: 62 (11.2%) - Other: 493 (88.8%) Relative risk of second neoplasms in multivariable Cox regression analysis -Sex male vs. female: 0.52 (95% CI 0.43-0.63) -Age at diagnosis: 1.07 (95% CI 1.06-1.09) -Alkylating agent yes vs. no: 1.30 (95% CI 1.09-1.56) -Radiation yes vs. no: 2.88 (95% CI 2.20-3.78) -GH yes vs. no: 2.15 (95% CI 1.33-3.47)	Strengths -Large cohort -Comparison population with CCS Limitations -Unclear how secondary neoplasms were detected or how surveillance for neoplasms was performed (i.e. patients with GH may have experienced more intensive surveillance) -GH treatment by self-reported (and verified in medical charts) -Treatment exposures unknown -Genetic predisposition unknown (e.g. NF) Other remarks -Non-melanoma skin cancers not included -Tumors occurred <5 years of diagnosis excluded -The risk of second neoplasm in GH-treated CCS is increased, but seems to diminish with increasing length of follow-up (RR 2.15 this study, RR 3.21 Sklar et al., 2002)

	Other, n=5851 (42.6%) <u>Age at primary cancer diagnosis:</u> GH treated; 3.5 ys (range 0-17.2) Non-GH treated; 7.1 ys (range 0-21) <u>Age at follow-up:</u> Not reported	GH therapy 4.6 yrs (range 0.1-14) Definition of GHD not reported	<u>Median time interval to neoplasms:</u> Latency time all second neoplasms in GH-treated ranges between 5.6 and 22 years after diagnosis Latency time meningioma in GH-treated 12.2 years vs. 19 years in GH-untreated ($p<0.01$) <u>Other outcomes</u> -If stratification for tumor diagnosis in multivariable analysis, no significant difference GH treatment yes vs. no *No association dose and duration of GH treatment and development second neoplasm *Percentage of deaths due to second neoplasms similar in GH treated vs. GH-untreated	<u>Risk of bias</u> A. Selection bias: low risk 14,108 of 14,352 (98.3%) survivors included. B. Attrition bias: high risk, surveillance/detection bias as for example meningiomas are often asymptomatic, and not systematic MRI screening performed in all patients. C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. D. Confounding: low risk, analyses were adjusted for important confounding factors.
<u>Conclusion</u> • In a study of **14,108** survivors of (mean follow-up time not reported), GH treatment did **increase** the risk for development of **second neoplasms**.				

WG4: What should be done when abnormalities are identified?				
W Leung, *Outcomes of growth hormone replacement therapy in survivors of childhood acute lymphoblastic leukemia*, Journal of Clinical Oncology (2002)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort study Treatment era: Treated between 1978-1989 Follow-up: Median 15.6 yrs (range 7.3-22.1)	Study population 910 childhood survivors of ALL, with a minimum follow-up of 18 months 47 survivors with GH treatment, 863 without GH treatment For safety analysis, 43 GH treated patients and 544 non GH treated patients were included Gender of GH treated survivors: Male n=34 (72.3%) Female n=13 (27.7%) Primary cancer diagnosis: All had ALL	Tumor treatment: CNS-directed therapy included intrathecal chemotherapy with or without cranial RT (18 to 24 Gy). Four had also testicular RT Cranial RT in 32 of 43 GH treated patients (74.4%) Cranial RT in 308 of 544 non-GH treated patients (56.6%) Treatment for HP disorder: Treatment type: synthetic GH, dose 0.3 mg/kg/week subcutaneously in three to seven divided doses. Treatment was continued until acceptable or final height achieved. GnRHa treatment in four patients with early puberty.	Adult height (SD) -Height decrease between cancer diagnosis and start GH treatment, 1.0 SD -After 4.5 yrs of GH therapy, SD scores improved and approached height SD at cancer diagnosis -Median adult height was 173.2 cm (range 157-191.9) for males and 158.1 (range 141-168) for females -Adult height was greater than predicted at baseline in 76% of male survivors and 46% of female survivors. Survivors with tumor recurrence or subsequent neoplasm Types of secondary tumors Study population (=GH treated patients, n=43): -Sclerosing sweat duct carcinoma -Myelodysplastic syndrome Control population (=non-GH treated patients, n=544):	Strengths -Large cohort -Long follow-up duration, with adequate follow-up Limitations -Treatment exposures not clearly reported -Descriptive and unadjusted analysis Other remarks X Risk of bias A. Selection bias: low risk, of the 910 eligible patients, 323 did not survive and were excluded for GH safety analysis, but this was before the 7-year landmark point as used for analysis in this study

	<u>Age at primary cancer diagnosis:</u> Not reported <u>Age at follow-up:</u> Not reported	GH Tx in all 47 survivors Age start GH treatment: median 10.9 (range 6.9-14.7) Delay in treatment: median 7.1 yrs (range 4.3-11.4) after ALL complete remission Duration of GH treatment: median duration of GH treatment, 4.5 yrs (range 1-8) GHD defined by GH peak response to two provocative tests (arginine + L-dopa) < 10 ng/ml	-n=16 had secondary tumor, types not reported <u>Median time interval to neoplasms:</u> -Time to sclerosing sweat duct carcinoma, 8yrs after ALL diagnosis, 4 months after GH therapy that lasted 3 years -Time to myelodysplastic syndrome was 12 years, 2 months after GH therapy that lasted 4 years <u>Risk for tumor recurrence, secondary tumors and mortality in univariable analysis</u> -Leukemia relapse, n=0 patients in GH treated group (n=43, 0%), n=8 patients in non-GH treated patients (n=544, 1.5%) -Secondary tumor, n=2 patients in GH treatment group (n=43, 4.7%), n=16 in non-GH treated patients (n=544, 2.9%) -No statistical evidence that GH replacement therapy was associated with relapse of ALL (P = 0.70 in Gray's test for 11-year landmark analysis) or second malignancy (P = 0.45 in Gray's test for 11-year landmark analysis) <u>Other outcomes</u> -None of the patients developed hyperglycemia or other adverse effects requiring discontinuation of GH	B. Attrition bias: low risk, 70.6% of the survivors had been followed-up within the past year, 92.5% in the past two years. C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. D. Confounding: high risk, no multivariable analysis performed
<u>Conclusion</u> • In a study of **47 survivors** of ALL (median follow-up time of 15.6 years), **height improved** after starting GH treatment. GH treatment did **not increase** the risk for **tumor recurrence** or development of **second neoplasms**				

WG4: What should be done when abnormalities are identified?				
S Mackenzie et al., Long-Term Safety of Growth Hormone Replacement after CNS Irradiation, Journal of Clinical Endocrinology and Metabolism (2011)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective matched pair analysis Treatment era: Not reported GH treatment between 1994 and 2009 Follow-up: Median 14.5 yrs (IQR 11-22)	Study population 110 survivors of childhood cancer, who received cranial RT and received GH treatment for at least one year. Male n=60 (54.5%) Female n=50 (45.5%) Comparison population: 110 matched controls with a history of cranial radiotherapy (between 1965-2009), but no GH treatment for any duration; They were matched for total radiation dose, age at	Tumor treatment: All received cranial radiotherapy RT details; Median 40 Gy (IQR 37.5-42.5 Gy) for both control and study population. Details about other treatment modalities not reported Treatment for HP disorder: Treatment type: GH, dose and preparation not recorded.	Survivors with tumor recurrence or subsequent neoplasm Types of secondary tumors Study population (=GH treated patients): -Meningioma: n=4 (3.6%) -Malignant nerve sheath tumor, NF1: n=1 (0.9%) Control population (=non-GH treated patients): -Meningioma: n=2 (1.8%) -Oligodendroglioma: n=1 (0.9%) Risk for tumor recurrence, secondary tumors and mortality in univariable analysis -Tumor recurrence, n=6 (5.5%) in study population (n=0 childhood onset, n=6 adult onset), n=8 (7.3%) in control population (n=4 childhood onset, n=4 adult onset). Differences in tumor recurrence between study and control population not significant.	Strengths -Reasonable number of CCS patients -Matched control group -Long duration of follow up -Single center, homogenous data -Imaging studies used to define tumor recurrence and second neoplasm Limitations -Retrospective study – GH deficiency diagnosis criteria and treatment details (dose, adherence) not known -Selection bias possible in GHRT group especially for second neoplasms. Other remarks X

	diagnosis, duration of follow up and target site of irradiation. <u>Primary cancer diagnosis:</u> Childhood cancer survivors (n=41) -Pituitary tumor, n=2 (4.9%) -Intracranial neoplasm, n=39 (95.1%) Adult cancer survivors (n=69) -Pituitary tumor, n=46 (66.7%) -Intracranial neoplasm, n=23 (33.3%) <u>Age at primary cancer diagnosis:</u> Median 33 yrs (IQR 14-45) <u>Age at follow-up:</u> Not reported	Age start treatment: not reported. Duration of treatment: Median 8.0 (IQR 4.0-10.0 years, range 1-19) Definition of GHD not reported	-Secondary tumor, n=5 (4.5%) in study population (n=5 childhood onset, n=0 adult onset), n=3 (2.7%) in control population (n=2 childhood onset, n=1 adult onset). Differences in secondary neoplasm between study and control population not significant. -Mortality, n=7 (6.4%; 5 were unrelated to tumor recurrence or secondary tumor, 2 were related) in study population, n=15 (13.6%; 4 were unrelated to tumor recurrence or secondary tumor, 7 were related and 4 unknown) in control population (P=0.03*) -No significant difference between study and control population in mortality by age at diagnosis or primary tumor - All-cause mortality was higher in the study population (n=7, 6.4%, 5 were unrelated to tumor recurrence of second neoplasm, 0 unknown) vs. control population (n=15, 13.6%, 4 were unrelated to tumor recurrence of second neoplasm, 4 unknown). <u>Incidence recurrence/neoplasms over time:</u> -No significant difference between study and control population for time to tumor recurrence (p=0.508) or secondary tumor (p=0.781) -Median latency time for detection of meningioma was similar in study and control population (24.0 yr vs 23.5 yr).	<u>Risk of bias</u> A. Selection bias: high risk, 224 patients were eligible, but only 110 (49.1%) are included for analysis B. Attrition bias: low risk, all patients received surveillance imaging C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. D. Confounding: high risk, no multivariable analysis performed
<u>Conclusion</u> • In a matched control study of **110 childhood and adult cancer survivors** (median follow-up time of 14.5 years), GH treatment did **not increase** the risk for **tumor recurrence**, **secondary neoplasms** or **mortality**.				

WG4: What should be done when abnormalities are identified?				
AL Ogilvy-Stuart., Growth hormone and tumour recurrence, BMJ (1992)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
<u>Study design</u> Retrospective single-center cohort study <u>Treatment era:</u> Diagnosed between 1965-1989 with a brain tumor, or between 1970-1989 with ALL <u>Follow-up:</u> Not reported	<u>Study population</u> 62 children aged below 14.4 years at cancer diagnosis who received cranial radiation for either brain tumor distant from the HP region (n=53, but six excluded from analysis) or ALL (n=15), treated with GH Male n=45 (66.2%) Female n=23 (33.8%)	<u>Tumor treatment:</u> All patients received RT RT details Brain tumor: median 30 Gy (range 15-47.5) and 36 children received a boost to the tumor site (median 15 Gy, range 10-20) ALL: median 24 Gy (range 18-42 Gy) Surgery: not reported 'most had surgery before radiotherapy and insertion of VP shunt before RT'	<u>Survivors with tumor relapse or second neoplasm</u> -Brain tumor group: tumor relapse, n=5 (11%) in study population of brain tumors, n=42 (26%) in control population. - ALL group: n=1 (6.7%) in study population of ALL patients, n=11 (7%) in control population -None of the patients developed a second primary tumor or leukemia <u>Incidence recurrence/neoplasms over time:</u> - Brain tumor group: median time for recurrence; 1.8 and 4.4 years after completion of GH treatment in two patients, 0.5, 0.7 and 3.3 years after starting GH treatment in the three patients during GH treatment. -ALL group: median time for recurrence; 1.7 yrs from starting GH treatment	<u>Strengths</u> -Relatively large cohort -Single center data (homogenous group) -Review of medical records -Control group with no growth hormone therapy included -Data on CT images before and after GH start <u>Limitations</u> -Older data, majority had pituitary GH vs. recombinant GH -Not all patients were uniformly screened for GH deficiency -GH treatment dose varied between before or after 1989

	Comparison population: Patients who received cranial radiation for a brain tumor or ALL, but who were never treated with GH (n=306) <u>Primary cancer diagnosis:</u> Patients treated with GH Medulloblastoma, n=26 (41.9%) Ependymoma, n=6 (9.7%) Juvenile astrocytoma, n=7 (11.3%) Adult astrocytoma, n=4 (6.5%) Other glioma, n=4 (6.5%) ALL, n=15 (24.2%) <u>Age at primary cancer diagnosis:</u> Only reported for children with a brain tumor: median 6.7 yrs (range 0.5-14.4) <u>Age at follow-up:</u>	Chemotherapy Brain tumor: n=23 (49%), vincristine alone or in combination with nitrosourea with or without procarbazine ALL: conventional chemotherapy <u>Treatment for HP disorder:</u> Treatment type: GH (pituitary and synthetic), dose 12 IU/week before 1989 and 0.5 IU/kg/week after 1989. In 56 patients without relapse, 27 patients (48.2%), completed GH treatment, and 29 patients (51.8%) were still on GH treatment. Age start GH treatment: not reported Duration of treatment: median 3.2 years in brain tumor group Start treatment: Median duration between cancer diagnosis and starting GH treatment was 4.5 years (range 2 -10.8). GHD defined by GH peak concentration below 15 mU/L after provocative testing (ITT or glucagon)	<u>Relative risk of tumor relapse in brain tumor patients in multivariable Cox regression analysis</u> Diagnosis (reference = medulloblastoma): p=0.24 -Ependymoma: estimate 0.49 (SE 0.43), RR 1.63 -Juvenile astrocytoma: estimate -0.52 (SE 0.38), RR 0.60 -Adult astrocytoma: estimate 0.17 (SE 0.57), RR 1.19 -Other glioma: estimate -0.39 (SE 0.78), RR 0.68 Sex female vs. male: estimate -0.87 (SE 0.35), RR 0.42, p<0.01 Age (reference ≤ 5yrs): p=0.18 - >5 yrs but ≤10 yrs: estimate 0.21 (SE 0.37), RR 1.23 - > 10 yrs: estimate 0.76 (SE 0.42), RR 2.15 Chemotherapy yes vs. no: estimate 0.7 (SE 0.44), RR 2.02, p=0.11 GH treatment yes vs. no: estimate -0.2 (SE 0.54), RR 0.82, p=0.71 <u>Relative risk for growth hormone on tumor relapse in brain tumor patients</u> -Unadjusted RR 1.35 (95% CI 0.49-3.73) -Adjusted (age, sex, diagnosis, chemotherapy) RR 0.82 (95% CI 0.28-2.37) -Adjusted minus chemotherapy RR 1.01 (95% CI 0.36-2.83) <u>Other Outcomes:</u> CT images before and after starting GH therapy: -n=44 had baseline CT around the time of starting GH therapy, of them 10 had residual tumor, 9 had non-enhancing low attenuation or cystic lesions at the original tumor area. -Of the 5 children who relapsed, 1 had residual tumor and 1 had low density non-enhancing lesion before GH start. -Of the 39 children who did not relapse, 14 had follow up scans of whom 4 had residual tumor at the time of GH start of which 2 resolved in follow up scans, and 2 had no change. In 3 children there were low density non-enhancing lesions- of which 2 resolved and 1 no change in follow up scans.	-Retrospective data analysis - so tumor surveillance may not be uniform -Adherence to GH therapy not reported <u>Other remarks</u> -Data on ALL very limited -No data on CCS other than brain tumor and ALL. -No mention of tumor predisposition. <u>Risk of bias</u> A. Selection bias: unclear how many patients were included in the original cohort of survivors B. Attrition bias: high risk in earlier years only patients with growth failure were referred, later all patients tested for GHD C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. D. Confounding: low risk, multivariable analysis adjusted for important confounders, although only performed for brain tumor diagnosis and not for ALL patients.

	Not reported			
Conclusion • In a study of **62 patients** with **childhood cancer**, GH treatment did **not increase** the risk for **tumor relapse**.				

WG4: What should be done when abnormalities are identified?				
RJ Packer et al., Growth Hormone Replacement Therapy in Children With Medulloblastoma: Use and Effect on Tumor Control, Journal of Clinical Oncology (2001)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective multi-institutional study (11 centers in North America) Treatment era: Diagnosed between 1980-1993 Follow-up:	Study population 545 children(≤ 15 yrs at diagnosis) diagnosed with medulloblastoma, Gender not reported Primary cancer diagnosis: Medulloblastoma in all patients	Tumor treatment: Surgery in all patients -Total/near total: n=353 (64.8%) -Subtotal: n=174 (31.9%) -Biopsy: n=13 (2.4%) -Missing: n=5 (0.9%) Other treatment modalities, such as radiotherapy or chemotherapy not reported	Prevalence of tumor recurrence compared with CCS: -No statistical evidence of association between the use of GH treatment and PFS in infants (p=0.71) or older children (p=0.138), or in those between 3-10 years (p=0.084) Progression free survival in multivariable Cox regression analysis (stratification by tumor stage and extent of tumor resection) -GH treatment RR 0.710 (95% CI 0.648-4.267) for infants	Strengths -Large multi-center study -Subanalysis in different age groups Limitations -Scarce data on patient and treatment characteristics Other remarks X

Not reported	<u>Age at primary cancer diagnosis:</u> Mean 6.2 years at diagnosis <u>Age at follow-up:</u> Not reported	<u>Treatment for HP disorder:</u> Treatment type: GH, dose and preparation not recorded. GH treatment in n=167; of whom n=153 (28.1%) treated before progression, and n=14 after progression (2.6%) cumulative incidence 33.3% Age start treatment: mean 10.1 years Duration of treatment: mean 49 months (range 1 to 125, SD 27.8) Start treatment: Mean duration between diagnosis and starting GH treatment was 3.9 years Definition of GHD not reported	-GH treatment RR 0.648 (95% CI 0.365-1.150) for older children After 2 and 3 year landmark analysis, PFS was similar among patients treated with GH, compared to those without GH treatment (p=0.55 for 2-year landmark analysis, n=24 on GH treatment) After 5 year landmark analysis, PFS was better among patients treated with GH, compared to those without GH treatment (p=0.019, n=85 on GH treatment) These findings were similar if the cohort was divided in different age groups.	<u>Risk of bias</u> A. Selection bias: low risk, all eligible patients were included for retrospective analysis (545 of 575 included, because 30 were ineligible) B. Attrition bias: low risk, 'data was relatively complete' C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. D. Confounding: high risk, analysis not adjusted for important confounders
<u>Conclusion</u> • In a study of **545 children** diagnosed with **medulloblastoma**, GH treatment did **not increase** the risk for **tumor recurrence**.				

WG4: What should be done when abnormalities are identified?				
BC Patterson, *Growth hormone exposure as a risk factor for the development of subsequent neoplasms of the central nervous system: A report from the childhood cancer survivors study*, JCEM (2014)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
<u>Study design</u> Retrospective cohort-study (with prospective follow-up) <u>Treatment era:</u>	<u>Study population</u> 12,098 childhood cancer survivors (<21 years at diagnosis), who survived at least 5 years;	<u>Tumor treatment:</u> <u>CRT:</u> Of GH treated patients Surgery only, n=1 (0.3%) Radiation only, n=2 (0.6%)	<u>Survivors with subsequent CNS neoplasms:</u> GH treated patients: Meningioma: 10 (3.0%) Glioma: 6 (1.8%) Non-GH treated patients: Meningioma: 138 (1.2%) Glioma: 49 (0.4%)	<u>Strengths</u> -Large cohort study with GH treatment verified through medical record review <u>Limitations</u>

Diagnosed between 1970-1986 <u>Follow-up:</u> Not reported	338 survivors treated with GH, 11,760 survivors not treated with GH Male n= 220 (65.1%) Female n= 118 (34.9%) <u>Primary cancer diagnosis of GH treated patients:</u> Leukemia, n=101 (29.9%) CNS tumor, n=165 (48.8%) Hodgkin lymphoma, n=1 (0.3%) Non-Hodgkin lymphoma, n=10 (3.0%) Wilms' tumor, n=1 (0.3%) Neuroblastoma, n=16 (4.7%) Soft tissue sarcomas, n=42 (12.4%) Bone malignancies, n=2 (0.6%) <u>Age at primary cancer diagnosis:</u> Age at primary cancer diagnosis 0–4, n=221 (65.4%) 5-9, n=97 (28.7%) 10-14, n=19 (5.6%) 15+, n=1 (0.3%) <u>Age at follow-up:</u> Not reported	Chemotherapy only, n=6 (1.8%) Surgery/radiation, n=71 (21.0%) Surgery/chemotherapy, n=8 (2.4%) Radiation/chemotherapy, n=43 (12.7%) Surgery/radiation/chemotherapy, n=205 (60.7%) Unknown, n=2 (0.6%) Of all patients, 4277 received cranial radiotherapy (35.4%) <u>RT details:</u> No radiotherapy, n=22 (6.5%) <10 Gy, n=13 (3.8%) 10-19.9 Gy, n=32 (9.5%) 20-29.9 Gy, n=50 (14.8%) 30-45 Gy, n=36 (10.7%) >45 Gy, n=72 (50.9%) Unknown, n=13 (3.8%) <u>Chemotherapy details:</u> Intrathecal methotrexate, n= 128 (37.9%) Alkylating agent, n=218 (64.5%) <u>Treatment for HP disorder:</u> Treatment type: GH, dose and preparation not recorded.	Other: 16 (0.1%) <u>Rate ratios for meningioma in multivariable Poisson regression analysis:</u> GH treatment yes vs. no: 0.8 (95% CI 0.4-1.7) Sex females vs. males: 1.8 (95% CI 1.3-2.6)* Age at primary cancer diagnosis 0-4 years vs. ≥15 years: 4.8 (95% 2.1-11.0)* Age at primary cancer diagnosis 5-9 years vs. ≥15 years: 2.6 (95% CI 1.2-5.5)* Age at primary cancer diagnosis 10-14 years vs. ≥15 years: 1.2 (95% CI 0.6-2.6) CRT ≤45 Gy and <10 years between CRT and CNS neoplasm vs. no CRT: 0.0 (95% CI 0.0-6.7) CRT ≤45 Gy and 10-19 years between CRT and CNS neoplasm vs. no CRT: 23.1 (95% CI 9.9-53.7)* CRT ≤45 Gy and ≥20 years between CRT and CNS neoplasm vs. no CRT: 22.0 (95% CI 9.7-50.2)* CRT >45 Gy and <10 years between CRT and CNS neoplasm vs. no CRT: 55.1 (95% CI 15.3-198.1)* CRT >45 Gy and 10-19 years between CRT and CNS neoplasm vs. no CRT: 47.3 (95% CI 19.4-115.2)* CRT >45 Gy and ≥20 years between CRT and CNS neoplasm vs. no CRT: 58.5 (95% CI 25.5-134.2)* Intrathecal methotrexate yes vs. no: 1.3 (95% CI 0.8-2.0) Estrogen and/or progesterone yes vs. no: 0.7 (95% CI 0.5-1.2) Alkylating agents yes vs. no: 0.7 (95% CI 0.5-1.0) <u>Rate ratios for glioma in multivariable Poisson regression analysis:</u> GH treatment yes vs. no: 1.9 (95% CI 0.7-4.8) Sex females vs. males: 0.9 (95% CI 0.5-1.7) Age at primary cancer diagnosis 0-4 years vs. ≥15 years: 2.0 (95% 0.5-7.8) Age at primary cancer diagnosis 5-9 years vs. ≥15 years: 0.9 (95% CI 0.2-3.5) Age at primary cancer diagnosis 10-14 years vs. ≥15 years: 1.8 (95% CI 0.6-5.6) CRT ≤45 Gy and <10 years between CRT and CNS neoplasm vs. no CRT: 7.9 (95% CI 2.7-23.0)* CRT ≤45 Gy and 10-19 years between CRT and CNS neoplasm vs. no CRT: 4.1 (95% CI 1.5-11.3)*	-Unclear how CNS neoplasms were detected -Frequency of CNS imaging is unknown -GH treatment is self-reported and includes 29 institutions and not clear if the treating guidelines are similar across institutions. **Risk of bias:** <u>Selection bias:</u> low risk, 12,098 out of 14,358 (84.3%) eligible survivors were included in the study. <u>Attrition bias:</u> unclear for how many survivors follow-up data was complete <u>Detection bias:</u> unclear if the outcome assessors were blinded for important determinants related to the outcome. <u>Confounding:</u> low risk, analyses were adjusted for important confounding factors.

		GH treatment in n=338 of 12098 patients (2.8%) Age start treatment: not reported Duration of treatment: not reported Start treatment: <15 years after diagnosis Definition of GHD: not reported	CRT ≤45 Gy and ≥20 years between CRT and CNS neoplasm vs. no CRT: 1.5 (95% CI 0.3-6.3) CRT >45 Gy and <10 years between CRT and CNS neoplasm vs. no CRT: 13.5 (95% CI 4.0-46.1)* CRT >45 Gy and 10-19 years between CRT and CNS neoplasm vs. no CRT: 13.4 (95% CI 4.8-37.6)* CRT >45 Gy and ≥20 years between CRT and CNS neoplasm vs. no CRT: 10.7 (95% CI 3.1-36.7)* Intrathecal methotrexate yes vs. no: 1.3 (95% CI 0.8-2.0) Estrogen and/or progesterone yes vs. no: 0.7 (95% CI 0.5-1.2) Alkylating agents yes vs. no: 0.7 (95% CI 0.5-1.0) <u>Rate ratios for any CNS neoplasm in multivariable Poisson regression analysis:</u> GH treatment yes vs. no: 1.0 (95% CI 0.6-1.8) Sex females vs. males: 1.6 (95% CI 1.2-2.2)* Age at primary cancer diagnosis 0-4 years vs. ≥15 years: 4.8 (95% 2.4-9.7)* Age at primary cancer diagnosis 5-9 years vs. ≥15 years: 2.5 (95% CI 1.3-4.7)* Age at primary cancer diagnosis 10-14 years vs. ≥15 years: 1.7 (95% CI 0.9-3.0) CRT ≤45 Gy and <10 years between CRT and CNS neoplasm vs. no CRT: 9.5 (95% CI 4.3-20.8) CRT ≤45 Gy and 10-19 years between CRT and CNS neoplasm vs. no CRT: 11.1 (95% CI 6.3-19.5) CRT ≤45 Gy and ≥20 years between CRT and CNS neoplasm vs. no CRT: 9.9 (95% CI 5.5-17.5) CRT >45 Gy and <10 years between CRT and CNS neoplasm vs. no CRT: 23.9 (95% CI 10.2-55.9) CRT >45 Gy and 10-19 years between CRT and CNS neoplasm vs. no CRT: 24.9 (95% CI 13.6-45.8) CRT >45 Gy and ≥20 years between CRT and CNS neoplasm vs. no CRT: 25.3 (95% CI 14.0-46.0) Intrathecal methotrexate yes vs. no: 1.3 (95% CI 0.8-2.0) Estrogen and/or progesterone yes vs. no: 0.7 (0.5-1.2) Alkylating agents yes vs. no: 0.7 (0.5-1.0) <u>Adjusted rate ratios for death in multivariable Poisson regression analysis:</u>	

			GH treatment yes vs. no: 1.6 (95% CI 0.5-4.9) <u>Cumulative incidence meningioma over time:</u> Increased incidence of meningioma over time in patients treated with CRT, regardless of GH exposure. Cumulative incidence highest in GH treated without cranial RT, however this concerns one patient. <u>Other outcomes:</u> -94.5% of meningiomas and 79.2% of gliomas occurred in patients exposed to RT, but GH treatment not associated in patients with second neoplasms after cranial RT, irrespective of dose. -n=66 died after diagnosis of second neoplasm; n=7 (10.6%) were treated with GH, n=59 (89.4%) were not treated with GH	
<u>Conclusion</u> • In a study of **12,098 childhood cancer survivors,** GH treatment did **not increase** the risk for **second neoplasms,** including **meningioma** or **glioma.**				

WG4: What should be done when abnormalities are identified?				
CA Sklar et al., Risk of Disease Recurrence and Second Neoplasms in Survivors of Childhood Cancer Treated with Growth Hormone: A Report from the Childhood Cancer Survivor Study, Journal of Clinical Endocrinology and Metabolism (2002)				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**

Study design Retrospective cohort-study (with prospective follow-up) Treatment era: Diagnosed between 1970-1986 Follow-up: Median 6.2 years (range 0.4-20.6) after initiation of GH	Study population 13,324 childhood cancer survivors (<21 years at diagnosis), who survived at least 5 years; 361 survivors treated with GH, 12,963 survivors not treated with GH Male n= 237 (65.7%) Female n= 124 (34.3%) Primary cancer diagnosis of GH treated patients: Medulloblastoma, n=73 (20.2%) Astroglial, n=68 (18.8%) Ependymoma, n=15 (4.2%) Germ cell, n=14 (3.9%) Miscellaneous, n=2 (0.6%) Acute leukemia, n=122 (33.8%) Soft tissue sarcoma, n=43 (11.9%) Neuroblastoma, n=17 (4.7%) Other, n=7 (1.9%) Age at primary cancer diagnosis: Median 3.5 yrs (range 0-17.2) Age at follow-up: Not reported	Tumor treatment: Not reported Treatment for HP disorder: Treatment type: GH, dose not reported. Various GH preparations, including human pituitary only (n=43, 11.9%), recombinant only (n=279, 77.3%), both (n=27, 7.5%) and unknown (n=12, 3.3%) GH treatment in n=361 of 13,324 patients (2.7%) Age start treatment: median 10 yrs (range 3.1-20.8) Duration of treatment: median 4.6 yrs (range 0.1-14) Start treatment: not reported Definition of GHD: not reported	Survivors with disease recurrence or second neoplasm -Tumor relapse, n=9 (2.5%) of which n=6 after starting GH in GH treated patients, n=502 (3.9%) in non-GH treated patients -Second neoplasm, n=16 (4.4%) in GH treated patients (n=15 after GH treatment), n=344 (2.7%) non-GH treated patients GH treated patients: -Osteogenic sarcoma, n=3 (20%) -Astrocytoma, n=1 (6.7%) -Glioma, n=1 (6.7%) -Meningioma, n=6 (40%) -Mucoepidermoid carcinoma, n=1 (6.7%) -Adenocarcinoma, n=1 (6.7%) -Spindle cell sarcoma, n=1 (6.7%) -Sarcoma, n=1 (6.7%) -Death, n=23 (6.4%) in GH treated patients, n=1102 (8.5%) non-GH treated patients Relative risk of disease recurrence in multivariable Cox regression analysis Radiation yes vs. no: 2.01 (95% CI 1.57-2.57)* Age at diagnosis (risk/yr): 1.03 (95% CI 1.01-1.05)* Chemotherapy yes vs. no: 1.52 (95% CI 1.16-1.98)* GH treatment yes vs. no: 0.83 (95% CI 0.37-1.86) Relative risk of disease recurrence in multivariable Cox regression analysis, stratified by tumor diagnosis CNS tumors, 0.31 (95% CI 0.13-0.77)* -Medulloblastoma, 0.13 (95% CI 0.02-0.94)* -Astroglial, 0.98 (95% CI 0.35-2.75) -Ependymoma, 0 (95% CI 0-13) -Germ cell, not applicable Acute leukemia, 0.85 (95% CI 0.12-6.14) Rhabdomyosarcoma, 0 (95% CI 0-4) Neuroblastoma, 0 (95% CI 0-35) Of note; no recurrence after GH therapy for ependymoma, germ cell tumor, rhabdomyosarcoma, neuroblastoma	Strengths -Large cohort study with GH treatment verified through medical record review. Limitations -GH treatment is self-reported and includes 29 institutions and not clear if the treating guidelines are similar across institutions. Other remarks -Data for secondary tumor occurrence was only available for 13,222 survivors Risk of bias A. Selection bias: high risk, of patients answered 'yes' to GH treatment, only 361 or 684 could be verified (52.8%). B. Attrition bias: unclear for how many survivors follow-up data was complete C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. D. Confounding: low risk, analyses were adjusted for important confounding factors.

			For all diagnoses, risk of disease recurrence was not greater for GH-treated versus non-GH treated survivors. <u>Relative risk of secondary tumors in multivariable Cox regression analysis</u> Radiation yes vs. no: 2.71 (95% CI 1.94-3.79)* Age at diagnosis (risk/yr): 1.06 (95% CI 1.02-1.08)* Alkylating agent yes vs. no: 1.44 (95% CI 1.15-1.79)* GH treatment yes vs. no: 3.21 (95% CI 1.88-5.46)* Gender, male vs. female: 0.55 (95% CI 0.44-0.69)* <u>Relative risk of secondary tumors in multivariable Cox regression analysis, stratified by tumor diagnosis</u> Acute leukemia, 4.98 (95% CI 1.95-12.74)* CNS tumors, 2.34 (95% CI 0.96-5.70) CNS tumors (meningiomas excluded), 1.46 (95% CI 0.31-6.79) Rhabdomyosarcoma, 1.82 (95% CI 0.41-8.01) Risk of secondary tumors was primarily driven in GH-treated survivors of leukemia, and marginal evidence for increased risk in survivors of CNS. <u>Relative risk of death in multivariable Cox regression analysis, adjusted for age at diagnosis, sex, radiation and chemotherapy</u> GH treatment yes vs. no: 1.21 (95% CI 0.75-1.94)	
<u>Conclusion</u> • In a study of **13,324 childhood cancer survivors**, GH treatment did **increase** the risk for **secondary neoplasms,** but **not disease recurrence** or **mortality**.				

WG4: What should be done when abnormalities are identified?

AJ Swerdlow et al., Growth Hormone Treatment of Children with Brain Tumors and Risk of Tumor Recurrence, Journal of Clinical Endocrinology and Metabolism (2000)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective multi-center cohort study Treatment era: GH treatment between 1965 - 1996 Follow-up: Average 6.4 years after initiation of GH, with maximum of 20 years.	Study population 1071 irradiated patients with brain tumor diagnosis in childhood, excluding craniopharyngioma, 180 treated with GH, and 891 childhood cancer survivors without GH treatment (except for 11 who were treated with GH after first relapse) Male n= 106 (59.2%) Female n= 73 (40.8%) Primary cancer diagnosis of GH treated survivors: Medulloblastoma, n=94 (52.5%) Ependymoma, n=12 (6.7%) Astrocytoma, n=36 (20.1%) Other glioma, n=17 (9.5%) Other, n=20 (11.2%) Age at primary cancer diagnosis: Not reported for entire group, only subgroups <3.5 yrs, n=49 (27.4%) 3.5-6.4 yrs, n=47 (26.3%) 6.5-9.9 yrs, n=55 (30.7%) 10-16 yrs, n=28 (15.6%)	Tumor treatment: Cranial radiotherapy in all patients Chemotherapy in 119 (66.1%) Details of other modalities not reported Treatment for HP disorder: Treatment type: GH (preparation unknown), dose between 15-20 IU/m^2/week or 0.5 IU/kg/week Age start treatment: not reported Age stop treatment: not reported Duration of treatment: not reported Start treatment: in one of three centers, treatment was only started after >2 years survival	Survivors with disease recurrence -Tumor relapse, n=35 (19.4%) in GH treated patients, n=434 (48.7%) in non-GH treated patients -Death without relapse, n=81 (7.6%) in entire cohort -Death in GH treated patients, n=12 (6.7%) Adjusted relative risks for tumor relapse in multivariable Cox regression analysis, with prognostic variable GH treatment vs non-GH treatment: Gender male, 0.8 (95% CI 0.5-1.3) Gender female, 0.4 (95% CI 0.2-0.8)* Age at tumor diagnosis (yr) <3.5, 0.5 (95% CI 0.1-2.0) Age at tumor diagnosis (yr) 3.5-6.4, 0.7 (95% CI 0.3-1.7) Age at tumor diagnosis (yr) 6.5-9.9, 0.7 (95% CI 0.3-1.4) Age at tumor diagnosis (yr) ≥ 10, 0.7 (95% CI 0.4-1.4) Histology, medulloblastoma, 0.5 (95% CI 0.2-0.9)* Histology, ependymoma, 1.1 (95% CI 0.3-3.6) Histology, astrocytoma, 0.7 (95% CI 0.3-1.4) Histology, other glioma, 1.0 (95% CI 0.3-3.0) Histology, other, 0.8 (95% CI 0.2-3.3) Calendar period of tumor diagnosis <1980, 1.3 (95% CI 0.5-3.5) Calendar period of tumor diagnosis 1980-1984, 0.3 (95% CI 0.1-0.8)* Calendar period of tumor diagnosis ≥1985, 0.7 (95% CI 0.4-1.1) Time since tumor diagnosis (yr) <2, 0.8 (95% CI 0.4-1.9) Time since tumor diagnosis (yr) 2-4, 0.5 (95% CI 0.3-0.9)* Time since tumor diagnosis (yr) ≥5, 0.9 (95% CI 0.4-2.0) Chemotherapy, none, 0.7 (95% CI 0.4-1.2) Chemotherapy, any 0.5 (95% CI 0.3-1.0)* Hospital of tumor treatment, Christie, 0.8 (95% CI 0.4-1.6) Hospital of tumor treatment, Great Ormond, 0.6 (95% CI 0.4-1.0) Hospital of tumor treatment, Royal Marsden, 0.4 (95% CI 0.1-2.8)	Strengths -Large study Limitations -GH treatment administered over a time period >30 years -Lots of details missing Other remarks X Risk of bias A. Selection bias: low risk, 1071 of 1084 (98.8%) patients included. B. Attrition bias: unclear for how many survivors follow-up data was complete. "Routine follow-up occurred more frequently for GH-treated than for untreated patients" C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. D. Confounding: low risk, analyses were adjusted for important confounding factors.

	Age at follow-up: Not reported	Definition of GHD: based on auxological and conventional provocative tests	**Total RR, 0.6 (95% CI 0.4-0.9)** Adjusted relative risks for tumor relapse in multivariable Cox regression analysis Time since start first GH treatment, <2 vs. no treatment, 0.6 (95% CI 0.1-1.0)* Time since start first GH treatment, 2-4 vs. no treatment, 0.5 (95% CI 0.3-1.2) Time since start first GH treatment, ≥ 5 vs. no treatment, 0.9 (95% CI 0.4-2.2) Adjusted for sex, age at tumor diagnosis, histology, time since tumor diagnosis, calendar period tumor diagnosis, chemotherapy, hospital of treatment Duration of GH treatment, <2 vs. no treatment, 0.7 (95% CI 0.4-1.1) Duration of GH treatment, 2-4 vs. no treatment, 0.4 (95% CI 0.2-0.9)* Duration of GH treatment, ≥5 vs. no treatment, 0.9 (95% CI 0.3-2.6) Adjusted for sex, age at tumor diagnosis, histology, time since tumor diagnosis, calendar period tumor diagnosis, chemotherapy, hospital of treatment Adjusted relative risks for death in multivariable Cox regression analysis Time since start first GH treatment, <2 vs. no treatment, 0.4 (95% CI 0.2-0.7)* Time since start first GH treatment, 2-4 vs. no treatment, 0.3 (95% CI 0.1-0.8)* Time since start first GH treatment, ≥ 5 vs. no treatment, 1.1 (95% CI 0.5-2.1) Adjusted for sex, age at tumor diagnosis, histology, time since tumor diagnosis, calendar period tumor diagnosis, chemotherapy, hospital of treatment	

			Duration of GH treatment, <2 vs. no treatment, 0.5 (95% CI 0.3-0.9)* Duration of GH treatment, 2-4 vs. no treatment, 0.5 (95% CI 0.2-0.9)* Duration of GH treatment, ≥5 vs. no treatment, 0.5 (95% CI 0.2-1.5) Adjusted for sex, age at tumor diagnosis, histology, time since tumor diagnosis, calendar period tumor diagnosis, chemotherapy, hospital of treatment <u>Other outcomes</u> -During follow-up, 469 patients of all patients (GH treated and non-GH treated) relapsed, 81 died without relapse, and 521 were alive and relapse-free at last contact. -Of the 35 relapses in the GH treated patients, 20 occurred during GH treatment and 15 after it - Risk of relapse was significantly reduced in GH-treated patients compared with untreated patients before adjustment (RR, 0.6; 95% CI, 0.4–0.9; and after adjustment (RR, 0.6; 95% CI, 0.4–0.9) - Risk for recurrence while on GH treatment was 0.5 (95% CI, 0.3– 0.7), and that for recurrence while on treatment or within 100 days of its cessation was 0.5 (95% CI, 0.3– 0.8). - The overall relative risk of mortality for patients treated with GH was **0.5 (95% CI, 0.3– 0.8)***	
<u>Conclusion</u> • In a study of **180 children** with a **brain tumor**, GH treatment did **not increase** the risk for **disease recurrence** or **mortality**. Also, there was no trend in the association between duration of GH treatment or time since treatment, and disease recurrence.				

WG4: What should be done when abnormalities are identified?				
WW Woodmansee et al., Incidence of second neoplasm in childhood cancer survivors treated with GH: an analysis of GeNeSIS and HypoCCS, European Journal of Endocrinology (2013)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective analysis of prospective cohort study (GeNeSIS and HypoCCS databases) Treatment era: GeNeSIS: GH treatment between 1999-2007 HypoCCS: GH treatment between 2002-2008 Follow-up: Not reported	Study population GeNeSIS: 421 patients with childhood malignancy (<21 years at diagnosis), 394 treated with GH in childhood, 27 not treated with GH Male n= 232 (58.9%) Female n= 162 (41.1%) HypoCCS: 280 patients with childhood malignancy (<21 years at diagnosis), 252 treated with GH in adulthood, 28 not treated with GH Male n= 117 (46.4%%) Female n= 153 (53.6%) Primary cancer diagnosis: GeNeSIS (total cohort): Medulloblastoma, n=140 (33.3%) Leukemia, n=63 (15.0%) HypoCCS (total cohort): Germinoma, n=60 (21.4%)	Tumor treatment: not reported Treatment for HP disorder: Treatment type: GH (humatrope; somatropin), dose not reported Age start treatment: GeNeSIS: median 10.8 yrs (Q1-Q3, 8.9-12.9) HypoCCS: not reported Age stop treatment: not reported Duration of treatment: GeNeSIS: median 2.9 yrs (Q1-Q3, 1.4-4.8) HypoCCS: median 6.8 yrs (Q1-Q3, 0.8-14.6) of GHD, with 2.9 (Q1-Q3, 1.5-5.1) follow-up	Prevalence neoplasms compared with CCS: GeNeSIS: -Second neoplasm, n=15 (3.8%, 95% CI 2.2-6.2) in GH treated patients, n=0 in non-GH treated patients GH treated patients: -Bone sarcoma, n=1 (6.7%) -Bone cyst, n=1 (6.7%) -ALL, n=1 (6.7%) -AML, n=1 (6.7%) -Lingual granular cell tumor, n=1 (6.7%) -Low-grade astrocytoma, n=1 (6.7%) -Low-grade glioma, n=1 (6.7%) -Meningioma, n=3 (20%) -Myelodysplastic syndrome, n=1 (6.7%) -Spinal cord neoplasm, n=1 (6.7%) -Pheochromocytoma, n=1 (6.7%) -Osteochondroma, n=1 (6.7%) -Neuroblastoma, n=1 (6.7%) -Death, n=7 (1.8%) in GH treated patients, n=1 (3.7%) in non-GH treated patients HypoCCS: -Second neoplasm, n=23 (9.1%) in GH treated patients, n=4 (14.3%) in non-GH treated patients. Second neoplasm during HypoCCS in n=15 (6.0%, 95% CI 3.4-9.6) GH treated patients after enrollment in HypoCCS, n=15:	Strengths -Large number, long follow up in adulthood Limitations -Lots of (sociodemographic and treatment) details missing, only one follow up visit necessary for inclusion -Data provided by study investigators -GH untreated group very small Other remarks X Risk of bias A. Selection bias: low risk, GeNeSIS 421 of 491 (85.7%) patients included; HypoCCS: 280 of 310 (90.3%) patients included B. Attrition bias: high risk, follow-up data is not complete. Data obtained from study investigators (endocrinologist instead of oncologist) C. Detection bias: unclear if the outcome assessors were blinded

	Leukemia, n=51 (18.2%) Medulloblastoma, n=44 (15.7%) Astrocytoma, n=44 (15.7%) <u>Age at primary cancer diagnosis:</u> GeNeSIS Median 5.4 years (Q1-Q3 3.0-8.5) HypoCCS Median 8.4 years (Q1-Q3 4.1-12.2) <u>Age at follow-up:</u> Not reported	Start treatment: not reported Definition of GHD: not reported	-Ewing's sarcoma, n=1 (6.7%) -Malignant melanoma, n=1 (6.7%) -Basal cell carcinoma, n=2 (13.3%) -Meningioma, n=5 (33.3%) -Hepatic adenoma, n=1 (6.7%) -Glioblastoma multiforme, n=1 (6.7%) -Benign nervous system neoplasm, n=1 (6.7%) -Gastrointestinal stromal tumor, n=1 (6.7%) -Glioblastoma, n=1 (6.7%) -Thyroid carcinoma, n=1 (6.7%) Before enrollment in HypoCCS, n=8 -Meningioma, n=3 (37.5%) -Hemangioma, n=2 (25%) -Thyroid carcinoma, n=2 (25%) -Basal cell carcinoma, n=1 (12.5%) Non-GH treated patients after enrollment in HypoCCS, n=2: -Glioblasmoa multiforme, n=1 (50%) -Breast cancer, n=1 (50%) Non-GH treated patients before enrollment in HypoCCS, n=2 -Meningioma, n=2 (100%) Death, n=3 (1.2%) in GH treated patients, n=1 (3.6%) in non-GH treated patients <u>Median time interval to second neoplasms:</u> GeNeSIS: -Median time from cancer diagnosis to second neoplasm was 8.4 yrs (Q1-Q3, 6.3-10.6) -Median time from start GH therapy to second neoplasm was 2.4 yrs (Q1-Q3, 1.6-4.4) HypoCCS	for important determinants related to the outcome. D. Confounding: high risk, no multivariable analysis performed.

			-Median time from cancer diagnosis to second neoplasm was 20.3 yrs (Q1-Q3, 18.1-28.9) <u>Other outcomes:</u> GeNeSIS: -All but one case of second neoplasm, occurred in patients who were exposed to both chemotherapy and radiotherapy -Patients with second neoplasm had medulloblastoma (n=10, 66.7%), ependymoma (n=1, 6.7%), leukemia (n=1, 6.7%), neuroblastoma (n=2, 13.3%) and ALL (n=1, 6.7%) -Mean GH dose after 1 yr, 0.22 (S.E.M. 0.03) mg/kg/week in GH treated with second neoplasm, 0.24 (S.E.M. 0.01) mg/kg/week in those without second neoplasm. -Mean baseline IGF-1 was -1.7 (S.E.M. 0.66) in those with second neoplasm, and -3.2 (S.E.M. 0.23) in those without second neoplasm. HypoCCS -Patients with second neoplasm had ALL (n=2, 8.7%), acute myeologenous leukemia (n=2, 8.7%), acute lymphoblastic lymphoma (n=1, 4.3%), non-Hodgkin's lymphoma (n=1, 4.3%), germinoma (n=4, 17.4%), pineal dysgerminoma (n=1, 4.3%), astrocytoma (n=2, 8.7%), optic glioma (n=1, 4.3%), medulloblastoma (n=6), pharynx cancer (n=1, 4.3%), pinealoma (n=1, 4.3%), choriocarcinoma (n=1, 4.3%) -Mean GH dose 0.472 (S.E.M. 0.071) mg/day in year 1, 0.554 (S.E.M. 0.098) mg/day in year 2, 0.517 (S.E.M. 0.109) mg/day in year 3 in GH treated with second neoplasm, 0.500 (S.E.M. 0.022) mg/day in year 1, 0.525 (S.E.M. 0.032) mg/day in year 2, 0.515 (S.E.M. 0.029) mg/day in year 3 in those without second neoplasm. -Mean baseline IGF-1 was -3.0 (S.E.M. 0.56) in those with second neoplasm, and -3.8 (S.E.M. 0.22) in those without second neoplasm.	

Conclusion
• In a study of **394 + 252 children** with childhood cancer, the incidence of second neoplasms was similar to previously published literature in childhood cancer survivors treated with GH, and thus consistent with an **increased risk** of **second neoplasm**.

WG4: What should be done when abnormalities are identified?				
A Corrias et al., Growth hormone treatment in irradiated children with brain tumors, Journal of Pediatric Endocrinology and Metabolism (1997)				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort study Treatment era: Not reported Follow-up: Not reported	Study population 25 children with a history of a brain tumor distant from the hypothalamic-hypophyseal area, treated with GH Male n=16 (64%) Female n=9 (36%) Comparison population: 100 irradiated patients with cerebral tumors who were not treated with GH Primary cancer diagnosis: Glioma, n=8 (32%) Medulloblastoma, n=11 (44%) Ependymoma, n=6 (24%)	Tumor treatment: Radiotherapy, n=25 (100%) Surgery, n=19 (76%) Chemotherapy, n=21 (84%) RT details Patients with glioma, cranial RT 40-50 Gy Patients with medulloblastoma and ependymoma, RT 34-36 Gy on the whole brain, 10-14 Gy on the posterior fossa and 10-36 Gy on the spine	Survivors with tumor recurrence -Study population: tumor relapse, n=4 (16%) and comparison population: tumor relapse n=18 (18%) Median time interval to tumor relapse: -Time interval between radiotherapy and tumor relapse, range 5.6-12.4 years -Time interval between GH therapy and tumor relapse, range 2-6.2 years Risk of tumor relapse No statistically significant difference for tumor relapse in GH-treated and non-GH treated patients, also not if subdivided according histological type	Strengths -Comparison group with non-GH treated survivors Limitations -Small cohort - Short duration of GH treatment - Short duration of follow-up Other remarks X Risk of bias A. Selection bias: unclear how many patients were included in the original cohort of survivors

	In comparison population Glioma, n=50 (50%) Medulloblastoma, n=35 (35%) Ependymoma, n=15 (15%) <u>Age at primary cancer diagnosis:</u> Not reported <u>Age at follow-up:</u> Not reported	<u>Treatment for HP disorder:</u> Treatment type: GH (subcutaneous biosynthetic GH), dose 0.6-0.9 IU/kg/week. Age start treatment: range 7.8-17 years Age stop treatment: not reported Duration of treatment: 1 year (n=7), 2 years (n=9), 3 years (n=9) Start treatment: range 2.1 to 12.1 years since completion of radiotherapy Definition of GHD: diagnosed by nocturnal spontaneous GH secretion and arginine-insulin tolerance tests		B. Attrition bias: low risk, patients were examined every three months C. Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. D. Confounding: high risk, analyses were not adjusted for important confounding factors.
<u>Conclusion</u> • In a study of **25** survivors **brain tumors** (+ 100 survivors as comparison population; mean follow-up time not reported), GH treatment did **not increase** the risk for development of **tumor recurrence**.				