Supplemental file for review

Supplement 1

Operational definitions
In case of a bone problem: all data were collected **until** occurrence of the bone problem in order to assess it as associated factor. In case of no bone problems: it was collected whether the variables were present at any time during follow-up.

Muscle problems. Muscle problems were defined according to the Medical Research Council (MRC)-scale. The MRC-scale ranges from 0 to 5, expressing total paralysis to normal force respectively. A MRC score of 3 or lower in one of the muscles of the lower extremities was categorized as an associated factor for bone problems. The lowest MRC during follow-up was included.

Inactivity. Relative inactivity was defined as 'sometimes' use of a wheelchair (e.g. for longer distances) OR not performing any sports. Total inactivity was defined as wheelchair use in daily life of the patient.

Chemotherapy and targeted therapy.
Treatment with chemotherapy was collected, including:
- Carboplatin
- Vincristine
- Vinblastine
- Cisplatin
- Cyclophosphamide
- Temozolomide
- Irinotecan
- Bevacizumab (targeted therapy)
- Trametinib (targeted therapy)
- Tovorafenib (targeted therapy)

The number of chemotherapy rounds was collected.

Weight problems due to hypothalamic dysfunction

- ***Diencephalic syndrome history.*** Diencephalic syndrome was defined as being underweight at brain tumor diagnosis. Underweight was defined according to the international cutoff points of the WHO for children < 2 years of age (BMI < -2.0 SDS) (1). In children ≥ 2 years of age, underweight was defined according to the international cutoff point of Cole et al. using BMI thinness grade 2 (2).

- ***Significant weight gain.*** Significant weight gain was defined in line with a previous manuscript (3); an increase in BMI ≥ +2.0 standard deviation score (SDS) from diagnosis (maximum within 3 months) to most recent moment of follow-up.

Visual problems. Visual problems were defined according to scoring and reporting by the ophthalmologist following the definitions of visual impairment and blindness based on the tenth revision of the International Statistical Classification of Diseases and Related Health Problems. Visual problems were categorized based on the scoring of the best eye (impairment had to be present in both eyes); mild or no visual impairment (best corrected visual acuity (BCVA) ≤0.5 logMAR [Snellen fraction (SF) ≥20/70]); moderate visual impairment (BCVA >0.5 to 1.0 logMAR [SF <20/70 to

≥20/200]); severe visual impairment (BCVA >1.0 to 1.3 logMAR [SF <20/200 to ≥20/400]); blindness (BCVA >1.3 logMAR [SF <20/400]) (4).

Vitamin D deficiency. Vitamin D deficiency was defined as moderate when 25-OH-vitamin D in blood measurements were below 50 nmol/L during follow-up. Severe vitamin D deficiency was considered as 25-OH-vitamin D in serum below 30 nmol/L during follow-up (5).

Glucocorticoids. Data was collected on the maintenance dose of glucocorticoids; a maintenance dose above 10 mg/m2 per day during follow-up was considered high. In addition, the number of hospital stays in the year before DXA scan was listed (as a reflection of stress of the body and thus need for extra hydrocortisone), more than 5 hospital stays were noted as an associated factor. Attending the hospital for a cure of chemotherapy was not considered a hospital stay.

Overweight and obesity

In children ≥ 2 years of age, overweight, and obesity were defined according to the international cutoff point of BMI by sex and age for overweight and obesity by Cole et al (defined to pass through a BMI of respectively 25 and 30 kg/m2 at the age 18) (6).

Hypothalamic syndrome.

For presence of hypothalamic syndrome, a score based on the diagnostic criteria for hypothalamic syndrome, as defined by Van Santen et al., was used in this study (7).

Hyperphagia

- *Mild (can be controlled by parental restriction or patient itself)*
- *Mild after specific intervention for hyperphagia OR severe (cannot be controlled by parents or patient itself or steals food)*

Hypophagia

- *Mild (can be stimulated to eat by parents/caregivers)*
- *Severe (cannot be stimulated to eat by parents/caregivers or requires tube feeding or eating)*

BMI

- *Normal weight or overweight*
- *Normal weight after specific intervention for hypothalamic obesity OR overweight after specific intervention for hypothalamic obesity OR obesity*

Behavioral problems

- *Mild (can be corrected by parents/caregivers)*
- *Mild after specific intervention for hypothalamic behavioral problems OR severe (cannot be corrected by parents/caregivers, requires specialist treatment)*

Sleep disorder

- *Mild (one or more sleep symptoms without disruption of school and/or family)*
- *Mild after specific intervention such as melatonin OR severe (disrupts school and/or family, diagnosis of obstructive sleep apnea syndrome)*

Temperature dysregulation

- *Mild, core-temperature multiple times between 35 and 36 degrees or above 37,5 degrees without infection*

- *Severe (needs intervention such as specialized heat clothing), core-temperature measured below < 35 degrees*

Pituitary dysfunction

- *Partial or complete pituitary dysfunction (with or without DI with adequate thirst feeling) OR SIADH OR history of central precocious puberty*
- *(Partial or complete) pituitary dysfunction including DI and adipsia (inadequate thirst feeling)*

Pituitary dysfunction.

Pituitary dysfunction was categorized as having any anterior pituitary deficiency (growth hormone (GH), thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), adrenocorticotropic hormone (ACTH)) or posterior pituitary deficiency (arginine vasopressin deficiency) or central precocious puberty (CPP).
Detailed description of pituitary deficiencies is included in *Supplement 2.*

Tumor recurrence / progression

Tumor recurrence was defined as any growth (greater than normal variability) of the tumor on MRI scan as described by radiologist.

Supplement 2 Definitions of pituitary deficiencies

Growth hormone deficiency. Growth hormone deficiency is defined as a shortage in growth hormone and is scored with CTC-AE grade. GH deficiency is present when:

- IGF-1 < -2 SD corrected for age and sex in combination with declining growth curve or lack of acceleration during pubertal development in combination with: o Peak GH in GH stimulation tests (Arginine, L-dopa propranolol, or Clonidine) < 30 mE/l or

- IGF-1 < 0 SD corrected for age and sex in combination with declining growth curve or lack of acceleration during pubertal development in combination with:

- Peak GH in GH stimulation tests (Arginine, L-dopa propranolol, or Clonidine) < 20 mE/l.

Hypogonadism. Hypogonadism was defined as presence of either hyper – or hypogonadotropic gonadal dysfunction (including estrogen deficiency and testosterone deficiency) and was scored with CTC-AE grade. Hypogonadism was defined present in case of:

- Female = Tanner stage B1 in girls equal or older than 13 years: low-normal LH/FSH values in combination with low estradiol
- Male = Testes volume <3 cc or no Tanner stage G2 at age >14 years in boys low-normal LH/FSH values in combination with low testosterone
- Treatment = with testosterone or estrogens given with diagnosis of hypogonadism by treating physician.

Hypothyroidism. Hypothyroidism was defined based on FT4 and TSH values and data in the medical chart and scored with CTC-AE grade. Hypothyroidism was defined present when:

- FT4 < 10.0 pmol/L or
- TSH > 5 mU/L
- Decline of FT4 in time > 20% with low-normal or slightly elevated TSH concentrations or
- Treatment already started with thyroxine and FT4 values within normal range with low TSH levels during treatment and diagnosis of central or primary hypothyroidism.

Hyperthyroidism.

Hyperthyroidism was defined as present in case of decreased levels of TSH (< 0.3 mE/L) and increased T4 (> 20 pmol/L), use of anti-thyroid medication, or defined as such in the medical chart.

Hypocortisolism. Hypocortisolism was defined based on cortisol levels and scored with CTC-AE grade. Hypocortisolism was defined present when:

- Morning cortisol < 80 nmol/L or peak cortisol in synacthen test < 550 nmol/L or 11-deoxycortiosl in metyrapon test < 200
- Treatment already started with hydrocortisone for diagnosis central hypocortisolism.
- If present the date of determination has to be noted down.

Supplement 3

Supplemental Table 1 Descriptive characteristics of children with supratentorial midline LGG until first bone problem (N = 161).

Patient characteristic	**% (n/N)**
Sex at birth, female	49.1% (79/161)
Age at brain tumor diagnosis, median in years (IQR)(full range)	4.7 (2.1 – 8.3)(0.1 – 17.9)
Follow-up time, median in years (IQR)(full range)	6.1 (3.3 – 10.6)(0.1– 19.9)
Age at follow-up, median in years (IQR)(full range)	12.6 (7.9 – 17.6)(2.5 – 28.1)
Histology	
- Pilocytic astrocytoma	44.1% (71/161)
- LGG NOS	3.7% (6/161)
- Glioneuronal tumor	1.9% (3/161)
- Gangliоglioma	1.2% (2/161)
- Diffuse astrocytoma	0.6% (1/161)
- Other forms	1.2% (2/161)
- No biopsy taken	47.2% (76/161)
Growth of primary tumor	
- Prechiasmatic	16.8% (25/149)
- Chiasmatic	55.0% (82/149)
- Postchiasmatic	28.2% (42/149)
Hydrocephalus at diagnosis, Yes	29.8% (48/161)
Metastases at diagnosis, Yes	8.1% (13/161)
Neurosurgical tumor treatment	
- Surgery, Yes*	55.3% (89/161)
- Number of surgeries in total, median (IQR)(range)*	2 (1 – 2)(1 – 6)
- Ventricular drainage at diagnosis	23.6% (38/161)
- Ventricular drainage during follow-up*	16.1% (26/161)
- Radical resection at diagnosis	0.6% (1/161)
- Limited resection at diagnosis	1.2% (2/161)
- Subtotal tumor resection at diagnosis	16.8% (27/161)
- Cyst drainage at diagnosis	3.7% (6/161)
- Performed surgery at diagnosis unknown	1.2% (2/161)
- Radical resection during follow-up	2.5% (4/161)
- Limited resection during follow-up	9.3% (15/161)
- Subtotal resection during follow-up	22.4% (36/161)
- Cyst drainage during follow-up	11.2% (18/161)
- Performed surgery at follow-up unknown	0.0% (0/161)
Chemotherapy treatment	
- Chemotherapy, Yes	70.2% (113/161)
- Number of chemotherapy treatment periods (IQR)(range)	2 (1 – 3)(1 – 5)
Targeteded therapy treatment	
- Targeteded therapy, Yes	27.3% (44/161)
- Bevacizumab	24.2% (39/161)
- Trametinib	9.9% (16/161)
- Tovorafenib	1.9% (3/161)
- Dabrafenib	1.2% (2/161)
Radiotherapy treatment	
- Radiotherapy, Yes	8.1% (13/161)
- Dose, median in Gy (IQR)(range) *N = 12*	54.0 (50.4 – 54.0)(50.4 – 54.0)

Multiple treatment modalities	
- Wait and see	14.3% (23/161)
- Surgery only	11.8% (19/161)
- Surgery + chemotherapy	23.0% (37/161)
- Surgery + chemotherapy + targeted therapy	13.7% (22/161)
- Surgery + chemotherapy + radiotherapy	1.9% (3/161)
- Surgery + chemotherapy + targeted therapy + radiotherapy	1.2% (2/161)
- Surgery + radiotherapy	3.7% (6/161)
- Chemotherapy only	17.4% (28/161)
- Chemotherapy + targeted therapy	12.4% (20/161)
- Chemotherapy + radiotherapy	0.6% (1/161)
Progression since primary cancer diagnosis, Yes	75.0% (111/148)
State of disease at follow-up time	
- Alive, free from tumor (complete resection)	2.6% (4/151)
- Alive with residual tumor	76.2% (115/151)
- Relapse after complete resection	1.3% (2/151)
- Progression of residual tumor	18.5% (28/151)
- Deceased	1.3% (2/151)
BMI at tumor diagnosis, mean in SDS (SD)(full range) *N = 115*	-0.1 ±1.9 (-5.4 – 4.1)
Weight category at tumor diagnosis	
- Underweight	16.5% (19/115)
- Normal weight	60.9% (70/115)
- Overweight	16.5% (19/115)
- Obesity	6.1% (7/115)
BMI at follow-up, mean in SDS (SD)(full range) *N = 153*	1.4 ±1.4 (-2.7 – 4.6)
Weight category at follow-up	
- Underweight	2.0% (3/153)
- Normal weight	52.9% (81/153)
- Overweight	29.4% (45/153)
- Obesity	15.7% (24/153)
ΔBMI SDS from diagnosis to follow-up (median)(full range) *N = 113*	1.0 (0.1 – 2.6)(-3.3 – 8.7)

Legend to Supplemental Table 1

*only neurosurgery, meaning that hydrocephalus surgery or revision of an existing hydrocephalus device was not counted for total numbers of surgeries

IQR = interquartile range

Supplemental Table 2 Covariates of the hypothalamic syndrome in children with bone problems compared to without bone problems, in only the children specifically assessed for bone problems (N = 99).

Covariate	Children with bone problems (%, n/N) N = 36	Children without bone problems (%, n/N) N = 125	p-value
Hypothalamic syndrome$^{\Omega}$, Yes	60.0% (15/25)	50.0% (29/58)	0.402
Hyperphagia			
- Mild	25.0% (5/20)	22.4% (13/58)	0.134
- Severe	0.0% (0/20)	17.2% (10/58)	
Hypophagia			
- Mild	5.0% (1/20)	0.0% (0/57)	**<0.001***
- Severe	20.0% (4/20)	0.0% (0/57)	
BMI			
- Normal weight or overweight	90.3% (28/31)	77.4% (48/62)	0.129
- Normal weight after specific intervention for hypothalamic obesity OR overweight after specific intervention for hypothalamic obesity OR obesity	9.7% (3/31)	22.6% (14/62)	
Behavioral problems			
- Mild	30.0% (6/20)	30.8% (16/52)	0.203
- Severe	0.0% (0/20)	13.5% (7/52)	
Sleep disorder			
- Mild	25.9% (7/27)	30.0% (18/60)	0.089
- Severe	33.3% (9/27)	13.3% (8/60)	
Temperature dysregulation			
- Mild	37.5% (3/8)	48.3% (14/29)	0.166
- Severe	25.0% (2/8)	3.4% (1/29)	
Pituitary dysfunction			
- Partial or complete pituitary dysfunction (with or without DI with adequate thirst feeling) OR SIADH OR history of central precocious puberty	45.7% (16/35)	46.8% (29/62)	0.270
- (Partial or complete) pituitary dysfunction including DI and adipsia (inadequate thirst feeling)	8.6% (3/35)	1.6% (1/62)	

Legend to Supplemental Table 2

Ω *Based on the scoring of van Santen et al (7) (supplemental file).*

Definitions of all variables are attached in *Supplement 1.*

P-value for between-group differences calculated with Pearson Chi-Squared Test and Fisher's Exact Test. If more than 20% of expected values were under five, Fisher's exact test was performed. For continuous variables (with non-normal distribution), the Mann-Whitney U test was used.

Supplemental Table 3 Covariates in children with bone problems compared to without bone problems, in all children (N = 161).

Covariate	Children with bone problems (%, n/N) N = 36	Children without bone problems (%, n/N) N = 125	p-value
Sex at birth, Female	52.8% (19/36)	48.0% (60/125)	0.613
Age at brain tumor diagnosis, median in years (IQR)(range)	3.2 (0.6 – 7.9)(0.3 – 16.5)	4.9 (2.8 – 8.9)(0.1 – 17.9)	**0.012***
Follow-up time, median in years (IQR)(range)	3.6 (2.2 – 5.9)(0.0 – 13.9)	7.1 (3.8 – 11.3)(0.0 – 19.9)	**<0.001***
Muscle problems, Yes	25.0% (5/20)	8.7% (9/104)	0.050
Inactivity			
- **Relative**	52.8% (19/36)	42.4% (53/125)	0.185
- **Total**	11.1% (4/36)	5.6% (7/125)	
Diencephalic syndrome history, Yes	50.0% (13/26)	6.7% (6/89)	**< 0.001***
Visual problems			**0.003***
- **No/mild**	43.5% (10/23)	79.4% (81/102)	
- **Moderate**	26.1% (6/23)	10.8% (11/102)	
- **Severe**	8.7% (2/23)	2.0% (2/102)	
- **Blindness**	21.7% (5/23)	7.8% (8/102)	
Vitamin D deficiency			0.597
- **Moderate**	23.1% (3/13)	32.4% (22/68)	
- **Severe**	23.1% (3/13)	29.4% (20/68)	
Pituitary dysfunction, Yes			
- **GH deficiency**	22.2% (8/36)	9.9% (12/121)	0.083
- **ACTH deficiency**	25.0% (9/36)	5.8% (7/121)	**0.002***
- **TSH deficiency**	27.8% (10/36)	9.9% (12/121)	**0.012***
- **LH/FSH deficiency**	2.8% (1/36)	1.7% (2/121)	0.545
- **Arginine vasopressin deficiency with thirst feeling**	11.1% (4/36)	3.3% (4/121)	0.082
- **Arginine vasopressin deficiency without thirst feeling**	8.3% (3/36)	0.8% (1/121)	**0.038***
- **No pituitary deficiency**	63.9% (23/36)	85.1% (103/121)	**0.008***
- **CPP**	38.5% (10/26)	30.1% (25/83)	0.474
- **Elevated IGF-1**	42.4% (14/33)	22.9% (25/109)	**0.044***
Overweight at follow-up/time of bone problem	25.8% (8/31)	30.3% (37/122)	0.667
Obesity at follow-up/time of bone problem	12.9% (4/31)	16.4% (20/122)	0.786
Significant weight gain	50.0% (12/24)	30.3% (27/89)	0.092
ΔBMI SDS from diagnosis to follow-up, median (IQR)(full range)	2.2 (0.5 – 4.8) (-1.0 – 8.7)	0.8 (0.1 – 2.3) (-3.3 – 7.0)	**0.016***
Surgery treatment, Yes	72.2% (26/36)	50.4% (63/125)	**0.023***
Number of surgeries, median (IQR)(range)	2 (1 – 2)(1 – 6)	2 (1 – 2)(1 – 5)	0.766
Chemotherapy. Yes	72.2% (26/36)	69.6% (87/125)	0.838
Number of chemotherapy rounds, median (IQR)(range)	2 (1 – 3)(1 – 4)	2 (1 – 3)(1 – 5)	0.640
Targeted therapy	27.8% (10/36)	27.2% (34/125)	0.999
- **Trametinib**	13.9% (5/36)	8.8% (11/125)	0.356
- **Tovorafenib**	0.0% (0/36)	2.4% (3/125)	0.999
VCR neuropathy	25.0% (9/36)	21.6% (27/125)	0.821

Tumor recurrence or progression, Yes	74.3% (26/35)	75.2% (85/113)	0.999

Legend to Supplemental Table 3

***indicates a significant p-value (p < 0.05)*

***Any clinical relevant weight problem associated with hypothalamic dysfunction includes: Diencephalic syndrome history OR significant weight gain*

Abbreviations: ACTH, Adrenocorticotropic hormone; DI, Diabetes Insipidus; GH, Growth hormone; IGF-1, insulin-like growth factor 1; LH/FSH, Luteinizing hormone/follicle-stimulating hormone; TSH, Thyroid stimulating hormone; SIADH, syndrome of inappropriate antidiuretic hormone.

Muscle problems: MRC of 3 or lower. Definitions of all variables are attached in *Supplement 1.*

P-value for between-group differences calculated with Pearson Chi-Squared Test and Fisher's Exact Test. If more than 20% of expected values were under five, Fisher's exact test was performed. For continuous variables (with non-normal distribution), the Mann-Whitney U test was used.

Supplemental Table 4 Associated factors with bone problems (multivariable analysis), in all children (N = 161).

Covariate	All children (N = 100) OR (95% CI)	P-value
Age at tumor diagnosis	0.97 (0.86 – 1.11)	0.663
Weight problems due to hypothalamic dysfunction or overweight/obesity at follow-up	1.49 (0.51 – 4.34)	0.463
Visual problems (moderate/severe/blindness vs. none)	3.56 (1.30 – 9.76)	**0.014***

Legend to Supplemental Table 4

****indicates a significant p-value (p < 0.05).*

Definitions of all variables are attached in *Supplement 1.*

Weight problems includes: Diencephalic syndrome history OR significant weight gain OR overweight at follow-up OR obesity at follow-up
Multivariable binary logistic regression. P-value calculated with Wald test.

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