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Neuroendocrine morbidity after pediatric optic gliomas: a longitudinal analysis of 166 children over 30 years

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Abstract

Context. 50% of pediatric low-grade gliomas affect the optic pathway, hypothalamus and suprasellar areas (OP/HSGs) resulting in significant long-term neuroendocrinopathy.

Objective. To dissect tumor- from treatment-related risk factors for OP/HSG-associated neuroendocrinopathy.

Design. Retrospective case notes analysis of 166 children with newly-diagnosed OP/HSGs at our quaternary center between 1980-2010 by multivariate Cox, linear and logistic regression.

Results. Patients were of median (range) age 4.9 (0.2-15.4) years at diagnosis and followed up for 8.3 (0.04-26.8) years. Despite high 20-year overall survival (81.0%), progression-free and endocrine event-free (EEFS) survival were 47.2% and 20.8% respectively. EEFS declined up to 15 years post-diagnosis, with hypothalamic involvement ($p<0.001$) being implicated more than radiotherapy ($p=0.008$) in earlier endocrinopathy; the reverse being true of its density (radiotherapy $p<0.001$; hypothalamic involvement $p=0.006$). GH deficiency (GHD) was commonest (40.3%), followed by central precocious puberty (CPP, 26.0%), gonadotropin (GnD, 20.4%), TSH (13.3%), and ACTH (13.3%) deficiencies. GHD increased

with later treatment eras ($p<0.01$), but replacement did not increase progression. CPP was associated with future GnD ($p<0.05$). Posterior pituitary dysfunction (PPD, 7.2%) occurred in 57.9% after only biopsies or shunt procedures, and was associated with 6/13 deaths. 50.2% became obese. Tumor extent, surgery and increased endocrinopathy, rather than radiotherapy, predicted visuo-cognitive morbidity.
Conclusions. This first longitudinal OP/HSG-specific study demonstrates that hypothalamo-pituitary dysfunction evolves hierarchically over decades. Tumor location predicts its speed of onset and radiotherapy its density. GnD can evolve from previous CPP, whilst life-threatening PPD can occur after any surgery. Our data suggest that recent radiation-avoiding chemotherapeutic strategies have increased GHD without improving survival.

Keywords: Pediatric optic glioma, juvenile pilocytic astrocytoma, survivorship, endocrine morbidity, neurology

Introduction

Over 40% of central nervous system tumors are low-grade gliomas (LGGs).(1) Although classed as benign grade I or II astrocytic tumors (the majority being juvenile pilocytic astrocytomas),(2) they exhibit unpredictable growth with the possibility of spontaneous involution, late-onset progression, or leptomeningeal metastases.(3-5) 10-16% are associated with neurofibromatosis type 1 (NF-1), behaving more indolently and occurring more anteriorly, bilaterally and multifocally.(5-11) Although 50-60% of pediatric LGGs involve the cerebellum, cerebral hemispheres or brainstem, 30-50% affect the optic nerves, chiasm, tracts, hypothalamus and suprasellar midline, collectively referred to here as optic pathway, hypothalamic and suprasellar gliomas (OP/HSGs).(9, 11)

The first international whole-brain LGG study (LGG1) showed that the highest overall- (OS) and progression-free survival (PFS) resulted from complete tumor resection.(10, 11) However, due to their proximity to vital hypothalamo-pituitary and visual structures, only 3% of OP/HSGs were resectable compared with 94% of cerebellar LGGs.(11) Despite high survival rates (86-100%)(8-13), survivors face significant endocrine, visual and neurocognitive morbidity. These deficits are multifactorial in origin, the relative patient-, tumor- and treatment-related contributions being unclear, although in clinical practice radiotherapy is frequently blamed.(9)

The reported incidence of neuroendocrinopathies in survivors varies from 39-100%,(14, 15) with studies limited to small retrospective cohorts,(16, 17) being of short duration (<10 years),(18, 19) focusing on radiotherapy-treated patients,(15, 20) or analyzing outcomes cross-sectionally, thereby not recognizing their temporal evolution.(9, 21) The only longitudinal report to date did not compare OP/HSG-specific outcomes with LGGs arising elsewhere in the central nervous system and omitted gonadotropin and posterior pituitary dysfunction (PPD) entirely.(9) Our aim was to determine risk factors for neuroendocrine dysfunction in our large single-center, 30-year OP/HSG-specific cohort by multivariate survival analysis, testing the a priori hypothesis: “the incidence and severity of neuroendocrine morbidity is independently predicted by tumor location and treatment strategy”.

Methods

Study cohort

Great Ormond Street Hospital for Children (GOSH) is a quaternary pediatric neuro-oncology center for southeast England. A search on 5 March 2012 of our central tumor registry identified all children <16 years with newly-registered OP/HSGs between 1 January 1980 and 31 December 2010. Cases were included if there was a biopsy-proven or radiologically-diagnosed OP/HSG treated and followed-up at GOSH. LGGs affecting the basal ganglia, thalamus and third ventricle were included as their suprasellar midline locations might affect long-term neuroendocrine morbidity. Patients treated elsewhere or those whose radiological diagnoses were subsequently proven histologically erroneous were excluded. A retrospective case note, laboratory and radiology data review was performed.

Definitions

Independent variables

Patient-related data on age at diagnosis (stratified as <1, 1-5, and >5 years),(11) sex, ethnicity, NF-1 status, the presence and duration of symptoms or diencephalic syndrome were collected, alongside tumor stage (as per the modified Dodge classification (MDC, Supplemental Table 1)),(7) hypothalamic involvement, and the presence of leptomeningeal metastases and hydrocephalus. Where tumors involved multiple regions, the highest (most posterior) MDC stage was recorded, whilst tumors outside MDC-defined regions (e.g. pure thalamic tumors) were coded as “other midline”. WHO histological tumor grade(2) was recorded where available.

Treatment modalities were recorded as surgical resections (any tumor debulking, including biopsies), decompression procedures (aimed at relieving raised intracranial pressure, e.g. cyst aspirations and shunt procedures), radiotherapy or chemotherapy, and were classified as being part of the initial (primary) or cumulative (final) treatment strategy. Focal radiotherapy was delivered to total doses of 48-55 Gy in 25-30 fractions. Chemotherapy was administered according to International Pediatric Oncology Society LGG trial protocols with 12- (LGG1, 1997-2004)(11) or 18-months (LGG2, 2005-2010)(22) first-line carboplatin and vincristine, and second-line cyclophosphamide, cisplatin, thioguanine, procarbazine, lomustine, temozolamide and/ or actinomycin-D. LGG1 was a non-randomized registry study testing chemotherapy as a means of avoiding or delaying radiotherapy in children <5 years of age, whilst LGG2, also non-randomized, extended this aim to children <8 years, reserving radiotherapy only for those ≥8 years of age. Prior to 1997, OP/HSGs were primarily treated by surgical resection with/ without radiotherapy. Patients were therefore stratified by treatment eras on this basis.

Primary outcomes

These were OS, PFS and endocrine event-free survival (EEFS), with time-to-event endpoints defined as death from all causes, first progression (according to international criteria)(23) or first hypothalamo-pituitary endocrine event respectively.

Secondary outcomes

These were the event-free survival for each hypothalamo-pituitary axis as assessed by departmental clinical and biochemical criteria (Supplemental Table 2): GH deficiency (GHD), central precocious puberty (CPP: in boys <9 years and girls <8 years at diagnosis), gonadotropin deficiency (GnD: in boys >14 and girls >13 years at last follow-up), ACTH deficiency (ACTHD), TSH deficiency (TSHD), hyperprolactinemia and PPD (central diabetes insipidus (CDI), syndrome of inappropriate antidiuretic hormone secretion (SIADH) or cerebral salt-wasting (CSW)) as well as obesity, insulin insensitivity or type 2 diabetes mellitus. The total number of hypothalamo-pituitary deficits at last follow-up was termed the endocrine morbidity score (EMS).(24). The requirement for supported or special educational needs schooling and blind or partial sightedness registration as per Department of Health England criteria(25) were surrogates for neurocognitive and visual outcomes respectively. More detailed analysis of visual and cognitive data is beyond the scope of this paper and will be published elsewhere.

Statistical analysis

Non-parametric data were summarized as medians and ranges. Categorical variables were compared using the $\chi 2$-test and the $\chi 2$-test for trend, whilst continuous variables were compared using the Kruskal-Wallis one-way analysis of variance. Kaplan-Meier survival curves were censored at last follow-up or death for all outcomes. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated by univariate and multivariate Cox proportional hazards regression, with the latter generated by forward stepwise selection (inclusion criterion $p<0.05$, exclusion criterion $p>0.10$). Predictors entered were age, sex, ethnicity, NF-1 status, MDC stage, tumor grade, presence of symptoms, diencephalic syndrome, hypothalamic involvement, leptomeningeal metastases and hydrocephalus at diagnosis, primary and final treatment modalities, number of progressions and surgeries, and treatment era. For PFS, the number of progressions, surgeries and final treatment modalities were excluded from analyses. Cross-sectional correlations with EMS and neuro-ophthalmic outcomes were examined by linear and logistic regression respectively, using the same forward stepwise selection criteria to estimate regression coefficients β and odds

ratios (ORs) with 95% CIs. Analyses were performed with IBM SPSS® version 21 (IBM Corporation, New York) with significance set at $p<0.05$.

Ethical approval
The GOSH Research & Development department approved this study as a case note review in March 2011.

Results
Patient recruitment (Table 1)
166 of 203 registered OP/HSG patients were eligible for analysis. The following patients were excluded: six for inappropriate histology (two meningiomas, one grade III astrocytoma, one Langerhans cell histiocytosis, one glioependymal cyst, and one Alexander disease), two for location outside the optic pathway or suprasellar midline (one right lateral ventricle, and one right temporal lobe), 14 for having had their treatment and/ or follow-up in other centers, 14 for whom no records could be located, and one for loss to follow-up. 16 of 166 eligible patients had no ethnicity recorded leaving 150 datasets for multivariate analyses. Two patients had LGGs arising post-chemotherapy for acute lymphoblastic leukemia. Tumor histology was only available for 63 patients (38.0%), therefore tumor grade was excluded from all multivariate models and only included in post hoc subcohort analyses of patients with histological verification.

Median ages at diagnosis and follow-up were 4.9 (0.2-15.4) and 15.5 (2.4-37.4) years respectively, with a median follow-up of 8.3 (0.04-26.8) years. Median symptom duration prior to diagnosis (n=134) was 135 (1-1825) days, being longer in posterior tumors (MDC 3/4 vs. 1: 210 (21-1460) vs. 90 (30-1460) days, $p<0.05$) and those without hypothalamic involvement (non-hypothalamic vs. hypothalamic: 150 (1-1825) vs. 90 (1-1460) days, $p<0.01$), but not in non-white patients or those presenting with endocrinopathies (p=NS).

The use of surgery and radiotherapy declined significantly over successive treatment eras in favor of chemotherapy (1980-1996 vs. 2005-2010: surgical resections 47.7% vs. 21.6%, radiotherapy 53.8% vs. 29.4%, chemotherapy 23.1% vs. 49.0%; $p<0.01$). The age at first radiotherapy exposure also increased with time (median age 1980-1996 vs. 2005-2010: 6.7 (0.6-15.9) vs. 10.2 (4.3-15.7) years; $p<0.01$). The proportions of non-white and symptomatic patients respectively increased (1980-1996 vs. 2005-2010: 10.8% vs. 47.1%; $p<0.001$) and decreased (1980-1996 vs. 2005-2010: 90.8% vs. 76.5%; $p<0.05$) with time, in keeping with service expansion and increased neuroimaging. No other independent variable followed this trend, nor were there differences in the proportion of patients undergoing biochemical endocrine testing (1980-1996 75.4%, 1997-2004 74.0%, 2005-2010 82.4%; p=NS) over time.

Primary outcomes (Figure 1a, Tables 2-3)
Survival for all primary outcomes plateaued by 20 years, with actuarial OS, PFS and EEFS being 81.0%, 47.2% and 20.8% respectively. Endocrine events occurred early with EEFS falling much more steeply than PFS and OS ($p<0.001$).

OS
13 (7.8%) patients died at a median of 8.2 (0.8-16.9) years from disease progression (nine), acute hydrocephalus (two), acute intratumoral hemorrhage (one) or a second primary cancer (one atypical teratoid rhabdoid tumor arising post-chemotherapy). Notably six (46%) had severe PPD (three CSW, two CDI, one SIADH) at the time of death. The only independent risk factor for mortality was age <1 year at diagnosis (Figure 1b, $p<0.01$). Subcohort analysis of biopsied tumors showed that non-white ethnicity independently reduced OS (HR 10.76 (1.12-103.78), $p<0.05$).

PFS (Figures 1c-e)
67 (40.4%) of OP/HSGs progressed at a median 2.1 (0.1-11.7) years from diagnosis; in 32.8% this was multiple (one progressing six times), whilst one underwent 27 operations for progression or hydrocephalus. Age <1 year ($p<0.01$) and hypothalamic involvement ($p<0.01$) were independent risk factors for progression, whilst patients with diencephalic syndrome ($p<0.001$) or hypothalamic involvement ($p=0.001$) were more likely to progress multiple

times (Supplemental Table 3). In the biopsied subcohort, primary chemotherapy was independently associated with an increased risk of progression (HR 2.05 (1.05-3.98), p<0.05), whilst primary resection was conversely associated with a reduced risk (HR 0.37 (0.18-0.73), p<0.01). Neither metastatic disease, tumor grade, treatment modalities nor treatment era affected OS or PFS. GH supplementation was not independently associated with PFS when included as part of a post-hoc multivariate model (data not shown).

EEFS (Figures 2b-e)

109 (65.7%) patients experienced their first endocrine event at a median of 0.8 (0.0-14.2) years from diagnosis. However, one patient with an anterior tumor (MDC stage 1) developed isolated GHD 14.2 years post-diagnosis after chemotherapy alone. Hypothalamic involvement was a stronger independent predictor of reduced EEFS (p<0.001) than primary radiotherapy (p<0.05). Subcohort analysis of biopsied tumors did not show any differences. The trend for reduced EEFS in the lattermost treatment era suggested by Kaplan-Meier analysis (Figure 2e) was not confirmed in the multivariate model.

Secondary outcomes

EMS (Figure 2a, Tables 2-4)

Endocrinopathy was unusual at diagnosis with gonadotropin dysfunction being commonest (11.4% CPP; 14.3% GnD). At last follow-up, 54.8% had at least one endocrinopathy (median EMS 1 (0-6)) with a clear hierarchical evolution. GHD occurred earliest and most frequently (40.3%) followed by CPP (26.0%), GnD (20.4%), TSHD (13.3%), ACTHD (13.3%) and CDI (4.2%). 11 (6.6%) had panhypopituitarism (four with CDI).

Treatment era was therefore a significant confounder in cross-sectional analysis for EMS (β=-0.38, 95% CI -0.63--0.13) and excluded from the multivariate model. Radiotherapy exposure (p<0.001) was a stronger predictor than diencephalic syndrome (p<0.01) of final EMS, which also increased with the number of surgical interventions (p<0.01) and decreased with female sex (p<0.05).

Specific endocrine event-free survival (Table 4)

Multivariate analyses of individual endocrinopathies revealed that hypothalamic involvement or the presence of diencephalic syndrome were more predictive of most endocrine deficits (CPP, GnD, ACTHD, TSHD, PPD) than treatment-related factors such as radiotherapy exposure. Radiotherapy was the strongest risk factor for GHD (p<0.001), but did not independently predict CPP, TSHD or PPD. GHD significantly increased in later treatment eras (p<0.01), whilst PPD significantly decreased between 1997-2004 (p<0.05). The protective effect of female sex on EMS was CPP- (p=0.03) and ACTHD-specific (p=0.009).

One GHD, two ACTHD (likely secondary to dexamethasone suppression) and ten PPD cases were reversible. Notably, CPP could evolve to future GnD (37.5% of CPP vs. 14.6% of non-CPP patients subsequently developed GnD, p=0.048; 50.0% of GnD vs. 19.6% of non-GnD patients had previous CPP, p=0.02). Most hyperprolactinemia was transient and only one galactorrheic patient (prolactin >1000 mU/l) required cabergoline. On multivariate analysis, surgery was the only treatment-related factor predicting PPD (p<0.05), the risk increasing with repeated operations (p<0.05, supplemental Table 4). Only three of 22 patients had PPD at diagnosis (two with hypothalamic tumors, one with a third ventricle tumor), the remainder having all undergone surgery prior to its onset; in 11/19 (57.9%) this was a biopsy or decompression procedure alone.

Visual and neurocognitive outcomes (Supplemental Tables 5 & 6)

At last follow-up, 21.1% of patients were registered blind or partially sighted, 36.1% had required supported schooling, and 15.7% had attended a special needs school. Poor visual and educational outcomes were strongly predicted by posteriorly extensive (MDC stage 3/4), multiply progressive, or metastatic tumors. Primary resection was associated with reduced special school attendance, although conversely, if part of the final treatment strategy, resections were associated with blind registration and special school attendance. Girls and patients treated in latter treatment eras were less likely to require supported or special needs schooling. Radiotherapy did not independently predict visual or cognitive dysfunction whilst a

higher EMS predicted a higher likelihood of requiring supported (p=0.001) or special needs schooling (p=0.004, data not shown).

Neurological morbidity was otherwise rare; three patients developed moya-moya disease (all post-radiotherapy, one with NF-1) and two patients suffered strokes after surgery and radiotherapy, one of whom also had chemotherapy.

Discussion

The high actuarial 20-year OS we report for OP/HSGs in this study is comparable to published literature.(9-11) Thus, minimizing future endocrine, visual and cognitive morbidity remains an important therapeutic goal in managing these tumors. Whilst endocrine dysfunction appears easily treatable, combined ACTHD and PPD can be life-threatening(26), GnD impairs future fertility, and obesity, with its long-term cardiovascular and metabolic sequelae, is in itself life-limiting. The lower concurrent PFS rates we and others have demonstrated (47-51%)(9, 10) additionally indicate that the optimal treatment strategy for these benign lesions remains elusive; whilst the absence of longitudinal neuroendocrine morbidity data limits our understanding of their etiology and evolution. Armstrong et al.'s single-center study is the only other longitudinal analysis of long-term LGG outcomes, but this was not OP/HSG-specific and thus biased by the larger proportion of more peripheral and easily resectable tumors.(9)

Our study uniquely examines the longitudinal evolution and predictors of neuroendocrine dysfunction over three decades in the largest OP/HSG-specific cohort reported to date. Our predictors of reduced OS and PFS (age <1 year and hypothalamic involvement) agree with previous reports, with hypothalamic tumors and patients with diencephalic syndrome progressing repeatedly.(10-13) Unlike LGGs elsewhere, OP/HSG-specific survival is not independently predicted by NF-1 status, tumor grade, or metastases; their effect probably negated by the intrinsic progressive nature of tumors in this location.(8, 11, 13, 27) Our study also supports the safety of GH supplementation in these cases with tumor progression rates being unaffected as previously reported.(28, 29)

Although tumor location, radiotherapy and surgery have all been implicated in OP/HSG-related endocrinopathy, these univariate cross-sectional studies fail to separate tumor- from treatment-related effects.(8, 17, 18) Contrastingly, our multivariate longitudinal analysis confirms our hypothesis that both tumor location and treatment modalities influence long-term neuroendocrine morbidity. By introducing the concept of EEFS, we show that whilst tumor location predicts the tempo of endocrinopathy, radiotherapy compounds its density, particularly GHD. The strong association between GHD and radiotherapy explains Armstrong et al.'s findings that complete resection, in a largely peripheral LGG cohort, reduces GHD by obviating the need for adjuvant irradiation.(9) Given the pre-existing hypothalamic disruption and the propensity for multiple disease progressions, it is unsurprising that infants with diencephalic syndrome were also more likely to develop multiple endocrinopathies.

The hierarchical evolution in hypothalamo-pituitary dysfunction observed echoes that previously described in OP/HSGs, craniopharyngiomas and other suprasellar tumors.(15, 27, 30, 31) Its pathogenesis is poorly understood but is thought to reflect a differential radiosensitivity(31) and/ or the embryonal transcriptional cascade regulating anterior pituitary development.(32) However, apart from GHD and insulin resistance, endocrinopathies were predicted more by hypothalamic involvement than treatment, supporting the idea that tumor mass causes primary hypothalamo-pituitary injury, and progression may thus cause further dysfunction.

We could identify no treatment modality as an independent risk factor for PPD, likely due to its rarity. However, all affected patients without PPD at diagnosis developed this exclusively in the immediate post-operative period, with >50% reported as having only had biopsies or decompression procedures without significant resection. Its association with 46% of deaths in our cohort highlights the need for careful risk-benefit analysis of any surgery, even in the absence of major tumor excision.

CNS tumor-associated obesity is etiologically multifactorial.(33) We demonstrate a previously unreported high prevalence in OP/HSGs (50% at 20 years), which together with insulin insensitivity is increased by radiotherapy. Although none of our patients developed frank type 2 diabetes, this may yet occur with longer follow-up (>30 years) and incur consequential cardiovascular risks. Patients with posteriorly extensive, multiply progressive, metastatic or surgically resected tumors were most likely to experience visual loss or require educational support. The association between EMS and cognitive morbidity suggests that both are markers of increased hypothalamo-pituitary injury.

Therefore, in aiming to improve long-term outcomes for OP/HSGs, there is a precarious balance between preventing disease progression and minimizing long-term treatment toxicity. The suggested reduction in EEFS (particularly GHD) we observed with successive treatment eras is concerning given the lack of a corresponding improvement in survival. Due to concerns regarding early cranial irradiation exposure and cognitive dysfunction, chemotherapy was increasingly incorporated into treatment regimens to delay or avoid radiotherapy.(34) Although radiotherapy has long been assumed to cause greater neuroendocrine toxicity, in our cohort it was only associated with GHD, GnD and ACTHD, and not with CPP, TSHD, PPD, obesity, insulin resistance, visual or cognitive dysfunction, the latter of which can occur even in the absence of radiotherapy.(35) Modern, focal radiotherapeutic techniques limiting exposure of healthy brain tissue have demonstrated less long-term neuroendocrine morbidity(36).

In our subcohort of biopsied patients, primary chemotherapy was associated with an increased likelihood of progression, confirming previous literature on chemotherapy's failure to stabilize disease and prevent visual deterioration.(3, 10, 11) Primary resection reduced progression rates as previously reported.(9-11) However, given the perioperative risk of PPD even with procedures not aimed at tumor resection and its possible association with mortality, attempts at resecting OP/HSGs must be carefully considered.

We thus postulate that failure of a first-line chemotherapeutic strategy in preventing OP/HSG progression necessitates multiple salvage surgical or radiotherapeutic interventions which can, together with tumor growth, compound neuroendocrine morbidity. Two other lines of evidence support this; firstly, the reduction in EEFS over time was largely GHD-specific and strongly predicted by radiotherapy, despite its less frequent use; and secondly, the association between multiple surgeries and a worse EMS suggests failure to stabilize disease necessitating repeated treatments. Furthermore, the improved cognitive outcomes seen after primary resection contrast with the increased visual and cognitive morbidity seen when surgery is part of the final treatment strategy, likely reflecting the ease of resectability – and hence cure or stabilization – of tumors selected for primary resection.

The protective effect of female sex on EMS and cognition are new unexplained findings requiring further study. The only prior evidence for sexually dimorphic neuroendocrine outcomes is converse– female cranially irradiated medulloblastoma and leukemia survivors experience a greater radiation-induced cognitive decline.(37, 38) Similarly, the association between non-white ethnicity and a reduced OS has never been described, possibly due to a lack of ethnicity data in multicenter international trials. It is unlikely to be due to differences in healthcare access given the similar times to diagnosis between groups, and may have an as yet undefined genetic basis coding for more molecularly unfavorable tumors.

The retrospective nature of this study limits our findings. We assumed normal endocrine function without clinical or biochemical evidence to the contrary which may underdiagnose endocrinopathies,(24) as illustrated by the late GHD diagnosis which may well have been an occult idiopathic GHD already present pre-treatment. The low incidence of endocrinopathies at diagnosis may reflect the difficulties of performing dynamic endocrine tests prior to oncological therapy, particularly to diagnose GHD and ACTHD. However, there was no change in the frequency of follow-up endocrine testing over successive eras. We also omitted primary endocrine dysfunction (three with autoimmune hypothyroidism, one with idiopathic primary ovarian failure) from our analyses as this was unlikely to be related to hypothalamo-pituitary injury.

Determining the degree of surgical resection achieved was difficult across treatment eras and between individual surgeons due to variations in the definition of terms such as “debulking”, “subtotal resection” and “incomplete resection”. Only seven tumors (4.2%, four MDC 1 and three third ventricle tumors) were completely resected. We did not assess tumor invasiveness beyond documenting MDC stage, grade, metastases, and hydrocephalus, as radiological parameters such as tumor volume, apparent diffusion coefficients or fractional anisotropy were impossible in the pre-MRI era.(39, 40) Although this is the largest OP/HSG-specific longitudinal neuroendocrine morbidity study to date, our cohort size still prevented sub-analysis of the effect of degree of resection, radiotherapy doses and various chemotherapy regimens on outcomes.

The third international LGG study (LGG3) is currently being designed and will, for the first time, collect prospective longitudinal neuroendocrine morbidity data as part of a randomized-controlled chemotherapeutic trial. Importantly, randomization will mandate tumor biopsy, and our data suggests that its impact on PPD and other neuroendocrine outcomes requires careful study. Although radiotherapy is not being considered for randomization, this may need careful consideration given the precision of modern irradiation techniques, a lack of evidence for the superiority of chemotherapy and our observation that many of the neuroendocrinopathies observed are secondary to tumor location rather than irradiation exposure. The hierarchical, evolutionary nature of endocrine deficits over prolonged intervals suggests that early routine and lifelong endocrine follow-up is paramount in all these patients, for instance to diagnose evolving GnD even in the presence of previous pubertal precocity. Longer-term subfertility, type 2 diabetes and cardiovascular outcomes require more prolonged data collection and a paradigm shift from measuring the quantity of survival to prioritization of its quality, implicit in the British Neuro-oncology Society’s recent recommendation that OP/HSGs be managed as a chronic disease rather than a classical malignancy.(22)

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Author contributions
H.W.G. and H.A.S. were involved in study conception and design, data interpretation and manuscript writing. H.W.G. was involved in data collection, coding, and statistical analysis. K.P. performed the registry search, provided tumor diagnosis, ethnicity and death registration data as well as useful manuscript editions. K.A., M.N.G. and R.H. provided significant input and amendments to the manuscript. H.A.S. oversaw the whole project.

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The authors have nothing to disclose.

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Table & Figure Legends

Table 1 Demographic, tumor- and treatment-related characteristics, and trends by treatment era. NF-1, neurofibromatosis type 1; MDC, modified Dodge classification; JPA, juvenile pilocytic astrocytoma; SEGA, subependymal giant cell astrocytoma; NOS, not otherwise specified. *p-values are for the $\chi 2$-test for trend or the Kruskal-Wallis one-way analysis of variance.

Table 2 20-year overall (OS), progression-free (PFS), endocrine event-free survival (EEFS) and endocrine morbidity score (EMS) at last follow-up with crude hazard ratios (HRs, 95% confidence intervals (CI)) and unadjusted regression coefficients β respectively. NF-1, neurofibromatosis type 1; MDC, modified Dodge classification. *All patients with leptomeningeal metastases survived to last follow-up. §All patients with diencephalic syndrome and/ or leptomeningeal metastases progressed. #All patients aged <1 year at diagnosis, with diencephalic syndrome, hypothalamic involvement or leptomeningeal metastases experienced ≥1 endocrinopathy.

Table 3 Predictors included in the multivariate Cox and linear regression models for overall (OS), progression-free (PFS), endocrine event-free survival (EEFS) and endocrine morbidity score (EMS), ranked by magnitude of hazard ratio (HR) or regression coefficient β. CI, confidence interval.

Table 4 Prevalence at diagnosis & last follow-up, 20-year event-free survival, predictors included in the multivariate Cox regression model, hazard ratios (HRs) and 95% confidence intervals (CIs) for individual endocrine events. GHD, growth hormone deficiency; CPP, central precocious puberty; GnD, gonadotropin deficiency; ACTHD, adrenocorticotropic hormone deficiency; TSHD, thyroid stimulating hormone deficiency; hyperPRL, hyperprolactinemia; PPD, posterior pituitary dysfunction; CDI, central diabetes insipidus; SIADH, syndrome of inappropriate antidiuretic hormone secretion; CSW, cerebral salt-wasting syndrome. For univariate HRs see Supplemental Table 4.

Figure 1 Kaplan Meier survival curves and life tables for (a) actuarial overall (OS), progression-free (PFS) and endocrine event-free survival (EEFS); (b) OS by age; (c-e) PFS by age, the presence of diencephalic syndrome (DS) and hypothalamic involvement respectively.

Figure 2 Kaplan Meier survival curves and life tables for endocrine event-free survival (EEFS) by (a) individual EEFS, (b) presence of hypothalamic involvement, use of radiotherapy as part of the primary (c) and final (d) treatment strategies respectively, and treatment era (e). GHD, growth hormone deficiency; CPP, central precocious puberty; GnD, gonadotropin deficiency; ACTHD, adrenocorticotropic hormone deficiency; TSHD, thyroid stimulating hormone deficiency; DI, diabetes insipidus; RT, radiotherapy.

Independent variable	n/ median (%/ range)	By treatment era (%)			p*
		1980-1996 (n=65)	1997-2004 (n=50)	2005-2010 (n=51)	
Age					
>5 years	81 (48.5)	30 (46.2)	27 (54.0)	24 (47.1)	
1-5 years	69 (41.6)	28 (43.1)	19 (38.0)	22 (43.1)	0.834
<1 year	16 (9.6)	7 (10.8)	4 (8.0)	5 (9.8)	
Sex					
Male	76 (45.8)	27 (41.5)	24 (48.0)	25 (49.0)	0.410
Female	90 (54.2)	38 (58.5)	26 (52.0)	26 (51.0)	
Ethnicity (n=150)					
White	114 (68.7)	43 (66.2%)	44 (88.0%)	27 (52.9%)	**<0.001**
Non-white	36 (21.7)	7 (10.8%)	5 (10.0%)	24 (47.1)	
Unknown	16 (9.6)	15 (23.1%)	1 (2.0%)	0 (0.0%)	
NF-1 status					
Negative	98 (59.0)	39 (60.0)	29 (58.0)	30 (58.8)	0.889
Positive	68 (41.0)	26 (40.0)	21 (42.0)	21 (41.2)	
Symptomatic					
No	27 (16.3)	6 (9.2)	9 (18.0)	12 (23.5)	**0.037**
Yes	139 (83.7)	59 (90.8)	41 (82.0)	39 (76.5)	
Diencephalic syndrome					
No	153 (92.2)	59 (90.8)	47 (94.0)	47 (92.2)	0.754
Yes	13 (7.8)	6 (9.2)	3 (6.0)	4 (7.8)	
Tumor stage					
MDC 1	29 (17.5)	12 (18.5)	8 (16.0)	9 (17.6)	
MDC 2	76 (45.8)	28 (43.1)	23 (46.0)	25 (49.0)	0.623
MDC 3/4	34 (20.5)	13 (20.0)	11 (22.0)	10 (19.6)	
MDC other midline	27 (16.3)	12 (18.5)	8 (16.0)	7 (13.7)	
Hypothalamic involvement					
No	99 (59.6)	38 (58.5)	31 (62.0)	30 (58.8)	0.947
Yes	67 (40.4)	27 (41.5)	19 (38.0)	21 (41.2)	
Leptomeningeal metastases					
No	160 (96.4)	63 (96.9)	48 (96.0)	49 (96.1)	0.801
Yes	6 (3.6)	2 (3.1)	2 (4.0)	2 (3.9)	
Hydrocephalus					
No	105 (63.3)	37 (56.9)	33 (66.0)	35 (68.6)	0.186
Yes	61 (36.7)	28 (43.1)	17 (34.0)	16 (31.4)	
Tumor grade					
Grade I	51 (30.7)	21 (32.3)	17 (34.0)	13 (25.5)	
JPA	40 (24.1)				
SEGA	2 (1.2)				
NOS	9 (5.4)				
Grade II	12 (7.2)	8 (12.3)	2 (4.0)	2 (3.9)	0.188
Diffuse fibrillary astrocytoma	6 (3.6)				
Pilomyxoid astrocytoma	3 (1.8)				
NOS	3 (1.8)				
Not biopsied/ no histology	103 (62.0)	36 (55.4)	31 (62.0)	36 (70.6)	
Primary treatment strategy					
Observation only	58 (34.9)	20 (30.8)	19 (38.0)	19 (37.3)	
Resection only	17 (10.2)	13 (20.0)	1 (2.0)	3 (5.9)	
Decompression without resection	4 (2.4)	3 (4.6)	1 (2.0)	0 (0.0)	
Radiotherapy	19 (11.4)	10 (15.4)	3 (6.0)	6 (11.8)	0.263
Chemotherapy	20 (12.0)	3 (4.6)	8 (16.0)	9 (17.6)	
Any surgery + radiotherapy	26 (15.7)	12 (18.5)	10 (20.0)	4 (7.8)	
Any surgery + chemotherapy	22 (13.3)	4 (6.2)	8 (16 .0)	10 (19.6)	
Any primary resection	53 (31.9)	26 (40.0)	16 (32.0)	11 (21.6)	**0.036**
Any primary decompression	50 (30.1)	23 (35.4)	14 (28.0)	13 (25.5)	0.241
Any primary radiotherapy	45 (27.1)	22 (33.8)	13 (26.0)	10 (19.6)	0.086
Any primary chemotherapy	42 (25.3)	7 (10.8)	16 (32.0)	19 (37.3)	**0.001**
Final treatment strategy					
Observation only	38 (22.9)	14 (21.5)	13 (26.0)	11 (21.6)	
Surgery only	21 (12.7)	12 (18.5)	3 (6.0)	6 (11.8)	
Radiotherapy only	15 (9.0)	4 (6.2)	5 (10.0)	6 (11.8)	
Chemotherapy only	20 (12.0)	2 (3.1)	7 (14.0)	11 (21.6)	0.729
Any surgery + radiotherapy	31 (18.7)	20 (30.8)	8 (16.0)	3 (5.9)	
Any surgery + chemotherapy	18 (10.8)	2 (3.1)	8 (16.0)	8 (15.7)	
Radiotherapy + chemotherapy	6 (3.6)	2 (3.1)	1 (2.0)	3 (5.9)	
Any surgery + radiotherapy + chemotherapy	17 (10.2)	9 (13.8)	5 (10.0)	3 (5.9)	
Any resection	60 (36.1)	31 (47.7)	18 (36.0)	11 (21.6)	**0.004**
Any decompression	67 (40.4)	32 (49.2)	19 (38.0)	16 (31.4)	**0.050**
Any radiotherapy	69 (41.6)	35 (53.8)	19 (38.0)	15 (29.4)	**0.007**
Any chemotherapy	61 (36.7)	15 (23.1)	21 (42.0)	25 (49.0)	**0.003**
Number of progressions	0 (0-6)	0 (0-6)	0 (0-4)	0 (0-5)	0.710
Number of surgeries	1 (0-27)	1 (0-27)	0 (0-24)	0 (0-12)	**0.043**

Table 1: Demographic, tumor- and treatment-related characteristics, and trends by treatment era. NF-1, neurofibromatosis type 1; MDC, modified Dodge classification; JPA, juvenile pilocytic astrocytoma; SEGA, subependymal giant cell astrocytoma; NOS, not otherwise specified. *p-values are for the χ^2-test for trend or the Kruskal-Wallis one-way analysis of variance.

Independent variable		OS (95% CI)			PFS (95% CI)			EEFS (95% CI)			EMS (95% CI)	
		20-year OS	**Crude HR**	**p**	**20-year PFS**	**Crude HR**	**p**	**20-year EEFS**	**Crude HR**	**p**	**Crude β**	**p**
Age	>5 years	88.7 (76.1-100.0)	1.00		53.4 (36.1-70.8)	1.00		23.8 (13.2-34.5)	1.00			
	1-5 years	80.0 (60.6-99.3)	1.05 (0.28-3.94)	0.945	49.5 (34.4-64.5)	1.17 (0.69-2.00)	0.566	**25.6 (11.1-40.0)**	**0.64 (0.43-0.97)**	**0.034**	-0.02 (-0.07-0.04)	0.600
	<1 year	**62.9 (32.6-93.1)**	**5.29 (1.32-21.22)**	**0.019**	**6.7 (0.0-23.2)**	**5.26 (2.66-10.42)**	**<0.001**	0.0#	1.40 (0.78-2.53)	0.260		
Sex	Male	78.8 (55.7-100.0)	1.00		45.7 (27.5-63.8)	1.00		26.7 (14.2-39.2)	1.00		-0.11 (-0.54-0.32)	
	Female	82.6 (59.4-95.8)	1.02 (0.34-3.03)	0.978	48.4 (36.8-60.1)	1.37 (0.84-2.23)	0.211	16.5 (5.6-27.5)	0.99 (0.68-1.45)	0.972		
Ethnicity (n-150)	White	88.3 (79.6-96.9)	1.00		46.8 (34.2-59.4)	1.00		21.9 (11.7-32.0)	1.00		0.01 (-0.53-0.55)	0.979
	Non-white	36.5 (0.0-89.5)	2.43 (0.73-8.13)	0.151	37.3 (15.6-59.1)	1.49 (0.85-2.62)	0.161	10.5 (0.0-27.4)	1.24 (0.79-1.96)	0.350		
NF-1	Negative	78.5 (63.4-93.7)	1.00		37.6 (24.9-50.3)	1.00		13.0 (4.7-21.3)	1.00		**-0.96 (-1.37--0.55)**	**<0.001**
	Positive	88.2 (73.6-100.0)	0.52 (0.14-1.90)	0.520	**62.8 (45.0-80.7)**	**0.43 (0.25-0.74)**	**0.002**	**33.0 (15.3-50.8)**	**0.45 (0.30-0.68)**	**<0.001**		
Symptomatic	No	95.7 (87.6-100.0)	1.00		73.9 (56.0-91.9)	1.00		10.6 (0.0-37.4)	1.00		**1.00 (0.44-1.56)**	**0.001**
	Yes	80.2 (67.3-93.1)	1.53 (0.20-11.96)	0.686	44.0 (32.9-55.1)	1.97 (0.85-4.56)	0.114	**20.1 (11.8-28.4)**	**1.93 (1.06-3.52)**	**0.032**		
Diencephalic syndrome												
	No	80.8 (66.8-94.8)	1.00		53.3 (42.5-64.1)	1.00		23.5 (14.3-32.7)	1.00		**1.40 (0.63-2.17)**	**<0.001**
	Yes	78.3 (50.8-100.0)	1.99 (0.44-9.04)	0.375	**0.0§**	**4.13 (2.19-7.79)**	**<0.001**	0.0#	1.74 (0.95-3.18)	0.073		
Tumor stage	MDC 1	89.1 (74.2-100.0)	1.00		68.3 (33.1-	1.00		54.4 (21.0-87.8)	1.00			
	MDC 2	82.8 (64.9-100.0)	0.81 (0.16-4.23)	0.806	100.0)	**3.64 (1.29-10.30)**	**0.015**	**13.5 (2.7-24.3)**	**4.31 (2.05-9.08)**	**<0.001**		
	MDC 3/4	80.0 (55.2-100.0)	0.71 (0.10-5.07)	0.735	**48.7 (34.3-63.2)**	**4.00 (1.34-11.97)**	**0.013**	**21.7 (6.4-37.0)**	**3.45 (1.55-7.70)**	**0.002**	**0.27 (0.05-0.49)**	**0.019**
	MDC other midline	80.4 (62.7-98.0)	1.82 (0.33-10.03)	0.491	**37.3 (13.8-60.9)** **33.6 (12.7-54.6)**	**4.93 (1.63-14.87)**	**0.005**	**14.1 (0.0-29.2)**	**3.94 (1.74-8.91)**	**0.001**		
Hypothalamic involvement												
	No	87.3 (76.4-98.3)	1.00		60.3 (46.4-74.3)	1.00		38.6 (25.9-51.3)	1.00		**1.11 (0.71-1.52))**	**<0.001**
	Yes	73.1 (49.7-96.5)	1.75 (0.59-5.20)	0.318	**27.9 (12.5-43.3)**	**2.86 (1.75-4.67)**	**<0.001**	**0.0#**	**3.03 (2.04-4.48)**	**<0.001**		
Leptomeningeal metastases												
	No	80.4 (67.4-93.3)	1.00		48.7 (37.8-59.5)	1.00		22.0 (13.3-30.7)	1.00		**1.46 (0.33-2.58)**	**0.012**
	Yes	100.0*	0.05 (0.00-∞)	0.630	0.0§	2.09 (0.76-5.78)	0.155	0.0#	0.95 (0.35-2.59)	0.922		
Hydrocephalus	No	87.4 (86.8-87.1)	1.00		54.5 (41.0-68.0)	1.00		24.6 (12.6-36.5)	1.00		**0.47 (0.03-0.91)**	**0.037**
	Yes	72.1 (47.5-96.8)	2.00 (0.67-5.99)	0.213	**35.0 (18.2-51.7)**	**1.64 (1.01-2.66)**	**0.045**	**14.9 (3.7-26.2)**	**1.65 (1.13-2.42)**	**0.010**		
Tumor grade (n=63)	Grade I	87.0 (76.7-94.7)	1.00		23.2 (6.93-39.5)	1.00		10.6 (0.0-21.4)	1.00		0.30 (-0.73-1.34)	0.559
	Grade II	60.3 (10.6-100.0)	2.71 (0.44-16.56)	0.280	35.9 (6.2-65.5)	1.02 (0.45-2.32)	0.961	5.6 (0.0-20.0)	1.86 (0.95-3.64)	0.072		
Primary treatment strategy												
	Untreated	91.9 (82.9-100.0)	1.00		59.3 (38.4-80.3)	1.00		33.3 (14.7-52.0)	1.00			
	Resection	78.0 (55.6-100.0)	0.70 (0.21-2.29)	0.553	42.7 (27.9-57.4)	1.39 (0.85-2.27)	0.184	**11.7 (1.0-22.5)**	**1.76 (1.20-2.59)**	**0.004**	**0.66 (0.21-1.11)**	**0.004**
	Decompression	68.7 (38.3-99.0)	1.52 (0.50-4.65)	0.466	33.3 (15.5-51.1)	1.61 (0.98-2.63)	0.060	**9.5 (0.0-19.6)**	**1.85 (1.25-2.74)**	**0.002**	**0.58 (0.12-1.04)**	**0.014**
	Radiotherapy	71.8 (47.6-95.9)	2.04 (0.68-6.11)	0.201	40.9 (21.2-60.6)	1.05 (0.62-1.77)	0.865	**4.1 (0.0-10.4)**	**2.99 (2.00-4.46)**	**<0.001**	**1.06 (0.60-1.51)**	**<0.001**
	Chemotherapy	84.7 (65.8-100.0)	1.01 (0.28-3.67)	0.989	39.9 (22.6-57.2)	1.64 (0.97-2.76)	0.063	9.1 (0.0-22.1)	0.87 (0.56-1.33)	0.515	-0.13 (-0.62-0.36)	0.603
Final treatment strategy												
	Untreated	100.0§	1.00		-	-	-	34.3 (8.2-60.4)	1.00			
	Resection	76.5 (57.3-95.7)	1.06 (0.35-3.19)	0.923	-	-	-	**11.9 (1.8-22.0)**	**1.68 (1.15-2.45)**	**0.008**	**0.76 (0.33-1.19)**	**0.001**
	Decompression	**68.1 (46.5-89.7)**	**3.27 (1.00-10.66)**	**0.049**	-	-	-	**10.1 (1.2-19.0)**	**1.75 (1.20-2.55)**	**0.004**	**0.64 (0.21-1.06)**	**0.004**
	Radiotherapy	73.5 (55.0-92.0)	2.41 (0.74-7.86)	0.145	-	-	-	**3.0 (0.0-8.2)**	**3.39 (2.28-5.04)**	**<0.001**	**1.37 (0.99-1.75)**	**<0.001**
	Chemotherapy	75.3 (52.0-98.5)	1.01 (0.33-3.10)	0.986	-	-	-	13.8 (1.0-26.7)	0.94 (0.64-1.39)	0.751	0.21 (-0.24-0.65)	0.355
Treatment era	1980-1996	78.0 (63.7-92.4)	1.00		51.8 (38.2-65.5)	1.00		24.9 (12.4-37.4)	1.00			
	1997-2004	88.7 (74.2-100.0)	0.53 (0.14-2.00)	0.529	39.8 (16.9-62.6)	1.01 (0.57-1.78)	0.968	20.5 (5.1-35.8)	0.92 (0.59-1.45)	0.728	**-0.38 (-0.63--0.13)**	**0.003**
	2005-2010	97.1 (91.5-100.0)	0.53 (0.06-4.80)	0.534	53.8 (38.2-69.5)	1.41 (0.77-2.61)	0.269	19.2 (1.4-36.9)	1.27 (0.80-2.04)	0.316		
Number of progressions		-	**1.43 (1.08-1.90)**	**0.012**	-	-	-	-	**1.16 (1.01-1.32)**	**0.030**	**0.40 (0.22-0.58)**	**<0.001**
Number of surgeries		-	1.04 (0.96-1.14)	0.327	-	-	-	-	**1.04 (1.01-1.08)**	**0.026**	**0.14 (0.08-0.19)**	**<0.001**

Table 2: 20-year overall (OS), progression-free (PFS), endocrine event-free survival (EEFS) and endocrine morbidity score (EMS) at last follow-up with crude hazard ratios (HRs, 95% confidence intervals (CI)) and unadjusted regression coefficients β respectively. NF-1, neurofibromatosis type 1; MDC, modified Dodge classification. *All patients with leptomeningeal metastases survived to last follow-up. §All patients with diencephalic syndrome and/ or leptomeningeal metastases progressed. #All patients aged <1 year at diagnosis, with diencephalic syndrome, hypothalamic involvement or leptomeningeal metastases experienced ≥1 endocrinopathy.

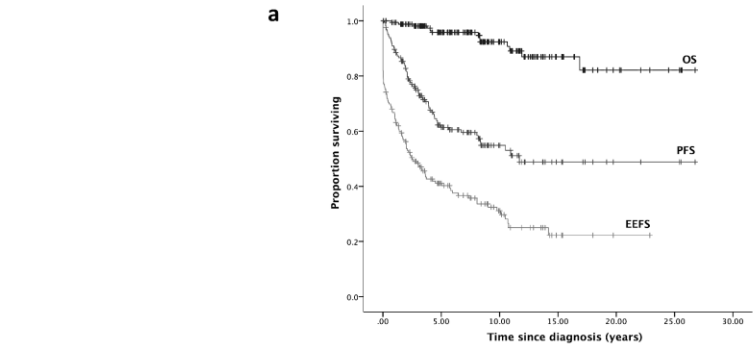
Outcome	Independent predictors	Adjusted HR/ β (95% CI)	p
OS	Age (vs. >5 years)		
	1-5 years	2.10 (0.46-9.66)	0.341
	<1 year	**17.38 (2.81-107.29)**	**0.002**
	Primary radiotherapy	3.88 (0.98-15.42)	0.054
	Non-white ethnicity	3.42 (0.97-12.02)	0.055
PFS	Age (vs. >5 years)		
	1-5 years	1.23 (0.71-2.13)	0.467
	<1 year	**3.11 (1.50-6.48)**	**0.002**
	Hypothalamic involvement	**2.33 (1.35-4.03)**	**0.003**
EEFS	Hypothalamic involvement	**2.20 (1.41-3.42)**	**<0.001**
	Primary radiotherapy	**1.98 (1.16-3.39)**	**0.013**
	Any radiotherapy	1.67 (0.95-2.94)	0.074
EMS	Any radiotherapy	**1.27 (0.88-1.65)**	**<0.001**
	Diencephalic syndrome	**0.93 (0.23-1.63)**	**0.009**
	No. of surgeries	**0.08 (0.03-0.13)**	**0.004**
	Female sex	**-0.41 (-0.78--0.03)**	**0.034**

Table 3: Predictors included in the multivariate Cox and linear regression models for overall (OS), progression-free (PFS), endocrine event-free survival (EEFS) and endocrine morbidity score (EMS), ranked by magnitude of hazard ratio (HR) or regression coefficient β. CI, confidence interval.

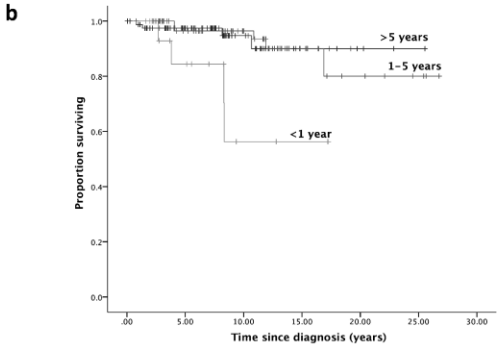
Endocrine event	n (%) At diagnosis	At last follow-up	20-year event-free survival (95% CI)	Independent predictors	Adjusted HR (95% CI)	p
GHD	1 (0.6)	67 (40.3)	39.2 (27.2-51.2)	Any radiotherapy	**5.76 (2.93-11.32)**	**<0.001**
				Treatment era (vs. 1980-1996)		
				1997-2004	0.89 (0.50-1.58)	0.682
				2005-2010	**2.48 (1.29-4.79)**	**0.007**
				Primary radiotherapy	**2.48 (1.36-4.52)**	**0.003**
				No. of surgeries	**1.09 (1.04-1.14)**	**<0.001**
CPP	14/123 (11.4)	32/123 (26.0)	69.7 (60.8-78.6)	Hypothalamic involvement	**4.42 (1.97-9.92)**	**<0.001**
				Female sex	**0.43 (0.21-0.90)**	**0.024**
				Any chemotherapy	**0.42 (0.20-0.90)**	**0.026**
GnD	1/7 (14.3)	21/103 (20.4)	58.4 (39.4-77.4)	Hypothalamic involvement	**5.09 (1.95-13.31)**	**0.001**
				Primary radiotherapy	**3.27 (1.35-7.94)**	**0.009**
ACTHD	1 (0.6)	22 (13.3)	75.6 (65.2-86.0)	Diencephalic syndrome	**15.72 (4.38-56.39)**	**<0.001**
				Primary radiotherapy	**5.16 (2.12-12.57)**	**<0.001**
				Female sex	**0.30 (0.12-0.74)**	**0.009**
				Any chemotherapy	**0.30 (0.10-0.92)**	**0.035**
TSHD	2 (1.2)	22 (13.3)	75.3 (64.6-86.0)	Hypothalamic involvement	**7.18 (2.41-21.38)**	**<0.001**
HyperPRL	5 (3.0)	5 (3.0)	78.1 (64.8-91.4)	-	-	-
PPD	4 (2.4)	12 (7.2)	79.2 (69.8-88.7)	Hypothalamic involvement	**5.82 (1.64-20.67)**	**0.006**
	1 CDI	7 CDI	86.1 (71.6-100.0)	Any resection	**4.61 (1.39-15.34)**	**0.013**
	2 SIADH	2 SIADH	86.8 (79.0-94.6)	Treatment era (vs. 1990-1996)		
	1 CSW	3 CSW	91.4 (84.4-98.5)	1997-2004	**0.19 (0.04-0.87)**	**0.032**
				2005-2010	1.25 (0.38-4.08)	0.716
Obesity	23 (13.9)	54 (32.5)	50.2 (35.4-65.1)	-	-	-
Insulin resistance	0 (0.0)	16 (9.6)	73.1 (55.9-90.3)	Primary decompression	**3.96 (1.43-10.93)**	**0.008**
				Primary radiotherapy	**3.91 (1.42-10.80)**	**0.009**

Table 4: Prevalence at diagnosis & last follow-up, 20-year event-free survival, predictors included in the multivariate Cox regression model, hazard ratios (HRs) and 95% confidence intervals (CIs) for individual endocrine events. GHD, growth hormone deficiency; CPP, central precocious puberty; GnD, gonadotropin deficiency; ACTHD, adrenocorticotropic hormone deficiency; TSHD, thyroid stimulating hormone deficiency; hyperPRL,

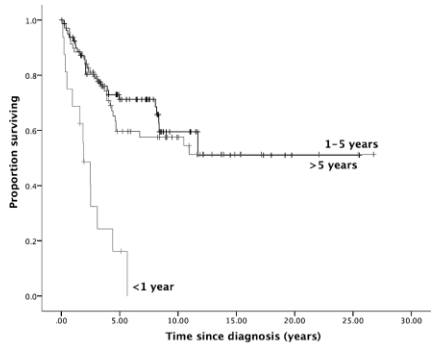
hyperprolactinemia; PPD, posterior pituitary dysfunction; CDI, central diabetes insipidus; SIADH, syndrome of inappropriate antidiuretic hormone secretion; CSW, cerebral salt-wasting syndrome. For univariate HRs see Supplemental Table 4.



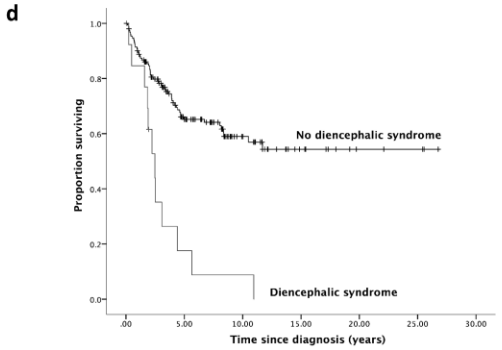
Probability (no. at risk)						
OS	1·00 (166)	0.96 (117)	0.93 (60)	0.86 (23)	0.81 (9)	0.81 (4)
PFS	1.00 (166)	0.61 (74)	0.54 (31)	0.47 (11)	0.47 (4)	0.47 (3)
EEFS	1.00 (166)	0.39 (50)	0.30 (23)	0.21 (5)	0.21 (1)	



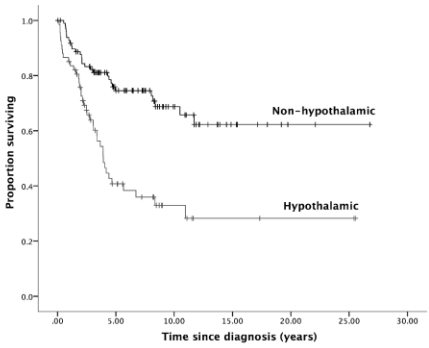
Probability (no. at risk)						
>5 years	1·00 (81)	0·97 (55)	0·95 (23)	0·89 (8)	0·89 (3)	0·89 (1)
1-5 years	1·00 (69)	0·97 (52)	0·97 (34)	0·89 (13)	0·80 (6)	0·80 (3)
<1 year	1·00 (16)	0·86 (10)	0·63 (3)	0·63 (2)		



Probability (no. at risk)						
>5 years	1·00 (81)	0·71 (41)	0·61 (11)	0·53 (5)	0·53 (1)	0·53 (1)
1-5 years	1·00 (69)	0·60 (31)	0·58 (20)	0·49 (6)	0·49 (3)	0·49 (2)
<1 year	1·00 (16)	0·20 (2)	0·07 (0)			

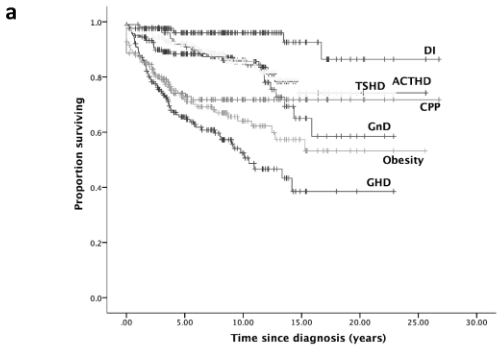


Probability (no. at risk)						
DS	1·00 (153)	0·65 (72)	0·59 (30)	0·53 (11)	0·53 (4)	0·53 (3)
No DS	1·00 (13)	0.20 (2)	0.10 (1)			



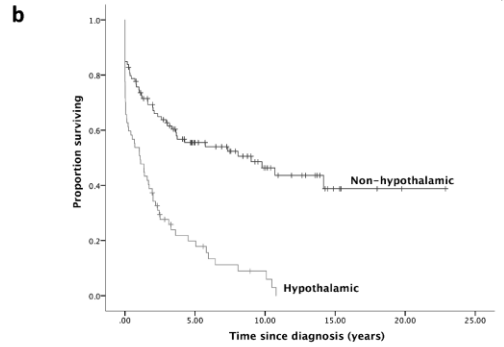
Probability (no. at risk)						
Non-hypothalamic	1·00 (99)	0·74 (54)	0·68 (24)	0·60 (8)	0·60 (2)	0·60 (1)
Hypothalamic	1·00 (67)	0·43 (20)	0·34 (7)	0·28 (3)	0·28 (2)	0·28 (2)

Figure 1: Kaplan Meier survival curves and life tables for (a) actuarial overall (OS), progression-free (PFS) and endocrine event-free survival (EEFS); (b) OS by age; (c-e) PFS by age, the presence of diencephalic syndrome (DS) and hypothalamic involvement respectively.



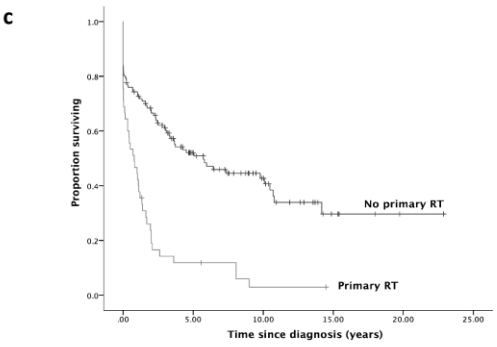
Probability (no. at risk)

GHD	1·00 (166)	0·65 (75)	0·52 (30)	0·39 (5)	0·39 (1)
CPP	1.00 (123)	0·72 (65)	0·70 (38)	0·70 (14)	0·70 (5) 0·70 (1)
GnD	1.00 (103)	0·92 (86)	0·85 (53)	0·67 (12)	0·58 (3)
ACTHD	1·00 (166)	0·87 (103)	0·85 (51)	0·76 (16)	0·76 (5) 0·76 (1)
TSHD	1·00 (166)	0·92 (108)	0·85 (52)	0·75 (14)	0·75 (3)
DI	1·00 (166)	0·96 (113)	0·96 (57)	0·93 (19)	0·86 (6) 0·86 (2)
Obesity	1·00 (166)	0·71 (86)	0·63 (39)	0·57 (14)	0·50 (3) 0·50 (1)



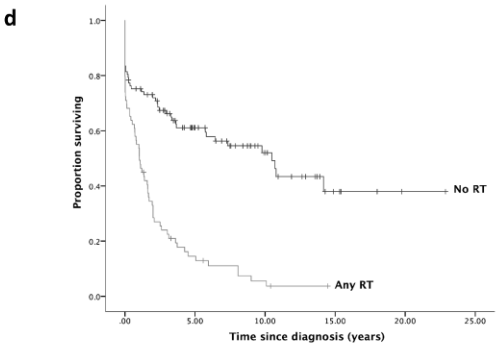
Probability (no. at risk)

Non-hypothalamic	1·00 (99)	0·54 (40)	0·45 (20)	0·39 (5)	0·39 (1)
Hypothalamic	1·00 (67)	0·19 (10)	0·09 (3)	0·00 (0)	



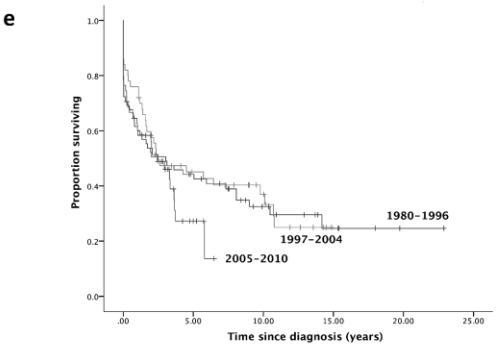
Probability (no. at risk)

No primary RT	1·00 (121)	0·50 (45)	0·41 (22)	0·28 (5)	0·28 (1)
Primary RT	1·00 (45)	0·12 (5)	0·04 (1)		



Probability (no. at risk)

No RT	1·00 (97)	0·59 (41)	0·50 (20)	0·36 (5)	0·36 (1)
Any RT	1·00 (69)	0·15 (9)	0·06 (3)	0·03 (0)	



Probability (no. at risk)

1980 - 1996	1·00 (65)	0·43 (26)	0·31 (12)	0·25 (5)	0·25 (1)
1996 - 2004	1·00 (50)	0·44 (19)	0·36 (11)	0·20 (0)	
2005 - 2010	1·00 (51)	0·29 (5)	0·19 (0)		

Figure 2: Kaplan Meier survival curves and life tables for endocrine event-free survival (EEFS) by (a) individual EEFS, (b) presence of hypothalamic involvement, use of radiotherapy as part of the primary (c) and final (d) treatment strategies respectively, and treatment era (e). GHD, growth hormone deficiency; CPP, central precocious puberty; GnD,

gonadotropin deficiency; ACTHD, adrenocorticotropic hormone deficiency; TSHD, thyroid stimulating hormone deficiency; DI, diabetes insipidus; RT, radiotherapy.