Radiotherapy and Oncology 130 (2019) 139–148

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Are hypothyroidism and hypogonadism clinically relevant in patients with malignant gliomas? A longitudinal trial in patients with glioma

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ARTICLE INFO

Article history:
Received 16 April 2018
Received in revised form 24 September 2018
Accepted 16 October 2018
Available online 30 October 2018

Keywords:
Hypothalamic–pituitary hormones
Radiation induced hormonal deficits
Adult brain tumor patients

ABSTRACT

Background: So far, the development and course of therapy-induced deficiencies in hypothalamic–pituitary hormones in adult patients with malignant gliomas has not received much attention. However, such deficiencies may impact patient's quality of life substantially.

Methods: In this monocentric longitudinal trial, we examined hormonal levels of TSH, T3, T4, fT3, fT4, FSH, LH, testosterone, estradiol and prolactin in patients with malignant high grade gliomas before the start of radiochemotherapy (RCT), at the end of RCT and then every three months for newly diagnosed patients and every six months in patients diagnosed more than two years before study inclusion. Growth hormone was not measured in this trial.

Results: 436 patients (198 female, 238 male) with high-grade gliomas, aged 19–83 years (median 50 years), were included in this study. Low levels of thyroid hormones were observed in around 10% of patients within the first six months of follow up and increasingly after 36 months. Half of premenopausal women at study entry developed premature menopause, 35% showed hyperprolactinemia. Low testosterone levels were measured in 37% of men aged less than 50 years and in 35/63 (55%) of men aged 50 years or older.

Discussion: The results of this study show that a significant percentage of patients with malignant gliomas develop hormonal deficiencies mandating regular clinical follow up, state of the art counseling and if clinically necessary substitution therapy.

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For several decades, radiation therapy (RT) has been a mainstay of treatment for malignant gliomas. By inducing DNA strand breaks, the growth of tumor cells is inhibited; however, also the neuro-endocrine organs of the hypothalamic–pituitary axis potentially suffer damage [1–5]. Moreover, most patients receive drug treatment including alkylating chemotherapy that exerts its action by inducing DNA damage, and many drugs given for symptom management that might also interfere with hormones of the hypothalamic–pituitary axis, such as corticosteroids, antiepileptic drugs, antidepressants and many others. Since patients with malignant gliomas survive for longer periods, focusing on quality of life (QOL) is becoming increasingly important. The impact of RT on the function of the neuroendocrine organs depends on the delivered biologically active radiation dose, e.g. not only on the total radiation dose, but also on the fraction size and the interval time between fractions [6–9].

For most patients treated for supratentorial malignant glioma, radiation fields might at least partly include the hypothalamus and/or the pituitary gland and, therefore, potentially induce a complex pattern of neuroendocrine dysfunctions during the follow up period.

Deficiencies of the anterior pituitary hormones, mainly of growth hormone (GH), have been reported in children after prophylactic cranial irradiation for leukemia, after total body irradiation – which both use lower radiation doses than those used for

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https://doi.org/10.1016/j.radonc.2018.10.014
0167-8140/

glioma treatment – as well as after irradiation for the treatment of craniopharyngiomas or in patients with pituitary tumors [10–12]. Littley and Darzy showed that in children, growth hormone (GH) deficiency is the first emerging hormonal deficit, with a 50% probability of reaching a decline to 50% secretion 2.5 years after radiation, followed by adrenocorticotropic hormone (ACTH), luteinizing hormone (LH) and follicle stimulating hormone (FSH) reaching a similar 50% decline 3.5 years after RT, whereas for thyroid stimulating hormone (TSH) a near 30% secretion level decline is reached with 50% probability after a follow-up period of ten years [6,7,13,14]. The complex symptoms of hormonal deficiencies caused by the treatment of high grade primary brain tumors, e.g. fatigue, stress-intolerance, generalized weakness, and hypogonadism leading to depression, increased risk of cardiovascular disease and of osteopenia show an insidious onset and great overlap with fatigue and listlessness caused by the underlying glioma. Although the development of hormonal deficiencies in patients with glioma after standard of care (SOC) treatment could be expected, timing and clinical impact of these side effects of treatment have not been determined so far. Regular controls of pituitary hormones and hormones of the respective hormonal glands are not consistently done in most centers caring for patients with gliomas.

Data on adult patients with pituitary deficiencies following therapy for gliomas are limited [4,15,16] but suggesting that the GH axis might be less, whereas thyroidal hormones more sensitive than in children. In a pilot trial on gonadal function in premenopausal women with high-grade gliomas, we found thyroid anomalies in 4/22 patients, mostly compatible with central hypothyroidism. The patients presented with symptoms of hypothyroidism such as fatigue, irritability, concentration deficits, lack of initiative and depression, overlapping with neurocognitive symptoms due to RT and CT-treatment for brain tumors or symptoms due to the tumor infiltration itself.

The objective of this prospective longitudinal study was (i) to record the occurrence of hormonal deficits affecting sexual and thyroid hormones in patients with high-grade gliomas and (ii) to assess the onset and magnitude of symptoms related to these hormonal deficits trying to evaluate their clinical impact in the follow-up of glioma patients.

Patients and methods

We conducted a prospective, single institutional longitudinal trial at the Medical University of Vienna from June 2008 to December 2016. All study participants were treated for primary malignant brain tumors, mostly histologically proven WHO grade III glioma or glioblastoma multiforme (GBM) WHO grade IV. All patients underwent 3D-conformal RT with 2 Gy per fraction given 5 days per week for 6 weeks up to 54 Gy or to 60 Gy with concomitant daily temozolomide (75 mg per square meter of body-surface area per day, from the first to the last day of radiotherapy), followed by six cycles of adjuvant temozolomide (150 to 200 mg per square meter for 5 days during each 28-day cycle) [17,18]. Image acquisition, treatment planning and RT were performed according to routinely used protocols for brain tumor patients at our department of RT. EFFICAST® was used as immobilization device for the planning computer tomography (CT) and during treatment. Post-operative treatment planning CT and MR were obtained with intravenous contrast medium using a multislice CT scanner and a 3-Tesla-MR with slice thickness of 2 mm. The T1-weighted and flair MR study sets were chosen for co-registration with the planning CT scan for structure delineation using BrainLab IPlan 4.1.1. The RT target was defined as postoperative residual tumor and cavity plus an isotropic margin of 2 cm [19]. The treatment planning was performed on Oncentra Masterplan 4.3.

Depending on the localization of the PTV (planning target volume) between three and five fields were applied to guarantee the required target coverage. The RT treatment planning was performed following the ICRU 50/62 recommendations for 3D-conformal RT [20,21]. Electronic portal imaging devices and on-board cone beam CTs were used during the first week of RT daily and followed by once weekly in order to verify the patients' position.

Pituitary, thyroid and gonadal hormones (TSH, T3, T4, fT3, fT4, FSH, LH, testosterone, estradiol and prolactin) were measured before the start of radiochemotherapy (RCT), in the fifth or sixth week of concomitant treatment and then every three months for newly diagnosed patients and every six months in patients diagnosed more than two years before study inclusion.

As the patients' collective consists of a group of patients with a still incurable, stigmatizing illness, we intended to minimize blood sampling by relating visit times to regular scheduled control visits, and keeping the patient expenditure of time and volume of drawn blood to a minimum by avoiding hormonal stimulation tests. Blood for sexual hormones was not as consistently collected as blood for thyroid hormones due to logistical reasons.

The study protocol was approved by the local ethics committee (EK 122/2008). All patients gave written informed consent.

Clinical assessment of hypothyroidism consisted of examining the skin and the hair of the patient for dryness, evaluating skin temperature of the fingers, monitoring weight, pulse, asking about fatigue and feeling cold.

Clinical assessment of hypogonadism consisted in females about asking on changes in the menstrual cycle and about their quality of life as women. Men were asked by a male physician if they wished to talk about their sexual issues.

Biochemical measurements

Serum concentrations of all hormones were measured at certified laboratories of the Department of Laboratory Medicine, Medical University of Vienna.

Although GH deficiency is usually the first and often the only manifestation of hypothalamic–pituitary damage in children and although the symptoms of GH deficiency show considerable overlap with the symptoms of fatigue and listlessness in glioma survivors, we did not measure GH levels in this study. Due to the pulsatile nature of GH secretion, reliable basal GH measurements require blood sampling in the early morning after an overnight fast and corrections for age, sex and body mass index [21], which would have caused too much logistical constraints and was therefore not feasible within this study.

We arbitrarily chose 50 years of age for both sexes, to describe sexual hormone levels between pre- and postmenopausal women and between younger and older men.

Statistical analyses

Descriptive statistics (median and standard deviation, as well as absolute and relative frequencies) were used to describe the development of hormone levels over time, after diagnosis and treatment of a malignant glioma. Patients had one and up to 32 recordings of hormone levels during follow-up, in median four.

The reference values of the institutional laboratory are used to calculate the proportion of patients whose hormone levels are outside the normal range. LRL and URL are the lower and upper limit of the reference-range. The limits are regarded as still belonging to the reference-range.

For each patient, the individual date of surgery is defined as time 0. The time point of each measurement is calculated as the time difference between the date of the measurement and the date

of first diagnostic surgery. The age of a patient is calculated for each measurement as the time difference of the date of measurement and the date of birth. The trajectories of median hormone levels with time are shown by boxplots. The lower and upper boundaries of the reference range are shown as horizontal lines.

Results

Patients

A total of 436 patients (198 female, 238 male) with supratentorial high-grade gliomas, aged 19 to 83 years (median 50 years), were included in this study. Baseline characteristics are shown in Table 1. 280 patients were diagnosed with glioblastoma (232 of them newly diagnosed), 122 patients with anaplastic astrocytoma, 34 patients with oligodendroglioma WHO grade III. At baseline, the WHO performance status of all patients was at least 2 or less, as required by our institution for starting treatment. Nearly all patients suffered one or more relapses during follow up. The first line treatment was uniform in all patients, including radiation with 54 for WHO grade III glioma or 60 Gy for GBM, concomitant and adjuvant chemotherapy with temozolomide.

Table 1
Patient- and disease specific characteristics (N = 436).

Patient's characteristics	
Age in median (range)	52 (19–83)
	n (%)
Sex	
Female	198 (45.4%)
Male	238 (54.6%)
Tumor histology	
GBM	280 (64.2%)
Anaplastic astrocytoma	122 (28.0%)
Anaplastic oligodendroglioma	34 (7.8%)
Newly diagnosed GBM	232 (53.2%)
GBM during follow up	58 (13.3%)
Other high grade gliomas during follow up	146 (33.5%)
Neurosurgical procedure	
Biopsy	137 (31.3%)
Partial resection	122 (27.8%)
Gross total resection	177 (40.4%)
WHO performance status	
0	121 (27%)
1	219 (50%)
2	96 (23%)

Thyroid hormones

The median values of measured thyroid hormones at the time points baseline, 3 months, 6 months, 12 months, second, third and fourth year of follow up are shown in Table 2.

Normal or decreased TSH levels with low T3, T4, fT3 and/or fT4 levels were observed already at baseline, but with a higher incidence at three months, affecting both sexes mainly after the age of 50 years. The number of patients with secondary hypothyroidism defined as low or normal TSH with simultaneous decreased thyroid hormones was up 98 patients during the period of acute "nonthyroidal illness" (>35%), decreased at 6 months and to 42 patients (17%) at one year, and remained higher than 10% of patients in later measurements. Evidence of primary hypothyroidism was limited to a cumulative number of 11 patients, compatible with the number of affected patients in the general population.

Fig. 1 shows the variations in time of the serum levels of TSH during 4 years of follow up compatible with a nonthyroidal illness syndrome during and shortly after radiochemotherapy (RCT), which is followed by a recovery period and then subtle decline.

In 57/171 (33%) patients with at least three blood samples with decreasing levels of circulating T3 or T4 (33%) during follow up were measured. Overt hypothyroidism with significant clinical symptoms requiring replacement therapy was noted in nine women and eleven men (7.5%), all of them reporting a significant symptomatic improvement of fatigue after initiation of a replacement therapy. Although the number of patients is very low, clinical symptoms of hypothyroidism seem to be more apparent in patients with lowered T4 levels, than with isolated lowered fT4 levels. Of note, none of the affected patients was treated concomitantly with low molecular weight heparin, which could raise the levels of fT4. Hyperthyroidism was observed in three patients, who were referred to the endocrinologists for further management.

Sexual hormones

Gonadotropin and sexual hormone levels were not consistently studied in all patients and therefore, the numbers of patients analyzed are lower than for thyroid hormones and unfortunately very low at baseline. Gonadotropin deficiency after radiation therapy may start with reduced peak secretion after stimulation tests and progress insidiously to decreased levels of circulating sex hormones in both sexes. Sexual hormones of female and male subjects, separated by an age cut off of 50 years are shown in Tables 3 to 6).

Female subjects

40/46 women (87%) aged less than 50 years reported variable periods of amenorrhea or oligomenorrhea, lasting three to up to fourteen months. Twenty-four of them developed increased FSH or LH levels (52%), with low levels of estradiol and progesterone, compatible with an early onset of menopause (Fig. 2). Prolactin levels were increased in 16/46 women (35%) aged less than 50 years and in 13/40 women (32.5%) aged 50 years or older. The patterns of elevated prolactin levels were different between younger and older women: whereas elevated prolactin developed slowly after eighteen months in premenopausal women, older women showed an earlier peak within the first year and then a later peak in the third year of follow up. In ten premenopausal women, high prolactin levels were associated with prolonged amenorrhea. Most women aged 50 years or older (33/40; 82%) showed the expected postmenopausal hormone pattern with elevated gonadotropins and very low estradiol and progesterone levels. Seven women aged 50 years or more showed a premenopausal hormone pattern and did not progress to menopause during the follow up period.

Male subjects

Serum levels of testosterone were decreased in 20/63 (31%) men aged less than 50 years and in 17/31 (55%) of men aged 50 years or older (Figs. 3 and 4, respectively). LH and FSH were within the normal range in 49/63 (77%) men younger than 50 years and in 23/31 (74%) men aged 50 and older. Only few men showed increased values of FSH or LH (4 men younger than 50 years and 4 men aged 50 years or older, 7% of all men) as compatible with a central origin of this anomaly. Of note, lowered testosterone values were already observed in 34% of men younger than 50 years and in up to 50% of men aged 50 years or older within the first 6 months after treatment start. However, there were signs of recovery of testosterone synthesis later in follow up. Prolactin levels were elevated in forty men.

Table 2
Thyroid hormones in glioma patients.

Hormone (normal range)	Baseline ± 3 weeks	3 months (4–13 weeks)	6 months (14 weeks–8 mo)	12 months (9–15 mo)	24 months (16–24 mo)	36 months (25–36 mo)	>37 months
TSH (0.44–3.77 μU/m)							
n	272	185	336	244	148	123	202
median (SD)	1.15 (1.90)	1.29 (1.43)	1.46 (2.14)	1.49 (1.25)	1.53 (0.95)	1.51 (1.2)	1.74 (1.16)
n pat < LNL (%)	57 (21%)	31 (16.8%)	38 (11.3%)	25 (10.2%)	2 (1.4%)	7 (5.7%)	22 (10.9%)
fT4 (0.76–1.66 ng/dl)							
n	200	157	302	215	130	106	173
median (SD)	1.24 (4.94)	1.19 (0.28)	1.2 (0.28)	1.22 (0.23)	1.14 (0.26)	1.15 (0.22)	1.15 (0.26)
n pat < LNL (%)	4 (2%)	1 (0.6%)	2 (0.7%)	1 (0.5%)	1 (0.8%)	0 (0%)	6 (3.5%)
fT3 (2.15–4.12 pg/ml)							
n	77	141	268	192	106	92	150
median (SD)	2.55 (0.68)	2.69 (0.64)	3.06 (0.68)	2.99 (0.59)	2.88 (0.47)	2.85 (9.94)	2.92 (0.51)
n pat < LNL (%)	21 (27.3%)	29 (20.6%)	28 (10.4%)	19 (9.8%)	5 (4.7%)	11 (12%)	11 (7.3%)
T4 (58–124 ng/ml)							
n	89	128	243	175	91	85	132
median (SD)	67 (19.68)	71 (18.94)	74 (18.59)	74 (15.75)	73 (17.12)	69 (19.65)	70 (17.65)
n pat < LNL (%)	23 (25.8%)	27 (21.1%)	41 (16.9%)	18 (10.3%)	15 (16.5%)	20 (23.5%)	23 (17%)
T3 (0.8–1.8 mU/ml)							
n	85	129	239	173	89	85	130
median (SD)	0.79 (0.3)	0.93 (0.92)	1.02 (0.29)	0.99 (0.23)	1.0 (0.37)	0.98 (2.18)	1.0 (0.26)
n pat < LNL (%)	45 (52.9%)	41 (31.8%)	50 (20.9%)	33 (19.1%)	14 (15.7%)	20 (23.5%)	33 (25%)
Secondary hypothyroidism							
Female <50 years (n = 47)	4	10	7	9	7	9	11
Female >50 years (n = 61)	19	30	17	13	6	6	4
Male <50 years (n = 72)	10	17	13	10	5	4	5
Male >50 years (n = 91)	22	41	19	10	8	7	5

n: number of patients with blood samples; n pat < LNL: number of patients with hormone levels lower than the lower normal institutional level.

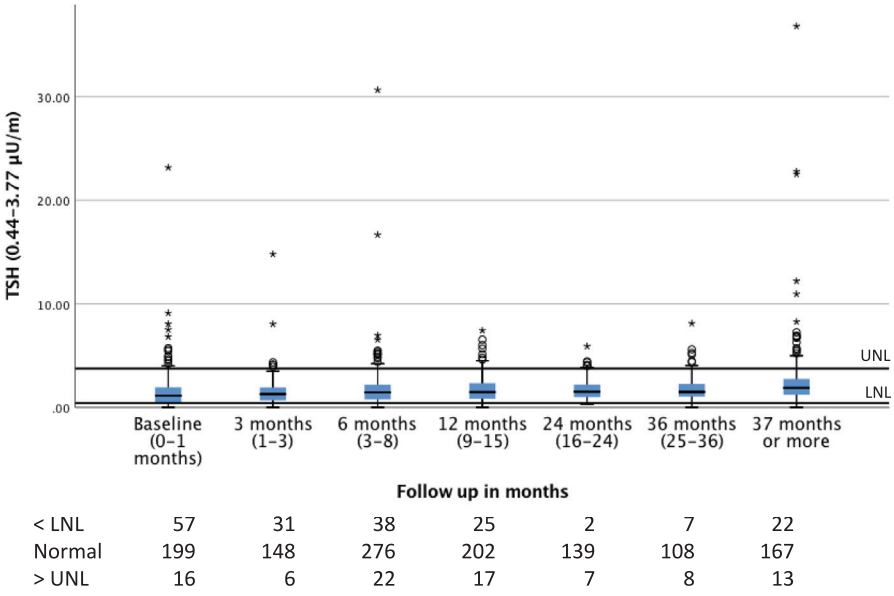


Fig. 1. Time course of median levels of TSH in all patients. Normal values: 0.44–3.77 μU/m.

Discussion

Deficiencies in hormones of the hypothalamic–pituitary axis and the downstream hormonal glands are expected side effects after the standard treatment of malignant gliomas consisting in radiation and chemotherapy. The reason is that the majority of gliomas are located within the temporal, parietal or frontal lobe and due to the CTV margins one has to expect large irradiated volumes and consequently quite a considerable proportion of the prescribed dose to parts of the hypothalamic–pituitary axis. Individual hormone deficiencies can develop after a dose as low as 10 Gy [22]. This effect might be enhanced by cytotoxic therapies and even more by new biological drugs [23] and drugs used for supportive care, e.g. corticosteroids.

In conclusion, all the recommended dose constraints which should be fulfilled to maintain the pituitary gland function should be reevaluated in context of the patients' age and modern anticancer treatments.

Here we show that low blood levels of thyroid and sexual hormones occur in a significant proportion of patients within the first

Table 3
Sexual hormones in female glioma patients younger than 50 years.

Hormone (normal range)	Baseline ± 3 weeks	3 months (4–13 weeks)	6 months (14 weeks - 8 mo)	12 months (9–15 mo)	24 months (16–24 mo)	36 months (25–36 mo)	>37 months
Prolactin (4.8–23.3 ng/ml)							
n	5	15	49	32	36	27	31
median (SD)	9.4 (9.86)	9.6 (5.15)	10.1 (6.05)	11.5 (5.93)	16.65 (9.67)	25 (18.96)	16.4 (19.9)
n pat > UNL (%)	1 (20%)	1 (2%)	1 (1.3%)	1 (3.1%)	8 (22.2%)	15 (55.6%)	8 (26%)
FSH (1.7–21.5 mu/ml)							
n	5	14	49	34	36	24	29
median (SD)	2.8 (1.8)	3.45 (30)	7.2 (43.75)	11.65 (37.69)	12.65 (26.97)	26.75 (21.28)	10 (27.7)
n pat > UNL (%)	0 (0%)	1 (7.1%)	16 (32.7%)	12 (35.3%)	15 (41.7%)	13 (54.2%)	7 (24%)
LH (1–95.6 mU/ml)							
n	5	14	49	33	36	24	29
median (SD)	3.9 (3.71)	3.2 (15.58)	5.7 (20.40)	8.5 (12.49)	7.75 (10.91)	8.05 (10.41)	4.6 (18.5)
n pat > UNL (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Estrogen (12.5–498 pg/ml)							
n	5	14	47	30	32	22	28
median (SD)	23 (18.04)	38.5 (161.01)	28 (79.52)	38.5 (98.09)	36 (145.90)	28 (67.88)	38.5 (135)
n pat < LNL (%)	1 (20%)	3 (21.4%)	10 (21.3%)	9 (30%)	11 (34.4%)	10 (27%)	9 (32%)
Progesterone (0.2–27 ng/ml)							
n	5	14	47	32	34	20	27
median (SD)	0.67 (0.38)	0.11 (5.92)	0.28 (3.79)	0.16 (7.33)	0.19 (11.61)	0.31 (10.13)	0.36 (7.7)
n pat < LNL (%)	1 (20%)	7 (50%)	19 (40.4%)	18 (56.3%)	17 (50%)	9 (45%)	8 (30%)

n: number of patients with blood samples; n pat < LNL: number of patients with hormone levels lower than the lower normal institutional level; n pat > UNL: number of patients with hormone levels above the upper normal institutional level.

Table 4
Sexual hormones in female glioma patients older than 50 years.

Hormone (normal range)	Baseline ± 3 weeks	3 months (4–13 weeks)	6 months (14 weeks–8 mo)	12 months (9–15 mo)	24 months (16–24 mo)	36 months (25–36 mo)	>37 months
Prolactin (4.8–23.3 ng/ml)							
n	9	32	44	29	10	6	19
median (SD)	12.7 (5.18)	12.8 (7.45)	11.85 (9.90)	8.9 (7.76)	13 (4.19)	17.55 (5.98)	12.8 (8.93)
n pat > UNL (%)	1 (11.1%)	6 (18.8%)	3 (6.8%)	3 (10.3%)	0 (0%)	1 (4.3%)	8 (42.1%)
FSH (25.8–134.8 mu/ml)							
n	9	32	44	29	10	6	20
median (SD)	85.2 (27.82)	72.2 (30.26)	76.25 (37.22)	69.8 (28.15)	100.85 (30.41)	49.5 (46.07)	57.4 (42.27)
n pat > UNL (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
LH (7.7–58.5 mU/ml)							
n	9	32	44	29	10	6	20
median (SD)	28 (14.97)	23.35 (15.85)	27.95 (17.53)	29.1 (13.12)	38.2 (16.28)	23.4 (13.92)	21.1 (17.49)
n pat > UNL (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Estrogen (0–54.7 pg/ml)							
n	8	32	45	28	9	6	16
median (SD)	5 (8.37)	0.0 (11.42)	0.0 (9.32)	0.0 (6.3)	0.0 (0.0)	0.0 (6.71)	0.0 (6.26)
n pat < LNL (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Progesterone (0.1–0.8 ng/ml)							
n	7	27	44	27	9	6	17
median (SD)	0.0 (0.08)	0.1 (2.69)	0.0 (0.12)	0.0 (0.12)	0.11 (0.12)	0.08 (0.12)	0.0 (0.16)
n pat < LNL (%)	5 (71.4%)	13 (48.1%)	26 (59.1%)	16 (59.3%)	4 (44.4%)	3 (50%)	11 (64.7%)

n: number of patients with blood samples; n pat < LNL: number of patients with hormone levels lower than the lower normal institutional level; n pat > UNL: number of patients with hormone levels above the upper normal institutional level.

months after initiation of therapy, compatible with a pattern of acute nonthyroidal illness. Later in follow up, we observed decreased thyroid hormones in about 20% of patients and decreased levels of sexual hormones in even more patients.

Acute nonthyroidal illness might be a coping mechanism of the body that contributes to the increased fatigue and weakness reported by many patients during the last weeks of RT and during the following months. This discomfort is mostly interpreted as acute toxicity of RT and/or as side effect of dexamethasone used for symptomatic treatment of vasogenic edema associated with the acute radiation toxicity combined to the toxicity of the concomitant and adjuvant administration of alkylating agents. It is plausible that hormonal deficiencies, especially of anabolic hormones, and lack of sexual functioning might contribute to an acute illness syndrome in this period, similar to unpredictable levels of central and serum levels of hormones in trauma and sepsis [24]. To date, there is no approved therapy for fatigue and weakness. Most interventions using modafinil, methylphenidate or other drugs intended to alleviate fatigue did not show convincing results [25–29]. It appears worthwhile to investigate, if patients suffering from fatigue and weakness and showing decreased levels of thyroid hormones and sexual hormones might benefit from a hormonal substitution.

Indeed, endocrine dysfunctions of the hypothalamic–pituitary axis might develop slowly over years as described by Littley and Darzy for pediatric patients [6–8,13]. In childhood cancer survivors, hormonal deficits develop in 6% [10] to 23% in 88 children after

Table 5
Sexual hormones in male glioma patients younger than 50 years.

Hormone (normal range)	Baseline ± 3 weeks	3 months (4–13 weeks)	6 months (14 weeks–8 mo)	12 months (9–15 mo)	24 months (16–24 mo)	36 months (25–36 mo)	>37 months
Prolactin (4–15.2 ng/ml)							
n	14	22	61	25	18	12	18
median (SD)	9.6 (12.25)	10.05 (10.18)	10.4 (4.35)	16.1 (7.34)	11.6 (9.1)	9.95 (2.73)	9.0 (10.2)
n pat > UNL (%)	2 (14.3%)	5 (22.7%)	11 (18%)	14 (56%)	4 (22.2%)	1 (8.3%)	2 (11%)
FSH (1.5–12.4 mu/ml)							
n	15	21	59	24	20	14	17
median (SD)	4.7 (3.03)	5.2 (4.02)	9.9 (11.98)	8.95 (6.84)	5.65 (5.12)	6.95 (5.12)	7.3 (6.1)
n pat > UNL (%)	1 (6.7%)	2 (9.5%)	27 (45.8%)	10 (41.7%)	4 (20%)	3 (21.4%	4 (23%)
LH (2.2–6.9 mU/ml)							
n	15	21	59	24	20	14	17
median (SD)	4 (2.38)	4.4 (2.73)	4.9 (2.71)	5.7 (2.42)	4.6 (2.16)	5.15 (1.74)	5 (2.52)
n pat > UNL (%)	2 (13.3%)	3 (14.3%)	15 (25.4%)	9 (37.5%)	4 (20%)	2 (14.3%)	5 (29%)
Testosterone (2.5–8.4 ng/ml)							
n	16	23	63	25	19	14	16
median (SD)	1.71 (2.26)	3.25 (2.83)	3.2 (1.89)	2.65 (1.8)	4.23 (2.13)	3.6 (3.97)	5.04 (2.12)
n pat < LNL (%)	9 (56.3%)	9 (39.1%)	21 (33.3%)	10 (40%)	5 (26.3%)	4 (28.6%)	2 (12.5%)

n: number of patients with blood samples; n pat < LNL: number of patients with hormone levels lower than the lower normal institutional level; n pat > UNL: number of patients with hormone levels above the upper normal institutional level.

Table 6
Sexual hormones in male glioma patients older than 50 years.

Hormone (normal range)	Baseline ± 3 weeks	3 months (4–13 weeks)	6 months (14 weeks–8 mo)	12 months (9–15 mo)	24 months (16–24 mo)	36 months (25–36 mo)	>37 months
Prolactin (4–15.2 ng/ml)							
n	15	30	41	35	14	15	16
median (SD)	9.9 (2.52)	12.45 (6.28)	10.3 (6.72)	10.8 (6.4)	9.3 (3.0)	9.9 (4.14)	11.3 (19.64)
n pat > UNL (%)	2 (6.7%)	11 (36.7%)	9 (22%)	7 (20%)	0 (0%)	4 (26.7%)	7 (43.8%)
FSH (1.5–12.4 mu/ml)							
N	14	31	42	36	14	14	17
median (SD)	7.1 (14.1)	6.7 (3.64)	10.45 (6.61)	9.1 (8.87)	7.1 (1.18)	6.15 (6.1)	6.2 (6.85)
n pat > UNL (%)	3 (21.4%)	5 (16.1%)	18 (42.9%)	11 (30.6%)	0 (0%)	2 (14.3%)	3 (17.6%)
LH (2.2–6.9 mU/ml)							
n	14	31	42	36	14	14	17
median (SD)	5.65 (7.0)	4.4 (1.69)	5.15 (2.71)	5.5 (2.42)	4.85 (1.66)	4.05 (2.36)	4.2 (2.47)
n pat > UNL (%)	1 (7.1%)	1 (3.2%)	10 (23.8%)	7 (19.4%)	2 (14.3%)	1 (7.1%)	4 (23.5)
Testosterone (1.9–7.4 ng/ml)							
n	11	30	42	37	14	12	18
median (SD)	1.55 (1.74)	1.65 (1.97)	2.25 (1.88)	2.47 (1.83)	3.41 (1.87)	2.31 (1.59)	2.0 (1.97)
n pat < LNL (%)	7 (63.6%)	18 (60%)	18 (42.9%)	13 (35.1%)	3 (21.4%)	4 (33.3%)	7 (39%)

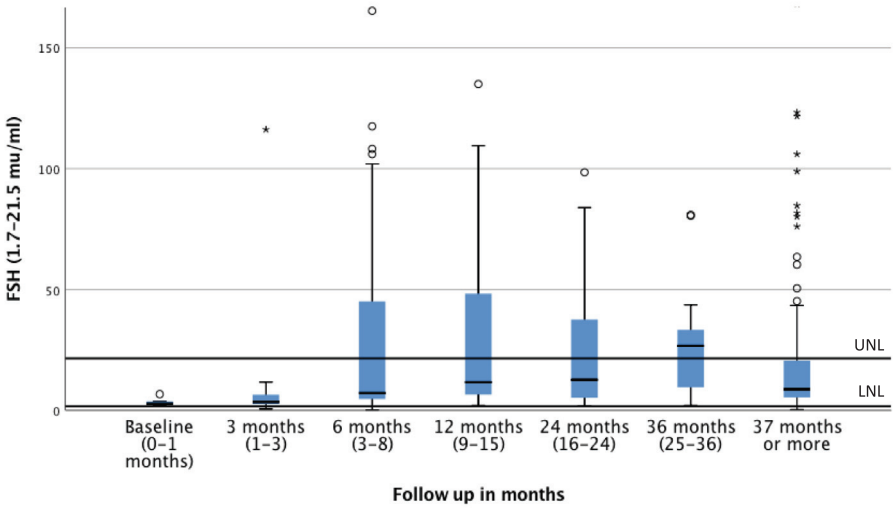
n: number of patients with blood samples; n pat < LNL: number of patients with hormone levels lower than the lower normal institutional level; n pat > UNL: number of patients with hormone levels above the upper normal institutional level.

embryonal brain tumors [14,30] 42% in children after Hodgkińs disease [31] and 46% in children after primary brain tumors [32,33]. Data on adult patients after focal RT to the brain with the treatment doses of 54 to 60 Gy are scarce [2,32,34]. However, there are some data from patients with mainly low grade glioma patients followed for more than three years which show pituitary deficits, mainly of growth hormone [1–3,5]. The incidence of hypothyroidism and deficits in sexual hormones within six months after treatment start has not yet been reported and a potential benefit of hormonal replacement therapies have not yet been studied, as most previous studies started their observation period in the second year after therapy or later. Our follow up data show that with prolonged survival periods, hormonal deficiencies occur in adult glioma survivors and will require adequate management in the future.

Thyroid hormones

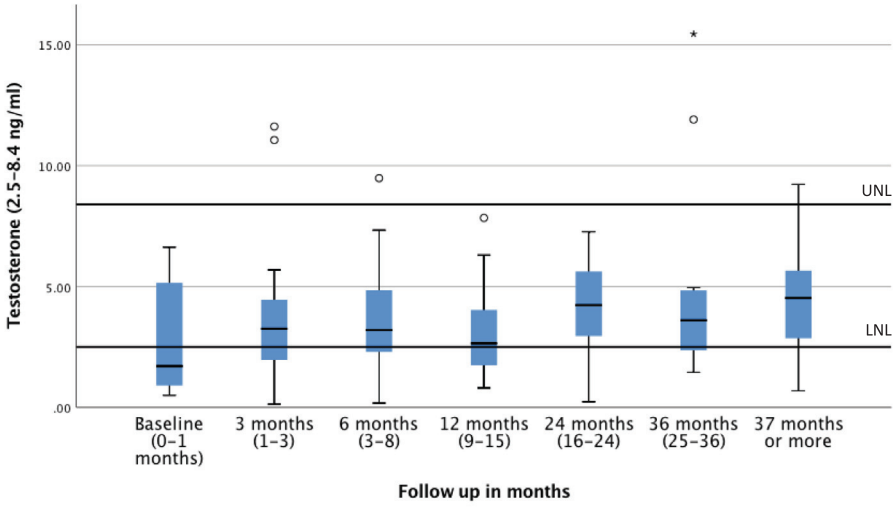
TSH secretion is thought to be less vulnerable than the other hormones of the hypothalamic pituitary axis as radiation damage develops late. However, therapy associated damage might lead to inconsistent TSH levels, making TSH into an inadequate parameter for estimating intactness of TSH secretion after irradiation of the brain. To quantify potential therapy induced damage, measuring the blood levels of the free circulating hormones thyroxine (fT4) and triiodothyronine (fT3) might provide more adequate information, since total T4 and T3 concentrations depend on the concentration of thyroxine binding globulin (TBG), which for instance, is lowered when patients are treated with steroids.

Our results showed that up to a third of patients feature decreased levels of thyroid hormones at repeated measurements. Previous investigations provided evidence that radiation-induced hypopituitarism is an insidiously starting, but irreversibly progressing degeneration of the endocrine tissue that leads to overt hypothyroidism only after more than ten years [7]. Our results, however, show that in patients treated for high-grade gliomas, there are at least two phases of disturbed pituitary function; an early, reversible phase of acute, nonthyroidal illness and the second phase with central hypothyroidism that might develop earlier than after ten years, possibly due to the intensity of combined radiochemotherapy with alkylating agents.



< LNL	0	2	2	0	0	0	1
Normal	5	11	31	22	21	11	21
> UNL	0	1	16	12	15	13	7

Fig. 2. Time course of median levels of FSH in women younger than 50 years. Normal values: 1.7–21.5 mu/ml.



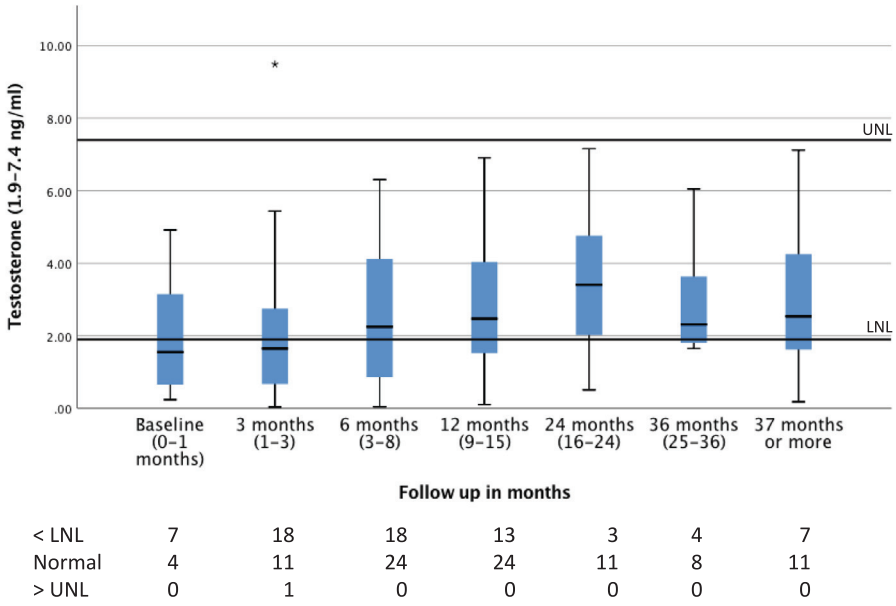
< LNL	9	9	21	10	5	4	2
Normal	7	12	41	15	14	8	13
> UNL	0	2	1	0	0	2	1

Fig. 3. Time course of median levels of testosterone in men younger than 50 years. Normal values: 2.5–8.4 ng/ml.

One of the principal targets of thyroid hormones in regulating energy expenditure is skeletal muscle as reflected by the frequency of pathognomonic myopathic symptoms in patients with thyroid dysfunction [34]. Normal muscle homeostasis requires binding of T3 to the thyroid hormone nuclear receptor in myocytes. Alterations in thyroid function may result in important changes of body composition as skeletal muscle makes up to 30–40% of body mass and as maintenance of the muscle mass and contractility are directly operated by thyroid hormones. Several authors have reported impairments of muscular strength in patients with newly diagnosed GBM, which was already evident at time of diagnosis and of high prognostic value for survival [35–38]. The loss of muscle strength involved particularly the thigh musculature which is needed for standing up from a sitting position, an essential skill for personal independence and activities of daily living. Therefore, careful monitoring and maintaining normal thyroid hormone levels might contribute to improve patient's QOL after glioma treatment.

Sex hormones

RT and CT with alkylating agents, the standard treatments of malignant gliomas, profoundly impact on sexual functioning in adult glioma patients. Gonadotropin deficiency after radiation therapy starts with a reduced peak secretion after stimulation tests and progresses insidiously to decreased levels of circulating sex



< LNL	7	18	18	13	3	4	7
Normal	4	11	24	24	11	8	11
> UNL	0	1	0	0	0	0	0

Fig. 4. Time course of median levels of testosterone in men older than 50 years. Normal values: 1.9–7.4 ng/ml.

hormones in both sexes. Despite thorough information and written informed consent to the treatment prior to the initiation of therapy, many patients are unaware of the sequelae with regard to sexual functioning a few weeks or months later. This may be attributable to the exceptional circumstances when confronted with the diagnosis of a life-threatening tumor with still poor prognosis.

However, as the prognosis for brain tumor patients has improved during the last decade, QOL and also fertility issues become more important. Fertility issues are very delicate to address and require medical and legal knowledge as well as much empathy to enable trustful exchange between physician and patients [39,40]. Before treatment planning, patients have to be actively interviewed about their wish of having children in the future and to get state of the art counseling on fertility issues as well as psycho-oncological support. Of note, the perception of these issues is fundamentally different for the patient as for the drug-prescribing oncologist. Whereas the physician may primarily be aware of preventing pregnancies, patients may perceive this issue as intrusion in their intimacy and the declining or practically ended fertility as a mutilation of their persona.

Aside from fertility issues, the profound alteration in sex hormones caused by a malignant glioma and its treatment were apparent in the patients of this study. Postmenopausal women may – at least biochemically – be the less affected group by these issues, all other patients may develop symptoms related to hypogonadism.

The age of menopause in women is highly variable, in median 51 years [41], whereas in men, andropause is awaited one to two decades later [42]. Most premenopausal women experienced amenorrhoic or oligomenorrhoic periods up to 14 months after therapy start, half of premenopausal women progressed to menopause. It is indeed well known that premature menopause is often associated with depressive symptoms, insomnia but also with weight gain, osteoporosis and increased risk of atherosclerosis and cardiac failure [43–45]. A third of the men younger than 50 years and half of older men showed low serum testosterone levels. Decreased serum testosterone levels are associated in men with decreased libido, erectile dysfunction and depressive symptoms [46,47] but also with metabolic symptoms like decreased muscle mass, increased abdominal fat and decreased energy, and with higher rates of hospital readmission and mortality rates in men with cardiac failure [48]. Clearly, hypogonadism needs more attention from physicians caring for patients with malignant gliomas and the respective individual symptoms should be assessed and adequate counseling and symptomatic therapy provided.

Moreover, serum prolactin levels were found to be increased in a significant number of patients, and seems to be related more to hypothalamic than pituitary irradiation [49] since PRL is predominantly negatively regulated via dopamine. Increased prolactin levels are not only associated with parental behavior across all species [50–52], but prolactin has also been found to be a stress biomarker [53,54] elevated in persons developing psychotic behavior, a risk factor for the development of hypertension in postmenopausal women, and to be linked with increased risk of breast cancer [55,56]. These results suggest that increased prolactin levels also could contribute negatively to the QoL of patients and should get more attention in the future.

Limitations of our study are the restricted number of patients and the limited duration and incompleteness of follow up, especially regarding sexual hormones as well as the fact that we did not assess growth hormone levels. We also did not take into account potential influence of concomitant medications, e.g. antiepileptic drugs and corticosteroids. The dosages of these drugs are being kept to a minimum in our center for many years. On the other hand, this study provides evidence that follow up of the hormones of the pituitary axis might detect significant hormonal deficiencies in a not negligible proportion of patients. Taking into account that the majority of gliomas are located in the frontal, temporal and/or parietal lobe (84% of all GBM at our center from 2003 to 2016, 5% occipital, 1% brainstem, rest stem ganglia and bilateral) and the standard target volume concepts (glioma + <15 mm CTV margin in the compartment) result in a significant dose to the pituitary gland of at least 50% of the prescribed dose. Substitution of hormonal deficits might provide clinical benefit and contribute to the QOL of patients treated for gliomas. As measuring thyroid and sex hormone levels is a routine laboratory test and replacement therapy is easily available, we postulate to consider adding assessment of thyroid function and sex hormones twice a year to the control measures for high-grade glioma patients.

Funding

No funding was available for this study.

Conflict of interest

No conflict of interest for Ammon Handisurya, Tamara Rumpold, Carola Caucig-Lütgendorf, Birgit Flechl, Aysegül Ilhan-Mutlu, Karin Dieckmann, Georg Widhalm, Anna Grisold, Adelheid Wöhrer, Johannes Hainfellner, Robin Ristl, Alois Gessl, Marco Hassler.

Matthias Preusser has received research support from Böhringer-Ingelheim, GlaxoSmithKline, Merck Sharp & Dome and Roche and honoraria for lectures, consultation or advisory board participation from Bristol-Myers Squibb, Novartis, Gerson Lehrman Group (GLG), CMC Contrast, GlaxoSmithKline, Mundipharma, Roche, Astra Zeneca and AbbVie.

Christine Marosi has received travel remuneration from Roche.

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