Available online at www.medicinescience.org

ORIGINAL RESEARCH

Medicine Science International Medical Journal

Medicine Science 2019;8(3):549-53

Assessment of pituitary function in patients with nasopharyngeal carcinoma: The effect of radiotherapy

Ozlem Ozkaya Akagunduz[1], Banu Sarer Yurekli[2], Ilgin Yildirim Simsir[2], Mustafa Esassolak[1]

[1]Ege University Faculty of Medicine, Department of Radition Oncology Izmir, Turkey
[2]Ege University Faculty of Medicine, Department of Endocrinology Izmir, Turkey

Received 26 January 2019; Accepted 07 February 2019
Available online 16.04.2019 with doi:10.5455/medscience.2019.08.9032

Copyright © 2019 by authors and Medicine Science Publishing Inc.

Abstract

Radiotherapy (RT) plays a very important role in nasopharyngeal carcinoma (NPC). The pituitary gland can be affected by radiation due to its proximity to the nasopharyngeal cavity. Our aim is to demonstrate the effect of radiotherapy given for NPC on anterior pituitary function with basal pituitary hormones and provocative tests. Patients with NPC that were treated with definitive chemoradioherapy were reviewed retrospectively. Serum ACTH, GH, PRL, FSH, LH, TSH and cortisol, DHEAS, IGF-1, E2, testosterone, fT3, fT4 levels were recorded to evaluate pituitary function. Insulin tolerance test was performed to investigate hypothalamic-pituitary-adrenal axis and GH -IGF-1 axis. Comparison between early tumor stage and advanced tumor stage for pituitary dysfunction was done. The median time interval between the RT and endocrinologic evaluation was 4.0 (1-13) years. ACTH deficiency was found to be most common hormonal problem with a frequency of 73.7%. Of these 71.4% were mild adrenal deficiencies. GH deficiency was seen in 60% of patients. fT3, TSH, GH and IGF-1 levels were significantly lower in patients with advanced tumor stage compared with early tumor stage ($p = 0.033$, $p = 0.022$, $p = 0.043$, $p = 0.022$, respectively). Growth hormone deficiency was found in all of advanced and in 43% of early tumor stage patients ($p = 0.017$). We found higher rates of ACTH and GH deficiencies followed by gonadotropin, corticotropin and thyrotropin deficiency. Basal pituitary hormones will not be sufficient to evaluate anterior pituitary failure. Annual and systematic dynamic tests together with basal anterior pituitary hormones would be needed.

Keywords: Pituitary dysfuntion, radiotherapy, nasopharyngeal carcinoma,radiation induced hypopituitarism

Introduction

Hypothalamic-pituitary axis is affected by radiotherapy (RT) in which RT induced hypopituitarism is a progressive, slow developing process. One or more pituitary hormone deficiencies can affect growth, body composition, sexual function and quality of life. The symptoms regarding hypopituitarism such as fatigue could be attributed to the primary disease itself by the patient and even by the physician [1]. Endocrinological evaluation including pituitary function is not a part of routine assessment of those patients. Besides, evaluation of basal pituitary hormones may not be enough for the assessment of pituitary failure and could lead to inaccurate diagnosis.

RT plays a very important role in head and neck tumors, especially with nasopharyngeal carcinoma (NPC). Concomitantchemotherapy (CT) with RT also improved the survival of NPC patients and has become the standard treatment for locally advanced NPC recently [2]. Development of RT technique, intensity-modulated radiotherapy (IMRT) has been an ideal method for the treatment of NPC, which leads to an improvement of both local control and normal tissue sparing. It was reported that recent RT technique can preserve most organs at risk such as the temporal lobes, parotid glands, cochlea, optic nerves, chiasm and other near structures [3]. However, it cannot effectively preserve all the organs at risk. The pituitary gland inevitably is affected by radiation more or less due to its proximity to the nasopharyngeal cavity. Besides the anatomic position of pituitary gland, the radiation induced hypopituitarism is also dependent on total radiation dose and fraction size [4].

In this study, we investigated the effect of RT given for NPC on anterior pituitary function with basal pituitary hormones and provocative tests.

Material and Methods

Twenty-eight patients with diagnosis of NPC were enrolled for this study. The records of the patients who received RT were investigated. The demographic parameters of the patients and TNM classification- according to 8th Edition of the American Joint Committee on Cancer Staging (AJCC) for NPC were recorded. NPC patients who were treated with definitive chemoradioherapy

***Coresponding Author:** Ozlem Ozkaya Akagunduz, Ege University Faculty of Medicine, Department of Radition Oncology Izmir, Turkey
E-mail: ozakagunduz@gmail.com

(CRT) at our institution between 2006 and 2015 were reviewed retrospectively. Patients with recurrent disease, history of prior RT to the same region, tumor invasion to the pituitary gland, endocrinological deficiency before CRT were excluded.

Total RT dose to the gross tumor volume was 70 Gy with 2 to 2.12 Gy daily fractions, 59 to 61 Gy to high-risk area, and 50 to 54 Gy to low-risk area. The prescription dose is the isodose surface that encompasses 95% of the planning target volume (PTV). The patients received 3 cycles of induction CT with cisplatin (75 mg/m2) and docetaxel (75 mg/m2) followed by cisplatin (75 mg/m2) with RT at 3-week intervals or concomitant cisplatin (40 mg/m2) with RT, weekly.

Endocrinological assessment

Serum levels of basal anterior pituitary and end-organ hormones as ACTH (adrenocorticotropic hormone), GH (growth hormone), PRL (prolactin), FSH (follicle stimulating hormone), LH (luteinising hormone), TSH (thyroid stimulating hormone) and cortisol, DHEAS (dehydroepiandrosterone sulfate), IGF-1 (insulin like growth factor-1), E2 (estradiol), testosterone, fT3 (free triiodothyronine), fT4 (free thyroxine), respectively were recorded to evaluate pituitary function. Insulin tolerance test (ITT) was performed to investigate hypothalamic-pituitary-adrenal axis and GH -IGF-1 axis. For ITT, 0.1 u/kg regular insulin was given intravenously and cortisol and GH levels were measured as response to hypoglycemia. ITT was not performed if there is a history of coronary artery disease or epilepsy. Cortisol response to hypoglycemia during ITT was measured in 19 patients; GH response to hypoglycemia was measured in 20 patients.

If peak cortisol response to hypoglycemia was ≥20 µg/dL, adrenal reserve was accepted as sufficient [5). During ITT, if peak GH level was ≥5 µg/L as response to hypoglycemia, it was accepted that there was no GH deficiency [6].

If testosterone levels were between reference range together with normal LH and FSH levels gonadal function was accepted as normal for males. In premenopousal women, regular menstrual cycle with normal E2 levels was accepted as normal gonadal function. In postmenopousal women, if there was normal increase in FSH levels as ≥ 40 mIU/mL, there was no gonadotropin deficiency.

Low fT4 levels together with low or normal TSH levels pointed to central hypothyroidism. We performed also TRH test to support the diagnosis of central hypothyroidism. TRH 200 µg was given intravenously and after that the blood was drawn at 30, 60 and 90 min. If TSH increase was <4 µIU/mL or peak TSH was delayed after 60 min in TRH test central hypothyroidism was diagnosed [7]. IGF-1 and PRL levels were evaluated according to reference ranges regarding age and gender. High PRL levels indicate the disturbance of hypothalamo-pituitary axis regarding dopamine through pituitary infundibulum. If there are low PRL levels, it will be indicated separately.

Statistical analysis

Statistical analysis was performed using SPSS version 18.0. Descriptive data were shown as mean and standart deviation or median and range. Comparison between early tumor stage and advanced tumor stage for pituitary dysfunction was analyzed by using Pearson Chi-square or Fisher exact test. Endocrinological tests were compared between same two groups for numerical values with Independent samples Student's t-test. Statistical significance was determined at $p < 0.05$ (2-tailed).

Results

Median age of patients was 28 (14-46) years during the endocrinological assessment. There were 11 female and 17 male patients. The time interval between the RT and endocrinological evaluation was 4.0 (1-13) years as median (min-max). Tumor has spread from nasopharynx to paranasal sinus, base of skull, cavernous sinus or brain parenchyma in 23% of patients. Twenty- two patients were treated with IMRT. General characteristics of the patients were given in Table 1.

Table 1. Demographical, clinical features and endocrinological hormone values of the patients

Characteristic of patientsn=28	Value
Age at diagnosis - median (range)	28 years (14-46)
Age at evaluation - median (range)	31 years (16-49)
Interval between diagnosis and evaluation- median (range)	4 years (1-13)
Gender	
Female	11 (39%)
Male	17 (61%)
Spread of tumor	
in nasopharynx	7 (25%)
into parapharyngeal space	14 (50%)
into paranasal sinuses/base of skull	5 (18%)
into brain parenchyma	2 (7%)
Stage (tumor)	
T1-2	21 (75%)
T3-4	7 (25%)
Stage grouping	
I	-
II	7 (25%)
III	17 (61%)
IVA	4 (14%)
Radiotherapy	
3D Conformal RT	6 (22%)
IMRT	22 (78%)
Chemotherapy	
Induction cisplatin-dosetaxel and concurrent cisplatin	7 (25%)
Concurrent cisplatin (weekly)	21 (75%)
Endorinological hormones	
*E2 (ng/L) (for only females)	47.00 (19.12-521.47)
fT3 (ng/L)	2.91 (2.43-3.63)
fT4 (ng/dL)	1.07 (0.84-1.40)
TSH (mU/L)	2.99 (0.71-12.20)
GH (µg/L)	0.17 (0.05-5.83)
IGF (µg/L)	181.0 (67.20-298.0)
DHEAS (µg/dL)	188.40 (45.20-321.70)
ACTH (ng/L)	20.20 (9.66-58.40)
Cortisol (µg/dL)	11.09 (6.73-17.03)

IMRT: Intensity Modulated Radiotherapy. E2: estradiol, fT3: free triiodothyronine, fT4: free thyroxine, TSH: thyroid stimulating hormone, GH: growth hormone, IGF: Insulin-like growth factor, DHEAS: Dehydroepiandrosterone sulfate, ACTH: Adrenocorticotropic hormone

* As different testosterone assays were used with different reference ranges median values for testosterone levels were not indicated.

ACTH deficiency was found to be most common hormonal problem with a frequency of 73.7%. Adrenal deficiency was divided into 2 groups according to the cortisol repsonse at ITT: severely deficient (cortisol response <13 µg/dL) and mildly deficient (cortisol response 13-19.9 µg/dL). According to this classificiation, 71.4% of the ACTH deficieny patients had mild adrenal deficiency. GH deficiency was seen in 60% of patients. Hypogonadism was observed in 16.7% of patients. The rate of TSH deficiency was 7.4%. Hyperprolactinemia was observed only in 2 patients (Figure 1).

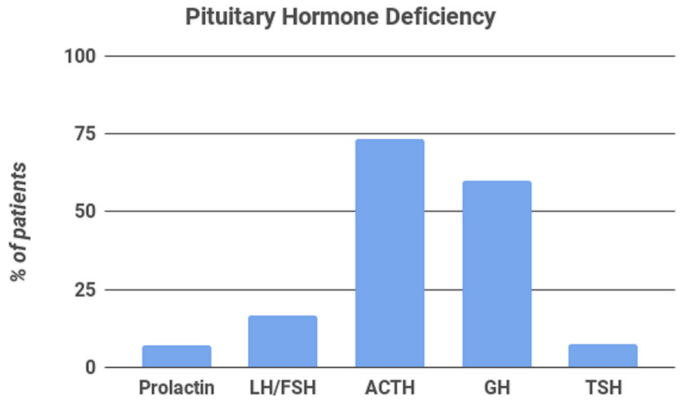

Figure 1. Rates of pituitary deficiency is shown in all patients

LH: Luteinizing Hormone, FSH: Follicle Stimulating Hormone, ACTH: Adrenocorticotropic hormone, GH: growth hormone, TSH: thyroid stimulating hormone

According to status of tumor spread (early vs. advanced tumor stage) fT3, TSH, GH and IGF-1 levels were lower significantly in patients with advanced tumor stage compared to the levels of patients with early tumor stage (p = 0.033, p = 0.022, p = 0.043, p = 0.022, respectively) (Table 2). When pituitary hormone deficiency was evaluated in patients with NPC according to the tumor stage; Growth hormone deficiency was found in 100% of advanced and in 43% of early tumor stage patients (p = 0.017). Hypogonadism was found in %50 of patients with advanced tumor stage and 6% of early tumor stage (p = 0.011). Comparison of patients between early and advanced tumor stage for all pituitary dysfunction was shown in figure 2.

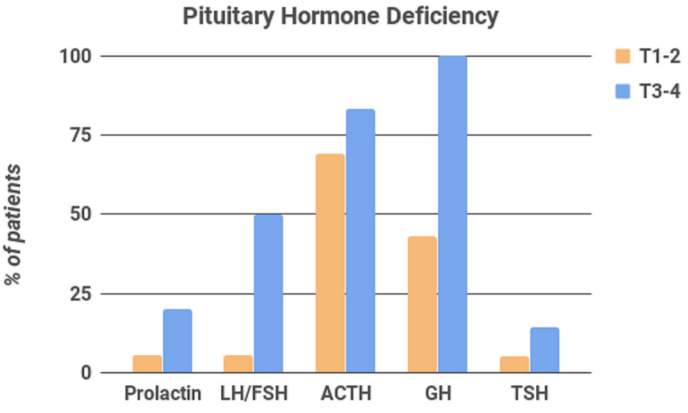

Figure 2. Comparison of patients (as percentage) between early tumor stage and advanced tumor stage for pituitary dysfunction.

Comparision was performed by Pearson Chi-square or Fisher exact test and represented as bar graphs.
Prolactin p= 0.395, LH/FSH p = 0.011, ACTH p = 0.48, GH p = 0.017, TSH p = 0.41
p <0.05 was considered as significant.

Table 2. Comparison between early tumor stage and advanced tumor stage for endocrinological tests (Independent samples Student's t-test)

Endocrine Test (value of mean±SD)	Early tumor stage (T1-T2)	Advanced tumor stage	p value**
*E2 (ng/L, females)	166.5±239.2	50.6±33.6	0.053
fT3 (ng/L)	3.1±0.3	2.6±0.2	0.033
fT4 (ng/dL)	1.1±0.1	1.1±0.2	0.613
TSH (mU/L)	4.2±2.8	1.7±0.9	0.022
GH (µg/L)	0.7±1.6	0.4±0.4	0.043
IGF (µg/L)	229.1±60.9	124.8±49.3	0.022
DHEAS (µg/dL)	200.2±74.3	159.07±97.2	0.173
ACTH (ng/L)	26.2±12.7	22.3±13.7	0.433
Cortisol (µg/dL)	11.8±3.1	10.6±1.8	0.358

* As different testosterone assays were used with different reference ranges median values for testosterone levels were not indicated.
** p<0.05 was considered as significant.
Values were presented as mean ± standard deviation.
E2: estradiol, fT3: free triiodothyronine, fT4: free thyroxine, TSH: thyroid stimulating hormone, GH: growth hormone, IGF: Insulin-like growth factor, DHEAS: Dehydroepiandrosterone sulfate, ACTH: Adrenocorticotropic hormone

Discussion

Hypothalamic-pituitary function shows different radiosensitivity in which clinical studies indicate that GH axis is the most radiosensitive one and gonadotropin, ACTH and TSH axes are affected later in this order [4]. GH axis is frequently affected with the low radiation dose which is less than 40 Gy. All anterior pituitary hormones are usually affected by radiation with dose of greater than 60 Gy. In our study, we figured out that ACTH deficiency was most common pituitary hormone deficency and GH deficiency was the second most common one. High radiation doses are necessary for definitive treatment in NPC, and 70 Gy is the recommended dose for gross tumor [8]. Pituitary gland would be exposed to high radiation doses when the tumor spreads to sphenoid sinus, cavernous sinus and base of skull. In this study, GH deficiency was shown in all NPC patients with advanced tumor stage. ACTH deficiency rate didn't change significantly between NPC patients with early and advanced tumor stages. When pituitary hormone deficiency was compared according to tumor stage, gonadotropin and GH deficiencies were seen at higher rates significantly in advanced tumor stage patients.

Age also can affect the susceptibility of hypothalamic-pituitary axis to radiation damage. In the literature, studies point to the fact that ACTH axis is more vulnerable in adults than children, the opposite is true for the GH axis. However, Darzy [4] indicates that GH deficiency is more common than ACTH deficiency in all age groups. As opposed to this, in our study we found that ACTH deficiency (73.4%) was more common than GH deficiency (60%).

Radiation induced hypopituitarism becomes worse with time most probably due to pituitary atrophy. Littley et al. [9] studied patients who had surgery for pituitary tumor and had been given RT. Before RT, 18% of patients had normal growth hormone secretion, 21% had normal gonadotropin secretion, 57% had normal corticotropin reserve and 80% had normal thyrotropin secretion. All patients developed growth hormone deficiency, 91%, 77% and 42% were gonoadotropin, corticotropin and thyrotropin deficient respectively by five years. Radiation induced hyperprolactinemia

is seen in 44.2% of patients in the cases of Littley et al. In our study hyperprolactinemia was seen in only 2 patients. They indicated that anterior pituitary hormone deficiencies frequently occured in the order of growth hormone, gonadotropin, corticotropin and thyrotropin. But sometimes corticotropin deficiency may occur before the gonadotropin deficiency. In the study of Ipekci et al. [10], GH deficiency was developed in 76.7% patients, ACTH deficiency in 73.3%, thyrotropin deficiency in 26.7% and gonadotropin deficiency in 6.7% of patients. Those findings point to the fact that the sequence of pituitary hormone deficiencies may not pe predicted all the time. In our cases, thyrotropin deficiency was seen in 7.4% of patients.

ITT was found to be most sensitive test to identify radiation induced GH deficiency [11]. We also performed glucagon stimulation test to investigate GH deficiency which increased to 82.4% in rate. But, it is stated that glucagon stimulation test can give false positive results regarding GH deficiency in the literature [12], so in this aspect we preferred to use ITT as main provacative test to evaluate GH reserve. Besides ITT, GHRH (growth hormone releasing hormone) + arginine stimulation test may be used, but it was shown that patient who hadn't shown increase in GH as response to hypoglycemia at ITT may generate discordantly high GH response [13]. In adults, if somatotroph cell mass is not critically reduced, GH release can be compensated by the increase in GHRH secretion. ITT is more predictive to define the need for hormone replacement of GH. Provocative test is certainly needed to evaluate GH deficiency in radiation induced hypopituitarism in which IGF-1 levels are mostly normal as in our study.

Hypothalamo-pituitary-adrenal axis is said to be most radioresistant site in patients given RT for nonpituitary tumors [4]. There was clinically remarkable ACTH deficiency only in 3% of patients who had received radiation dose of 40-50 Gy [14,15]. When radiation dose was given higher than 50 Gy, the rate of ACTH deficiency increased to 27-35%. But, most of the patients developed partial ACTH deficiency so that only few patients needed hydrocortisone replacement. Supporting those findings, most of our patients denied any finding of adrenal insufficency although ACTH deficiency rate was high in our study group with a rate of 73.7%. None of our patients had basal cortisol level <5 µg/dL. When cortisol response of <13 µg/dL to hypoglycemia at ITT was accepted as severe ACTH deficiency, only 28.6% of patients with corticotropin deficiency was severely ACTH deficient. The importance of mild ACTH deficiency detection comes from the recommendation of steroid replacement in stress situations. Toogood et al. [16] indicated that low DHEAS levels may be pointing to the abnormal ACTH secretion but in our study group, DHEAS levels were all in normal reference range.

Hypothalamo-pituitary-thyroid axis is also known as radioresistant. Secondary hypothyroidism has not been documented after prophylactic irradiation with a dose of 18-24 Gy [17,18]. TSH deficiency was seen in rate of 3-6% in nonpituitary brain tumors [19]. We have found that 7.4% of patients had TSH deficiency. Thyroid gland itself can be affected by the radiation, as well. Low fT4 and low-normal TSH levels are diagnostic for TSH deficiency but primary hypothyroidism together with central hypothyroidism could be challenging to diagnose. For this reason, we also performed TRH test to see the TSH response in addition to the basal thyroid function test.

In the literature, a retrospective study by Lam et al. [20] investigated 32 patients with NPC. Out of 14 patients who had possible anterior pituitary hormone deficiency according to basal hormone levels had undergone LHRH (luteinising hormone releasing hormone), ITT and TRH tests. GH deficiency, ACTH deficiency, gonadotropin deficiency and central hypothyroidism were detected in rates of 19%, 6%, 22%, and 13%, respectively. In another study by Bhandare et al. [21] clinical and subclinical hypopituitarism was defined in 14.1% and 33.8% of patients, respectively. Some studies in the literature regarding the effect of RT on pituitary function in NPC patients conducted dynamic tests only in patients with abnormal basal pituitary hormones, so the ratios about RT induced hypopituitarism could be misleading in those cases [20,22]. As in our study, although basal levels of cortisol and IGF-1 levels were all normal, the highest ratio for deficiency was relevant for ACTH and GH axis.

Conclusion

In conclusion, anterior pituitary hormone deficiency is seen due to RT in non pituitary tumors as in NPC. Although higher incidence of GH deficiency and thereafter gonadotropin, corticotropin and thyrotropin deficiency occur in order, we found higher rates of ACTH and GH deficiencies. This sequence may change according to hormonal tests and cut-off values chosen for evaluation. The literature and our findings show that basal pituitary hormones will not be enough to investigate anterior pituitary failure. Annual and systematic dynamic tests together with basal anterior pituitary hormones would be needed in order not to cause underestimation of pituitary failure.

Competing interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Financial Disclosure
The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical approval
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Ozlem Ozkaya Akagunduz ORCID:0000-0002-5438-9969
Banu Sarer Yurekli ORCID:0000-0003-1809-2655
Ilgin Yildirim Simsir ORCID:0000-0002-6801-8499
Mustafa Esassolak ORCID:0000-0001-9937-9505

References

1. Fernandez A, Brada M, Zabuliene L, et al. Radiation-induced hypopituitarism. Endocr Relat Cancer. 2009;16:733–72.
2. Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. J Clin Oncol. 1998;16:1310–7.
3. Su SF, Han F, Zhao C, Chen CY, et al. Longterm outcomes of early-stage nasopharyngeal carcinoma patients treated with intensity-modulated radiotherapy alone. Int J Radiat Oncol Biol Phys. 2012;82:327–33.
4. Darzy KH. Radiation-induced hypopituitarism after cancer therapy: Who, how and when to test. Nat Clin Pract Endocrinol Metab. 2009;5:88–99.
5. Finucane FM, Liew A, Thornton E, et al. Clinical insights into the safety and

utility of the insulin tolerance test (ITT) in the assessment of the hypothalamo-pituitary-adrenal axis. Clin Endocrinol (Oxf). 2008;9(4):603-7.

6. Mark E. Molitch, David R. et al. Evaluation and Treatment of Adult Growth Hormone Deficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab.2011;96:1587–1609.

7. Persani L, Brabant G, Dattani M, et al. European Thyroid Association (ETA) Guidelines on the Diagnosis and Management of Central Hypothyroidism. Eur Thyroid J. 2018;7(5):225-237.

8. Lee AWM, Perez CA, Law CK, et al. Nasopharynx in Principles and practice of radiation oncology. 5th edition. Philadelphia: Lippincott Williams and Wilkin. 2008;820–57.

9. Littley MD, Shalet SM, Beardwell CG et al. Hypopituitarism following external radiotherapy for pituitary tumours in adults. Q J Med. 1989;70:145– 60.

10. Ipekci SH, Cakir M, Kiyici A, et al. Radiotherapy-induced hypopituitarism in nasopharyngeal carcinoma: the tip of an iceberg. Exp Clin Endocrinol Diabetes. 2015;123(7):411-8.

11. Lissett CA, Saleem S, Rahim A, et al. The impact of irradiation on growth hormone responsiveness to provocative agents is stimulus dependent: results in 161 individuals with radiation damage to the somatotropic axis. J Clin Endocrinol Metab.2001;86:663–8.

12. Dichtel LE, Yuen KC, Bredella MA, et al. Overweight/Obese adults with pituitary disorders require lower peak growth hormone cutoff values on glucagon stimulation testing to avoid overdiagnosis of growth hormone deficiency. J Clin Endocrinol Metab. 2014;99:4712.

13. Darzy KH, Aimaretti G, Wieringa Get al. The usefulness of the combined growth hormone (GH)-releasing hormone and arginine stimulation test in the diagnosis of radiation-induced GH deficiency is dependent on the post-irradiation time interval. J Clin Endocrinol Metab.2003;88: 95–102.

14. Constine LS, Woolf PD, Cann D et al. Hypothalamic–pituitary dysfunction after radiation for brain tumors. N Engl J Med.1993;328:87–94.

15. Livesey EA , Hindmarsh PC , Brook CG, et al. Endocrine disorders following treatment of childhood brain tumours. Br J Cancer.1990;61:622–25.

16. Toogood AA. Endocrine consequences of brain irradiation. Growth Horm IGF Res. 2004;14:118–24.

17. Littley MD, Shalet SM, Morgenstern GR, et al. Endocrine and reproductive dysfunction following fractionated total body irradiation in adults. Q J Med. 1991;78:265–74.

18. Ogilvy-Stuart AL, Clark DJ, WallaceWH, et al. Endocrine deficit after fractionated total body irradiation. Arch Dis Child. 1992;67:1107–10.

19. Oberfield SE et al. Thyroid and gonadal function and growth of long-term survivors of medulloblastoma/ PNET. In Late Effects of Treatment for Childhood Cancer. Eds Green DM and D'Angio GJ. 1992;55–62 New York: Wiley–Liss.

20. Lam KSL, Ho JHC, Lee AWM et al. Symptomatic hypothalamic-pituitary dysfunction in nasopharyngeal carcinoma patients following radiation-therapy – a retrospective study. Int J Radiat Oncol Biol Phys. 1987;13:1343–50.

21. Bhandare N, Kennedy L, Malyapa RS et al. Hypopituitarism after radiotherapy for extracranial head and neck cancers. Head Neck. 2008;30:1182–92.

22. Snyers A, Janssens G, Twickler MB et al. Malignant tumors of the nasal cavity and paranasal sinuses: Long-term outcome and morbidity with emphasis on hypothalamic-pituitary deficiency. Int J Radiat Oncol Biol Phys. 2009;73:1343–51.