

A Prospective Study on Hypopituitarism after Radiotherapy in Non Pituitary Brain Tumors

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ABSTRACT

Objective: Pituitary function and hypopituitarism have not been well evaluated in adult patients with non-pituitary brain cancer.

Methods: Thirty-one (31) patients treated with primary or postoperative radiotherapy (RT) for various cancers in the brain region without pre-existing hypothalamic pituitary (HP) disorder from other causes were prospectively evaluated. Serum samples were obtained from the patients to determine levels of growth hormone (GH), thyroid-stimulating hormone (TSH), and free thyroxine (FT4). Serum samples were measured before treatment, 3 and 6 months after completion of radiation therapy (RT). The hypothalamus-pituitary axis (HPA) and dose volume histograms (DVH) of the patients were derived from their computed tomography-based treatment plans.

Results: Clinical hypopituitarism was not observed, but 83% of patients who tested for hypopituitarism demonstrated subclinical hypopituitarism after a median interval of 6 months. Subclinical GH and TSH deficiency were observed in 17 (54%) and 9 (29%) participants, respectively. Significant declines in TSH ($p < 0.021$), FT4 ($p < 0.009$), and T4 ($p < 0.036$) levels after the RT course that can be interpreted as subclinical central hypothyroidism were observed. Adjuvant chemotherapy and surgery did not significantly influence the hypopituitarism ($p = 0.698$, $p = 0.287$, respectively). The doses of radiation to the HPA region ranged from 241 to 5941 cGy (2.4-59.4 Gy). The mean received dose (D_{mean}) and biological effective dose (BED) to the pituitary were 36 and 59.6 Gy, respectively. Subclinical findings of late radiation effects were observed in the HPA.

Conclusion: Radiation-induced hypopituitarism and central hypothyroidism are regarded as primary damage to the pituitary gland. Time after therapy is critical and so with time the incidence of growth hormone deficiency and thyroid stimulating hormone deficiency is likely to significantly increase and to no longer be subclinical. Neuronal cell death and degeneration because of the direct effects of radiation seem to play basic roles.

INTRODUCTION

Despite technical advances, such as the introduction of stereotactic treatment planning systems and new dose delivery techniques (intensity-modulated radiation therapy, cyber knife, three-dimensional, and proton therapy), irradiation to non target organs like the

pituitary gland and HPA during radiation therapy for patients with brain tumors remains inevitable. The pituitary gland is a small gland attached to the base of the brain. It produces a variety of different hormones such as GH, TSH, and so on. In adults, GH deficiency may cause a decrease in energy and physical activity, changes in body composition (increased fat, decreased muscle mass), a tendency toward increased cardiovascular risk factors/diseases, and decreased quality of life.¹ TSH deficiency causes thyroid hormone deficiency; symptoms include weakness, difficulty losing weight, feeling cold, difficulty with memory, and an inability to concentrate. In addition, anemia, high cholesterol levels, and liver problems may occur.^{1,2} Hypopituitarism refers to the loss of pituitary gland

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hormone production and may involve the loss of one, several, or all pituitary hormones. Thus, an evaluation is needed to determine which hormone or hormones are deficient and need to be replaced. Radiation that focuses on the whole or part of the brain can result in the loss of pituitary hormone production over time. In fact, it should be an expected consequence of radiation therapy. However, it may not occur for months or even years after treatment. Thus, regular monitoring of pituitary hormone production is essential. The hypothalamus plays a critical role in the functioning of the HPA, and radiation-induced damage seems to affect both the pituitary and the hypothalamus.³ On the other hand, as an etiologic mechanism, the biological effects come from neuronal cell death and vascular damage.⁴ Radiation damage to the HPA may happen to any or all of its physiologically functional components. Both the pituitary and the hypothalamus may suffer radiation-induced damage, which could lead to hypopituitarism.⁵ It seems that no prospective study has been performed in short intervals after RT to brain tumors. The purpose and our novelty of the current study were to evaluate the HPA function in adult survivors of primary non-pituitary brain tumors and its association with treatment-related factors such as received dose to the organs at risk, age at irradiation, surgery, and adjuvant chemotherapy in patients treated with RT for brain tumors. Moreover, it aimed to achieve the threshold incidence of late effects because of irradiation to HPA, improve the management of these patients, and improve their quality of life after treatment.

PATIENTS AND METHODS

Thirty-one patients (19 males, 12 females) who received cranial RT for brain tumors were chosen to participate in this study between September 2014 and August 2015. Consent was obtained from each patient before the study. The protocol in this study was reviewed and approved by the Ethical Committee of Shahid Beheshti University based on standards set by the committee and in compliance with the 1975 Helsinki Declaration and its revision in 2000.

Patients were identified and recruited from the radiation oncology clinic at Shoahda Tajrish Hospital in Tehran, Iran (Table 1). Inclusion criteria were age over 18 years at the time of RT, primary brain tumor that was distant from the HPA, and the passage of at least 1 year since the last dose of irradiation. Exclusion criteria were known HP dysfunction, glucocorticoid treatment in the previous 6 months, malignant astrocytic tumors (World Health Organization grades III or IV), epilepsy, heart disease, and the condition of being too ill to undergo testing.

Table 1: Demographic, clinical, and treatment characteristics of the patients

Characteristic	No. of patients (%)
Sex	
Male	19 (%62)
Female	12 (%38)
Age (years)	
Mean	39.62
Median	36
Range	18-62
Cancer site	
Temporal lobe	6 (%19.3)
Frontal lobe	12 (%38.7)
Parietal lobe	4 (%12.9)
Occipital lobe	3 (%9.6)
Other	6 (%19.3)
Chemotherapy	
Concomitant chemo radiation	12 (%38.7)
No concomitant chemo radiation	19 (%61.3)
Surgery	
No surgery	22 (%70.9)
Non-pituitary gland surgery	9 (%29.1)
Received dose to HPA (cGy)	
Minimum	241
Maximum	5941
Mean	3576
Median	4339
BED (Gy) [median (range)]	59.6 (4-99)
Mean prescription dose (Gy)	55.9 (40-74)

TREATMENT CONSIDERATION

RT

The RT was applied with a high-energy linear accelerator (LINAC) using 6 MV photons and an isocentric technique delivering 1.8 to 2 Gy/day over 5 successive days per week. Transverse computed tomography (CT) scans in 2-mm slice thicknesses were obtained on a dedicated CT scanner (Siemens SOMATOM Emotion 16-slice). CT data was then transferred to the treatment planning system (TPS) in a digital imaging and communications in medicine (DICOM, National Electrical Manufacturers Association [NEMA], and <http://dicom.nema.org>) format. The pituitary and the HPA were contoured on the CT scans by an experienced radiation oncologist. All or part of the hypothalamus and pituitary gland were in the field of radiation. The dose reaching the HPA was calculated by dose-volume histograms (using planning computerized tomography, ISO gray software version 4.2 from Dosisoft Company, France). The dose calculation algorithm was the point kernel, collapsed cone (CP) algorithm. Patients were treated with either RT or a combination of surgery, postoperative RT, and chemotherapy. BED was calculated for patients using the quadratic model as follows: $BED = D \times [1 + d/(\alpha/\beta)]$, where

D is the total dose, d is the fraction size, α represents the linear non-repairable component of cell killing, β represents the quadratic component of cell killing, and $\alpha/\beta = 3$ for late responding tissue such as nerve tissues.^{6,7}

Endocrine Assessment

The baseline serum samples were evaluated. Subsequently, blood samples were obtained from each patient before treatment and 3 and 6 months after the last RT treatment step. Patients had no history of seizures, and so were studied using the insulin tolerance test (ITT).⁸⁻¹² The plasma blood glucose, GH level was measured at 0, 30, 60, 90, and 120 min after insulin administration. Normal growth hormone reserve was considered by a peak growth hormone level of ≥ 20 mIU/L during the ITT.⁸⁻¹³ For the ITT, GH deficiency (GHD) was considered as a peak response less than 5 $\mu\text{g/liter}$ and severe GHD as a peak response less than 3 $\mu\text{g/liter}$.^{14,15} TSH deficiency was considered by a low serum FT₄ level (after excluding artifactual causes) without appropriate elevation in serum TSH.^{6,16} Thyrotropin (TSH) concentration, free thyroxine (FT₄), and thyroxine (T₄) were measured by ELISA Kit (Pishtaz Teb, Tehran, IRAN). Normal reference ranges were as follows: free T₄: 11.5–23.2 pmol/l, TSH: 0.27–5 mIU/l, T₄: 5.1–14.1 $\mu\text{g/dl}$. The definitions for basal hormonal tests were as follows: thyrotroph deficiency—low serum free T₄ (below the lab range) without appropriate rises in TSH levels.^{13-15,17} Table 2 presents the general criteria for the diagnosis of central hypothyroidism (CH) or primary hypothyroidism (PH) and clinical or subclinical hypothyroidism.¹³ PH was characterized by an elevated serum TSH concentration and low serum free thyroxine (FT₄)/T₄ ratio; central hypothyroidism characterization involved one or more of the following: the presence of a low serum FT₄/T₄ ratio but low or occasionally normal, and in rare cases even slightly elevated, serum TSH owing to the secretion of TSH with reduced biologic activity but retained immunoactivity.¹⁸⁻²⁰

Statistical Analysis

Descriptive analysis was performed on the results of the baseline and dynamic hormonal tests. The results were presented as percentage or mean \pm (SD) or median (range). The normality of the data was investigated by using

Table 2: Classification of hypothyroidism

Type	Serum FT ₄	Serum TSH	Clinical manifestation
PH			
Clinical	Low	High	Symptoms present
Subclinical	Normal/ low-normal	High	Vague symptoms/ no symptoms
CH			
Clinical	Low	Low/ low normal	Symptoms present

FT₄: Free thyroxine, TSH: Thyroid-stimulating hormone, PH: Primary hypothyroidism, CH: Central-hypothyroidism

one-sample Kolmogorov - Smirnov (K-S) with Lilliefors correction test. Parametric methods such as the student test, Pearson correlation, and analysis of covariance model were used. Nonparametric methods such as the Mann-Whitney test and Spearman's coefficient (r_s) correlation were also used. Statistical analyses were conducted using SPSS version 15, and a level less than 5% was considered significant.

RESULTS

A summary of demographic, clinical, and treatment characteristics of the patients is shown in Table 1. Thirty-one patients (19 males/12 females) who had brain tumors were treated either with RT alone or in combination with surgery and chemotherapy. All of patients were followed 6 months. Clinical HP dysfunction was not present in short intervals after 3 and 6 months follow-up, but subclinical HP dysfunction was present in 26 patients (83%). Twelve patients (40%) had single-axis deficiency, whereas 8 patients

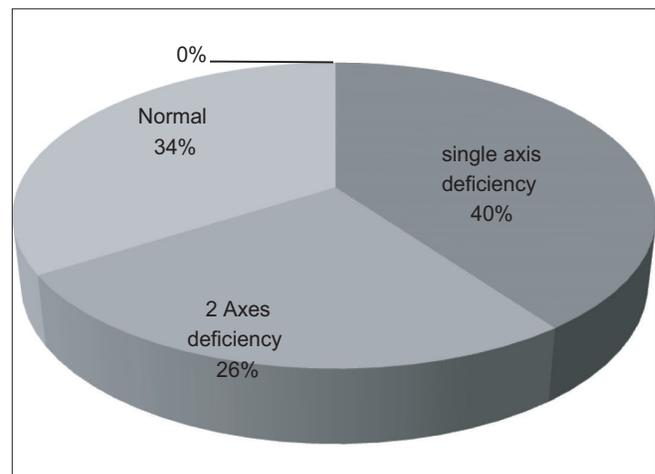


Figure 1: Prevalence of HP dysfunction according to number of hormonal axis involvement, post HPA irradiation

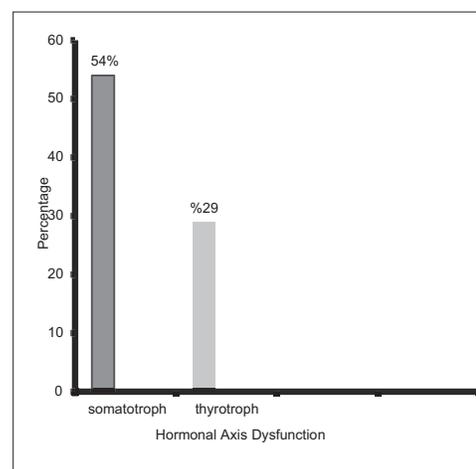


Figure 2: Frequency of each anterior pituitary hormone dysfunction post irradiation for HPA

(26%) had two-axes deficiency. Only 10 patients (34%) had normal pituitary hormone levels after 6 months of RT (shown in Figure 1). Fifteen (54%) of the 31 patients failed to get an adequate GH response during the ITT, representing somatotroph deficiency. The thyrotroph axis was least affected and subclinical thyrotroph deficiency was seen in only 9 patients (29%) as CH. The patients did not show PH. The abundance of different pituitary hormone involvement is shown in Figure 2. Analysis of the variables showed that the time elapsed post-irradiation is significantly associated with the development of HP dysfunction ($p < 0.001$). Adjuvant chemotherapy and surgery did not significantly influence hypopituitarism ($p = 0.698$, $p = 0.287$, respectively). The D_{mean} to the pituitary gland of patients with brain tumor was 35.76 Gy. To evaluate the probable effect of received dose to HPA on thyroid hormones and its significance for the results, data from patients was first excluded and then analyzed again. Table 3 shows the means (\pm SD) and p values

Table 3: Thyroid function tests before and after different sessions of radiation treatment

Test	Mean \pm SD	Mean \pm SD results after the session		
	Results before RT	3 months	6 months	p value*
TSH	2.81 \pm 1.3	2.41 \pm 0.99	1.75 \pm 1.07	0.021
FT4	20.52 \pm 3.9	18.43 \pm 3.75	15.66 \pm 2.34	0.009
T4	9.43 \pm 2.07	9.08 \pm 2.00	8.33 \pm 1.33	0.036

Table data show means \pm SD and p values of thyroid functional tests before and after different sessions of radiation treatment. *A $p < 0.05$ indicates significant difference in the results compared to values before RT

Table 4: Correlation between hormones' levels and time after radiotherapy

Hormone	Time	Correlation (r_s)
GH	3 months	-0.681
	6 months	-0.861
TSH	3 months	-0.196
	6 months	-0.358

Table data show the Pearson correlation between means hormones' levels and time after different sessions of radiation treatment

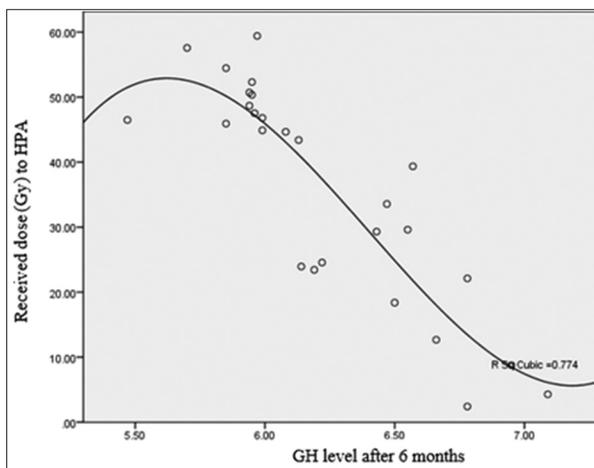


Figure 3: Dose response curve for GH hormone levels of the patients after 6 months

of thyroid functional tests obtained from that analysis. As can be noted from Table 3, there is a significant fall in TSH, FT4, and T4 levels after the RT course which can be interpreted as subclinical CH. Table 4 shows the Pearson correlation between hormones' levels and time. As shown in Table 4, there were significant correlations between means of hormones' levels and time after RT. Dose response curve was prepared according to the GH hormone levels after 6 months (Figure 3).

DISCUSSION

It is well known that primary radiation causes pituitary functional changes and may cause different degrees of damage.^{3,5,13} Many retrospective studies have reported hypopituitarism as the most frequent complication or late effect after irradiation.^{6,10,11,16,21} The etiology of radiation-induced HPA injury suggested by a few investigators^{13,22,23} is shown by neuronal cell death and destruction because of the direct effects of radiation on the vascular pathway between the hypothalamus and the pituitary. However, to the best of the authors' knowledge, functional changes or damage done to the HP axis in short interval conditions after RT to brain tumors in clinical practice have not yet been evaluated or reported. In this study, changes in pituitary hormone levels before and after RT pointed out the basic mechanism of the HPA complications. It was originally planned that the late effects of radiation on the HP axis would be studied by following the patients for a long period after treatment. However, considerable changes (in pituitary hormones, in the incidence of radiation-caused HPA damage) were found when the findings 3 and 6 months after the patients' RT were analyzed. These changes were reported as primary results, because no similar report was found in the literature. Radiation to the HPA causes a particular decrease pattern in hormone levels, and reduction of the growth hormone is the first and often only sign of damage to the HPA after cranial irradiation. The threshold dose for the induction of HPA dysfunction seems to be 10 Gy (Figure 3), and all patients, especially those who have symptoms of hypopituitarism before undergoing RT, should be considered for acute hypopituitarism. The GH level is the best indicator of pituitary function during RT. The occurrence rate is strongly dependent on the dose, and it is intensified with increasing duration of follow-up.^{24,25} Bhandare et al.⁵ observed clinical hypopituitarism in 14.1% patients after a median interval of 5.6 years and subclinical hypopituitarism in 33.8% patients. In the current study, no clinical hypopituitarism was observed, but subclinical hypopituitarism was considerable (83%) after a median interval of 6 months. The higher rate of subclinical pituitary dysfunction in this study probably reflects the short interval between RT and evaluation and represents the occurrence of clinical dysfunction in the future if follow-up is continued. Ratnasingam et al.¹³

evaluated HPA dysfunction amongst nasopharyngeal cancer survivors and reported hypopituitarism in 82% of patients, 30% single-axis and 28% two-axes. In the current study, subclinical hypopituitarism was observed in 83% of patients, 40% single-axis and 26% two-axes. Agha *et al.*⁶ studied 56 adult patients who received external beam RT for primary nonpituitary brain tumors at time intervals of 12–150 months after RT and reported hypopituitarism in 41% of patients. In the current study, however, subclinical hypopituitarism was observed in 83% of patients who tested for hypopituitarism at a time interval of 6 months. It seems that clinical hypopituitarism occurs long after RT. The current study reports a subclinical GHD of up to 54%, which is the most common and most vulnerable axis to radiation injury as reported by other studies.^{6,25} Previous studies represented that the somatotroph is more radiosensitive and dysfunction develops earlier compared to the thyrotroph axes.^{22,26} The current study results prove it in such a way that subclinical GH and TSH deficiency were 53% and 29%, respectively. The presence of GH deficiency could prove to be a useful sign for other hormone deficiencies. Among patients who were irradiated during adulthood, the rate of secondary hypothyroidism was 9%.^{6,24} A higher occurrence of secondary hypothyroidism was noted in patients with pituitary tumors than in those with non-pituitary tumors.²⁴ None of the patients developed primary hypothyroidism, although this is represented as one of the most common complications affecting the thyroid following radiotherapy (Table 3). However, primary hypothyroidism has mainly been observed several months following completion of radiotherapy with doses exceeding 60 Gy.²⁷ In this research, it was observed that 9/31 (29%) patients developed subclinical hypothyroidism. As expected, both males and females regardless of their age were at equal risk of developing HP dysfunction, as reported by others.¹³ Several studies have shown that hypopituitarism was more common in irradiation given in childhood or in younger adults.^{12,13} The current study did not show a difference in prevalence of hypopituitarism related to age at the time treatment was received, perhaps because all the patients were older adults (mean 39±13.3) with the youngest being 18 years of age. Outcome studies on the H-P axis have indicated that the development of both clinical and subclinical hypopituitarism and central hypothyroidism (CH) related to RT are significant. Elson *et al.*³ evaluated the effect of treatment modality on the hypothalamic-pituitary function of 33 patients treated with radiation therapy for pituitary adenomas; they concluded that the prevalence of disorder was minimal in the gamma knife method, moderate in IMRT, and maximum in LINAC. Although there is no cure for hypopituitarism, it is treatable. Successful hormone replacement therapy can enable a patient to live a normal life, feel well, and not have the consequences of hormone deficiency. Therefore, it seems to

be better to use new modalities in patients for whom HPA irradiation is inevitable.

CONCLUSION

HPA dysfunction among brain cancer survivors who had radiation therapy is common and mainly affects the somatotroph and, to a lesser extent, the thyrotroph axis. Hypopituitarism was seen at a dose of 10 Gy, administered to patients for treatment of brain cancer. As far as the literature is concerned regarding adult survivors of pediatric childhood cancer, time after therapy is critical and so with time the incidence of growth hormone deficiency and thyroid stimulating hormone deficiency is likely to significantly increase and to no longer be subclinical. This study will be continued until one year as a regular assessment to achieve the threshold incidence of late effects because of irradiation to HPA and, if necessary, replace the hormone therapy on time until the quality of life is improved and mortality is reduced in hypopituitary patients after treatment. However, that will hopefully be reported in a future publication, when patient follow-up is finished, so that the patients' late effects can be assessed and the needed analyses performed.

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Ethical Issue Notification

The procedures carried out on the patients in this study were reviewed and approved by the Ethical Committee of Shahid Beheshti University of Medical Sciences in accordance with the standards set by the committee and in compliance with the 1975 Helsinki Declaration and its revision in 2000.

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