Target Gland Dysfunction Following External Cranial Radiation for Extrasellar Tumours

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Abstract

Background : Diseases of the pituitary gland manifest as increased or decreased production of one or more of these hormones that in turn trigger a series of secondary hormonal changes in target glands (Thyroid, Adrenal and Gonad). Dysfunction of target glands may follow treatment with external radiation when hypothalamo-pituitary axis lies within the field of radiation. The present study has been undertaken with the aim to study target gland dysfunction and their relationship with dose of radiotherapy and duration after radiotherapy in patients who have received extracranial radiation for extrasellar tumours.

Methods: In this study, 96 patients who underwent cranial radiation 12 months ago were evaluated. Basal 8 am venous blood samples were taken for estimation of triiodothyronine (T_3), thyroxine (T_4), thyrotropin stimulating hormone (TSH) and basal cortisol estimation. Pooled samples (three samples taken 20 minutes apart and pooled together) were taken for LH, FSH and testosterone (TE) estimation. Insulin tolerance test was performed for stimulated cortisol levels.

Results: Target gland dysfunction was present in 72 (75%) patients. Hypogonadism was present in 48 (53%) of post-pubertal patients. 36% of male patients had hypogonadism whereas 100% of female patients had hypogonadism. Patients with hypogonadism were older, received higher doses of radiation and evaluated earlier after radiotherapy than without hypogonadism. Serum testosterone level declined significantly with increasing doses of radiation. Hypoadrenalism was present in 44 patients (46%). There was no significant difference of age, radiation dose and radiation fraction among patients with or without adrenal insufficiency. Proportion of patients with hypoadrenalism increased with increasing duration after radiotherapy. Hypothyroidism was present in 12 patients (13%). Proportion of patients with hypothyroidism doubled with increasing dose of radiation. Serum T_3 level declined significantly with increasing doses of radiation. Patients with hypothyroidism had significantly low T_3 and T_4 level, but significantly higher TSH and basal and peak cortisol levels than patients without hypothyroidism.

Conclusion: Target gland dysfunction is common after extracranial radiation for extrasellar tumours. Hypogonadism was the commonest followed by hypoadrenalism and hypothyroidism. Target gland dysfunction was related to age, radiation dose and duration after radiotherapy, but not with fraction of radiation.

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Key Words : Adrenal insufficiency; Cranial radiation; Hypogonadism; Hypothyroidism

Introduction

Diseases of the pituitary gland are often hormone related and may manifest as increased or decreased production of one or more of these hormones that in turn trigger a series of secondary hormonal changes in target glands (Thyroid, Adrenal, and Gonad) [1]. Cranial irradiation has significant long-term deleterious effects, in the form of endocrinopathies. With the better prognosis of certain types of brain tumours, chronic damage following external irradiation of the normal pituitary, delivered during radiotherapy of the neoplasms of head, is more commonly appreciated than in the past [2-12]. Patients with brain tumours who are treated with radiation frequently have growth hormone deficiency, but other neuro-endocrine abnormalities are presumed to be uncommon [2]. Clinical damage to the pituitary gland is usually manifested months to years

after treatment and is preceded by a long subclinical phase. However, there is a paucity of such studies in Indian literature. The present study has been designed with the aim to study target gland dysfunction and its relationship with dose of radiotherapy and duration after radiotherapy in patients who have received extracranial radiation for extrasellar tumours.

Material and Methods

In this observational study, 96 patients who underwent cranial radiation (theratron 870 E cobalt 60 teletherapy unit), at least 12 months before, at the radiotherapy department were evaluated. The diagnosis and radiation profile details, including the total dose, dose fraction, duration and the year were retrieved from the files.

After detailed clinical examination the hematological, renal and hepatic functional parameters were assessed. Endocrine evaluation included assessment of:-

Thyroid and Gonadal Function: Basal 8 am venous blood samples were taken for serum T_3 , T_4 and TSH estimation. Pooled samples (three samples taken 20 minutes apart and pooled together) were taken for LH, FSH and TE estimation. The serum was separated and stored at -20°C until the time of assay.

Adrenal Function: Basal 8 am venous blood samples were taken for estimation of basal cortisol. Insulin tolerance test was performed after overnight fasting unless contraindicated (history of ischemic heart disease, cerebrovascular accident or convulsions). The test and symptoms of hypoglycemia were explained in detail to the patient. A heparin lock venous cannula was placed in the morning. Blood was drawn at 0 minutes for glucose and cortisol estimation. Then 0.1 unit per kg body weight of regular insulin was injected intravenously. Pulse and blood pressure were measured at base line and at the time of blood sampling at 30, 60, 90 and 120 minutes. Clinical signs of hypoglycemia and blood glucose less than 40mg/dl or 50% of basal glucose was taken as evidence of adequate hypoglycemia, which was then reversed with intravenous 10% dextrose solution. A serum cortisol of 18 $\mu\text{g/dl}$ was taken as an adequate response. Serum was separated and stored at -20°C until the time of assay.

Hormonal Assays

The serum T_3 , T_4 and LH were estimated by radioimmunoassay (RIA) by kits supplied by Bhabha Atomic Research Centre (BARC), Mumbai. The normal range of T_3 , T_4 and LH were 80-200 ng/dl, 5.5-13.5 $\mu\text{g/dl}$ and 5-15 mIU/ml respectively. Serum TSH was estimated by an immunoradiometric assay, using a commercial kit supplied by BARC. Normal range of serum TSH was 0.2-4.5 mIU/litre. Serum cortisol was estimated by Gammacoat cortisol ^{125}I RIA kit by Diasorin, Stillwater, Minnesota, USA. Normal morning cortisol ranged from 5-25 $\mu\text{g/dl}$. Serum total testosterone was estimated by RIA using commercial kits supplied by Diasorin, Stillwater, Minnesota, USA. Normal level for adult male was 3.0-10.0 ng/ml. For all, assay-interassay coefficient of variation was less than 15% and intra-assay variation was less than 10%.

Statistical Methods

Statistical analysis was done by ANOVA test using computer programme EPI-6. Chi-square test was used for analysis of nonparametric data. Results were expressed in mean $\pm$ standard error.

Criteria For Deficiencies

Hypothyroidism: Hypothyroidism was defined when T_4 levels were $< 5.5 \mu\text{g/dl}$ with normal or low TSH. However, in the literature secondary hypothyroidism was defined as $T_4 < 4.0 \mu\text{g/dl}$ [13], but in our study we defined hypothyroidism as T_4 levels $< 5.5 \mu\text{g/dl}$ because lower level defined by BARC for the Indian population was $> 5.5 \mu\text{g/dl}$.

Hypogonadism: Hypogonadism in post-pubertal male was defined by serum testosterone levels $< 3.0 \text{ ng/ml}$ and females by presence of amenorrhoea with normal or low FSH levels in premenopausal women; and normal or low FSH in

postmenopausal women.

Hypoadrenalism: Adrenal insufficiency was defined by either basal cortisol levels $< 5.0 \mu\text{g/ml}$ or peak cortisol levels $< 18.0 \mu\text{g/ml}$ after insulin induced hypoglycemia.

Results

Mean age of the patients was 32 ± 0.10 years (8-60 years). Maximum number of patients (88%) were in the age group 16-45 years. Male to female ratio was 3:1. Commonest cranial tumour was astrocytoma in 63% cases, followed by oligodendroglioma (17%), glioma (6%), nasopharyngeal carcinoma (5%), meningioma (3%), rhabdomyosarcoma (2%), glioblastoma (2%) and hemangioblastoma (2%). Most of the patients (63 patients-66%) received chemotherapy with agents, vincristine, carmustine, methotrexate and prednisolone, within 6 months of radiotherapy. There was no involvement of hypothalamus and pituitary before radiotherapy.

Among all patients, 84 (88%) had evidence of pituitary dysfunction either alone or in combination. Target gland dysfunction was present in 72 (75%) patients. Hypogonadism was present in 48 (53%) of post-pubertal patients. 13 patients had isolated hypogonadism; 5 each had associated either GH deficiency or adrenal insufficiency; rest were part of panhypopituitarism. Hypogonadism increased with increasing age (Table-1). 36% of male patients had hypogonadism where as 100% of female patients had hypogonadism manifesting as amenorrhoea in premenopausal females and normal LH and FSH values in postmenopausal patients. Symptoms of decreased libido and impotence were present in 51 (77%) of post-pubertal males. Males with symptoms had significantly lower levels of testosterone than those who had no symptoms (Table-6). Male patients with hypogonadism had low testosterone level ($1.64 \pm 0.02 \text{ mIU/ml}$) and inappropriately normal FSH ($8.78 \pm 0.34 \text{ mIU/ml}$) and LH ($13.70 \pm 0.13 \text{ mIU/ml}$). Patients with hypogonadism were older (35 ± 0.17 vs 32 ± 0.21 , $p=0.075$), received higher doses of radiation (5551 ± 8 vs 5349 ± 16 , $p=0.074$) and evaluated earlier after radiotherapy (28 ± 0.38 vs 41 ± 0.64 , $p=0.01$) than without hypogonadism. Prolactin levels were higher among patients with hypogonadism but difference was not statistically significant (12.11 ± 0.13 vs 10.60 ± 0.22 , $p=0.65$). Patients who had received doses higher than 5000 rads were more likely to develop hypogonadism than those who had received less radiation ($p=0.007$) (Table-2). Serum testosterone level declined significantly with increasing doses of radiation ($p=0.03$) (Table-5). Radiation fraction had no effect on development of hypogonadism (Table-3). Hypogonadism was evident in more than 50% of cases even within 18 months after radiotherapy. It significantly increased to 72% at three years ($p=0.038$) (Table-4).

Hypoadrenalism was present in 44 patients (46%). Six patients had isolated adrenal insufficiency; 13 had associated GH deficiency and 5 hypogonadism; rest were part of panhypopituitarism. Most of the patients (77%) with adrenal insufficiency belonged to the age group 16-45 years. However, it was more common at extremes of age (Table-1). Mean basal

Table 1**Target gland dysfunction**

Age (years)	Total	Hypo-gonadism#	Hypo-adrenalism	Hypo-thyroidism
5-15	6*	-	4 (67%)	2 (33%)
16-25	22	6 (27%)	10 (45%)	4 (18*)
26-35	26	18 (69%)	10 (38%)	2 (8%)
36-45	36	20 (56%)	14 (39%)	4 (11%)
46-55	4	2 (50%)	4 (100%)	0
56-65	2	2 (100%)	2 (100%)	0
Total	96	48 (53%)	44 (46%)	12 (13%)

*Not included in hypogonadism, #Calculated among 90 postpubertal patients

Table 2**Radiation dose and target gland dysfunction**

Dosage of radiation	Hypo-gonadism	Hypo-adrenalism	Hypo-thyroidism
Upto 5000 rads (24)	6 (25%)	14 (59%)	2 (8%)
5001-6000 rads (63)	43 (68%)	26 (41%)	10 (16%)
> 6000 rads (9)	5 (56%)	4 (44%)	-
Chi square	14.35	2.05	2.32
P value	0.007	0.36	0.31

and peak cortisol levels among patients with hypoadrenalism were 6.05 ± 0.07 and 10.0 ± 0.08 $\mu\text{g/dl}$ respectively. There was no significant difference of age (33.3 ± 0.26 vs 31.19 ± 0.16 , $p=0.29$), sex (male 53% vs 47%), radiation dose (5376 ± 12 vs 5499 ± 12 , $p=0.29$), radiation fraction (184 ± 0.39 vs 186 ± 0.37 , $p=0.71$), and chemotherapy (75% vs 58%, $p=0.11$) among patients with or without adrenal insufficiency. There was more proportion of patients with hypoadrenalism with increasing duration after radiotherapy, which was not statistically significant (Table-4).

Hypothyroidism was present in 12 patients (13%). Two cases had isolated hypothyroidism, 2 had associated GH deficiency, and rest were part of panhypopituitarism. All cases belonged to the age group below 45 years. Mean age of patients with hypothyroidism was lower compared to patients without hypothyroidism (27 ± 9.6 vs 32.9 ± 9.9 , $p=0.05$). Though there was no significant difference in the radiation dose received by patients with or without hypothyroidism (5440 ± 30 vs 5443 ± 7 , $p=0.98$), proportion of patients with hypothyroidism doubled with increasing dose of radiation (Table-2). With increasing dose of radiation, level of T₃ decreased significantly (Table-5, Fig. 1), but there was no statistically significant decline in T₄ and TSH. Fraction of dose given per day had no effect on development of hypothyroidism (Table-3). Hypothyroidism was present more often in those who underwent endocrine evaluation before 18 months of radiotherapy or after 36 months of radiotherapy (Table-4). Patients with hypothyroidism had significantly low T₃ (105 ± 2.42 vs 124 ± 0.32 ng/dl, $p=0.024$) and T₄ level (3.97 ± 0.09 vs 8.67 ± 0.02 $\mu\text{g/dl}$, $p<0.00001$), but surprisingly TSH levels were significantly higher (4.05 ± 0.37 vs 1.77 ± 0.02 mIU/L, $p=0.0004$) than patients without hypothyroidism.

Table 3**Radiation dose fraction and target gland dysfunction**

Dose fraction (n)	Hypo-gonadism	Hypo-adrenalism	Hypo-thyroidism
Upto 150 rads (12)	8 (67%)	4 (33%)	2 (17%)
151-200 rads (82)	44 (54%)	39 (48%)	9 (11%)
> 200 rads (2)	2 (100%)	1 (50%)	1 (50%)
Chi-square	3.38	0.89	2.94
p value	0.18	0.64	0.23

Table 4**Duration after radiation and target gland dysfunction**

Duration (n)	Hypo-gonadism	Hypo-adrenalism	Hypo-thyroidism
< 18 months (30)	17 (57%)	12 (40%)	6 (20%)
19-36 months (32)	23 (72%)	12 (38%)	2 (6%)
> 36 months (34)	14 (41%)	20 (59%)	4 (12%)
Chi-square	5.73	3.62	2.70
p value	0.05	0.16	0.25

These patients also had significantly high basal (12.71 ± 0.30 vs 8.82 ± 0.06 $\mu\text{g/dl}$, $p=0.006$) and peak cortisol (23.02 ± 0.66 vs 15.87 ± 0.08 $\mu\text{g/dl}$, $p=0.001$).

Discussion**Hypogonadism**

Radiation treatment to the head may cause a broad spectrum of hypothalamo-pituitary-gonadal abnormalities. The resultant thyroid, GH or adrenal deficiency may have indirect effects on reproductive system. In this study, 48 patients (53%) had hypogonadism. Proportion of patients with hypogonadism increased with age. All female patients had evidence of hypogonadism whereas only 36% of males had evidence of hypogonadism. Hypogonadism has been reported in 8-72% patients by various authors [3,6-8,11,12]. This can be explained by variation in age of patients, radiation dose and duration after radiotherapy among various studies.

Fig. 1 : Effect of radiation dose on mean T₃ levels

Table 5**Radiation dose and hormone levels**

Dosage of radiation (n)	T ₄ (mg/dl)	T ₃ (ng/dl)	TSH (mIU/L)	Testosterone (ng/ml)
Upto 5000 rads (24)	8.14 ± 0.09	141 ± 1.08	1.98 ± 0.06	3.9 ± 0.05
5001-6000 rads (63)	7.96 ± 0.04	115 ± 0.43	2.12 ± 0.04	3.5 ± 0.03
> 6000 rads (9)	8.77 ± 0.21	111 ± 0.89	1.76 ± 0.14	2.8 ± 0.21
p value	0.59	< 0.008	< 0.87	0.03

Table 6**Relation of testosterone levels and symptoms in postpubertal males**

Symptoms	No.	Testosterone levels (ng/ml)	p value
Present	51 (77%)	2.79 ± 0.03	
Absent	15 (23%)	6.27 ± 0.04	< 0.00001

77% of post-pubertal males had symptoms of loss of libido and erectile dysfunction. This group of patients also had significantly low testosterone levels compared to those without symptoms. This signifies the fact that patients without symptoms are unlikely to have hypogonadism. In present study, male hypogonadism was defined by total testosterone level < 3 ng/ml. Patients with symptoms also had low testosterone level, but above the level of defined criteria, hence not considered as a case of hypogonadism. Some of these patients may have hypogonadism. This could have been detected by GnRH testing or free testosterone measurement, which was not measured and was the limitation of this study. However, normal response to GnRH will not exclude hypothalamic hypogonadism, but subnormal response may confirm pituitary hypogonadism [3,7].

The predominant symptom in female patients was amenorrhoea. This observation was similar to Woo et al [8], where all 3 female patients (100%) had amenorrhoea-galactorrhoea. Seven of 10 female patients (70%) had amenorrhoea in one study [11]. However, incidence of gonadotropin deficiency was harder to quantify in that study, because 7 of their patients were pre-pubertal children, in whom pituitary gonadal function is difficult to assess. Samman et al [3] noted subnormal LH levels after LHRH administration in 4 patients. However one of these patients had primary amenorrhoea with normal LH response to LHRH, suggesting hypothalamic lesion. Similarly Lam et al [7] also observed impaired gonadotropin response to LHRH in two patients. Woo et al [8] observed low testosterone level in 62% of patients and all females were amenorrhoeic in their study. They reported impotence and decreased libido in 2 out of 8 male patients (25%) who received radiotherapy for nasopharyngeal carcinomas. The low incidence in their study could probably be due to a small sample size.

Patients with hypogonadism received higher doses of radiation and serum testosterone level declined significantly when dose of radiation increased above 5000 rads. Slater et al [9] also reported low testosterone levels in three males between 14-45 months after radiotherapy. Eight of 16 patients (50%) evaluated 12 months after radiotherapy had evidence of hypogonadism. Thirteen patients (39%) had isolated hypogonadism.

Adrenal Insufficiency

The most frequent cause of adrenal dysfunction in patients with brain tumour is prolonged use of pharmacological doses of glucocorticoid, which may continue for months [14]. However, patients in this study were studied only after one year of radiotherapy, hence this confounding factor was eliminated. There were 44 patients (46%) with evidence of adrenal insufficiency. Of these 44 patients, 90% had generalized fatigue. None of the patients had symptoms suggestive of acute adrenal crisis. In this study ITT was used to evaluate adrenal function, which remains the gold standard [14]. Of these 44 patients, 26 had basal cortisol less than 5 µg/dl with subnormal response to ITT, whereas 18 patients had normal basal cortisol but had subnormal response to ITT. This suggests that in patients with basal cortisol < 5 µg/dl ITT does not add to any further information. Irradiation to hypothalamo-pituitary region causes ACTH deficiency and adrenal insufficiency in 9-50% of treated patients [3,6-9,11,12]. Samaan et al [3] reported adrenal insufficiency in 40% of patients, detected by insulin hypoglycemia test, which is similar to our data. However, they reported signs and symptoms of adrenal crisis in 2 patients, unlike asymptomatic patient of ours. Lam et al [7] found impaired cortisol responses to ITT, and gradual but diminished cortisol responses to ovine corticotrophin releasing factor (CRF-41) in four patients (50%). There was no significant difference between mean peak increments in response to ITT and those in response to CRF-41, suggesting similar value of both tests in assessing hypothalamo-pituitary-adrenal axis. Woo et al [8] reported low basal cortisol in 2 patients (18%), however, no stimulation test was performed. Slater et al [9] observed corticotrophin deficiency in two patients after proton radiation for tumours of upper clivus. Constine et al [11] reported adrenal insufficiency in 42% patients,

but in their study, basal pituitary-adrenal function was normal. Responses to corticotropin and CRH stimulation tests were normal or slightly increased. Their cases were detected by metyrapone stimulation test. They have not performed ITT, which is ideal to assess hypothalamo-pituitary-adrenal axis. Five and ten year actuarial rates of hypoadrenalism were 19% and 28% following high-dose conformal fractional proton-photon beam radiotherapy to the base of skull region in 107 adults [12].

Adrenal insufficiency may occur as early as the first two years after radiotherapy [11], although median time for occurrence is five years [15]. In this study 40% patients had evidence of adrenal insufficiency as early as 18 months after radiotherapy. Proportion of cases with adrenal insufficiency increased significantly three years after radiotherapy, which emphasizes the need for yearly evaluation of pituitary function after cranial radiotherapy.

Thyroid Hormone Deficiency

Irradiation to the head and neck is an important cause of thyroid dysfunction. Radiation doses greater than 25 Gy to the thyroid gland can result in primary hypothyroidism; doses of 50 Gy or more to the hypothalamic-pituitary region are associated with secondary or tertiary hypothyroidism [4,5,8,10]. There appears to be a linear time related diminution in TSH secretion after treatment with 38-75 Gy for brain tumours [16] or nasopharyngeal carcinoma [7,8]. Fifteen to 20% had diminished TSH secretion at 5 years and approximately 35% at 10 years and after [24,52,55]. Hypothyroidism due to pituitary dysfunction ranged from 9-62% in various studies [3,6-8,11,12]. In this study there were 12 (13%) patients with hypothyroidism. None had symptoms referable to hypothyroidism like weight gain, cold intolerance etc. However, 6 of 12 patients (50%) complained of generalized fatigue. This observation was similar to the one by Samaan et al [3], where they observed generalized fatigue in 5 out of 15 patients (33%). In a similar study of 8 patients with nasopharyngeal carcinoma by Woo et al [8] two patients (25%) had cold intolerance. Constine et al [11] detected high number of cases (62%) with secondary hypothyroidism. However, in their study, they defined hypothyroidism if any one of the values for free T_4 , total T_4 , and total T_3 were found subnormal. Free T_4 was not done in present study, measurement of which was important in detecting the cases of hypothyroidism in the study by Constine et al [11]. If only total T_4 is considered in their study, the number of hypothyroid cases was only 20%. However, if we consider patients with low T_3 and normal T_4 and TSH values as hypothyroidism in present study, then ten more cases

are included, with resultant increase in the prevalence of hypothyroidism to 23%. However, low T_3 alone should not be considered as an indicator of pituitary hypothyroidism because it can occur as a part of the euthyroid sick syndrome, and could also be explained by associated GH deficiency, which is postulated to convert T_4 to T_3 [17]. Patients with hypothyroidism had significantly lower T_4 and T_3 levels. However TSH level was detected to be higher than patients without hypothyroidism. This can be due to dysregulation of hypothalamo-pituitary-thyroid feedback system. Shalet et al also observed significantly higher basal TSH level than control after cranial radiation [18]. Higher TSH was more apparent in GH deficient children. In present study ten of 12 patients of hypothyroidism were also GH deficient. GH is postulated to increase conversion of T_4 to T_3 [17] and T_3 is active hormone, which inhibits thyrotrophs. Hence comparatively low T_3 level could have resulted in compensatory increase in TSH levels. Furthermore, serum T_3 levels were relatively lower in patients with isolated GH deficiency compared with patients with normal endocrine function (123 ± 3.08 vs 131 ± 1.25). Another possibility can be secretion of biologically inactive TSH secreted from thyrotroph cells [19] affected by radiation, because cells continue to function after radiation till next mitotic event [5]. Patients with hypothyroidism had significantly higher level of total testosterone and basal and stimulated cortisol. Thyroid hormone is known to increase metabolism of cortisol [20].

There was no case of primary hypothyroidism in this study as most of the patients (90%) had cranial tumours and required only cranial irradiation. Primary hypothyroidism occurs mostly in patients who require neck irradiation, which explains the high incidence of primary hypothyroidism in some studies [3,4,10]. Low prevalence of hypothyroidism rather than other pituitary hormone deficiency in this study could be due to differential sensitivity of thyrotrophs to radiation because of their slower turnover time. Within the range of doses conventionally employed in external radiation therapy, cell killing is usually a post mitotic event. Despite the fact that damage occurs immediately following radiation, the cell continues to function until a subsequent mitotic division when killing effect of radiation is expressed and the cell dies [5]. Hence hypothyroidism is a late complication of cranial radiation. In present study, 65% patients had radiation three years before endocrine evaluation, hence late event may not become evident. Skylar et al [15] observed that growth hormone deficiency occurs at doses as low as 18Gy, whereas gonadotropin, TSH and ACTH deficiency are seen with doses in excess of 40Gy. This further highlights the

postulation of differential sensitivity of adenohypophyseal cells. Moreover pituitary contains least number of thyrotrophs about 5% compared to 50% somatotrophs [1], hence may escape random radiation effect [21].

Target gland dysfunction is common after extracranial radiation for extrasellar tumours. Hypogonadism was the commonest followed by hypoadrenalism and hypothyroidism. Target gland dysfunction was related to age, radiation dose and duration after radiotherapy, but not with fraction of radiation. Target gland functions can be assessed by measuring serum concentrations of gonadotropins, testosterone, TSH and thyroxine, but dynamic test is required to assess cortisol secretion. This study further highlights that target gland function may not develop after many years in these patients. Such patients should therefore have annual assessment of target gland function for the rest of their lives.

References

- Moss WT. The pituitary gland. In : Cox JD editor. Moss's Radiation Oncology: Rationale Technique, Results. 7th ed, Mosby, Philadelphia. 1994;782-92.
- Duffner PK, Cohen ME, Thomas PR, Lansky SB. The long term effects of cranial irradiation in the central nervous system-Cancer 1985;56:1841-6.
- Samaan NA, Bakdash MM, Caderao JB, Cagir A, Jesse RH, Ballantyne AJ. Hypopituitarism after external irradiation: Evidence for both hypothalamic and pituitary origin. Ann Intern Med 1975;83:771-5.
- Rosenthal MB, Goldfine ID. Primary and secondary hypothyroidism in nasopharyngeal carcinoma. JAMA 1976;236:1591-3.
- Fuks Z, Glatstein E, Marsa GW, Bagshaw MA, Kaplan HS. Long term effects of external Radiation on the Pituitary and Thyroid glands. Cancer 1976;37:1152-61.
- Danoff BF, Cowchock FS, Marquette C, Mulgrew L, Kramer S. Assessment of the long term effects of primary radiation therapy for brain tumors in children. Cancer 1982;49:1580-6.
- Lam KS, Wang C, Yeung RT et al. Hypothalamic Hypopituitarism following cranial irradiation for nasopharyngeal carcinoma, Clin Endocrinol (Oxford) 1986;24:643-51.
- Woo E, Lam K, Yu YL, Wang C, Yeung RTT. Temporal lobe and hypothalamic-pituitary dysfunction after radiotherapy for nasopharyngeal carcinoma. Journal of Neurology, Neurosurgery and Psychiatry 1988;51:1302-7.
- Slater JD, Austin-Seymour M, Munzenrider J et al. Endocrine function following high dose proton therapy for tumors of the upper clivus. Int J Radiat Oncol Biol Phys 1988;15:607-11.
- Livesey EA, Brook CGD. Thyroid dysfunction after radiotherapy and chemotherapy of brain tumors. Arch Dis Child 1989;64:593-5.
- Constine LS, Woolf PD, Cann D et al. Hypothalamic-pituitary dysfunction after radiation for brain tumors. N Engl J Med 1993;328:87-94.
- Pai HH, Thornton A, Katznelson L et al. Hypothalamic/pituitary function following high-dose conformal radiotherapy to the base of skull: demonstration of a dose-effect relationship using dose-volume histogram analysis. Int J Radiat Oncol Biol Phys 2001;49:1079-92.
- Garg MK, Tandon N, Gupta N, Varma A, Singh VP. Target gland functional status in patients with non-Cushing's pituitary macroadenomas undergoing trans-sphenoidal microsurgery. JAPI 2001;49:221-6.
- Grinspoon SK, Biller BM. Laboratory assessment of adrenal insufficiency. J Clin Endocrinol Metab 1994;79:923-31.
- Skylar CA, Constine LS. Chronic neuroendocrinological sequelae of radiation therapy. Int J Radiat Oncol Biol Phys 1995;31:1113-21.
- Shalet SM, Clayton PE, Price DA. Growth and pituitary function in children treated for brain tumours or acute lymphoblastic leukemia. Horm Res 1988;30:53-61.
- Jorgenson OL, Pedersen SA, Laurberg P, Weeka J, Skakkeback E, Christiansen JS. Effects of growth hormone therapy on thyroid function of growth hormone-deficient adults with and without concomitant thyroxine-substituted central hypothyroidism. J Clin Endocrinol Metab 1989;69:1127-32.
- Shalet SM, Beardwell CG, Morris Jones PH, Pearson D. Pituitary function after treatment of intracranial tumors in children. Lancet 1975;2:104-7.
- Faglia G, Bitensky L, Pinchera A et al. Thyrotropin secretion in patients with central hypothyroidism: evidence for reduced biological activity of immunoreactive thyrotropin. J Clin Endocrinol Metab 1979;48:989-98.
- Samuel H. Principles of Cancer Management: Radiation Therapy. In : De Vita VT Jr, Samuel H, Rosenberg SA, editors. Cancer, Principles and Practice of Oncology. J B Lippincott Co. Philadelphia. 6th ed 2001;265-88.
- Tsatsoulis A, Johnson EO, Kalogera CH, Seferiadis K, Tsolas O. The effect of thyrotoxicosis on adrenocortical reserve. Eur J Endocrinol 2000;142:231-5.