

Cover Page



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Title: Long-term consequences of growth hormone replacement and cranial radiation on pituitary function

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Chapter 3

Pituitary dysfunction in adult patients after cranial irradiation for head and nasopharyngeal tumours

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ABSTRACT

Background: Pituitary insufficiency after radiotherapy in the hypothalamic pituitary region is a well-known complication. However, endocrine assessments are not incorporated in the follow-up after cranial irradiation for head and neck tumours.

Aim of the study: to evaluate pituitary function in patients cranially irradiated for non-pituitary tumours.

Patients and Methods: Evaluation of pituitary function in all available patients treated at our center with cranial radiotherapy for head and neck tumours.

Results: We included 80 patients. Forty patients were treated for cerebral tumours, 15 for nasopharyngeal tumours, and 25 for different tumours like meningioma or cerebral metastasis. Mean age was 47.5 (18.6-89.7) years. Mean radiation dose delivered at the pituitary region was 56.27 Gy (40.0-70.0). Pituitary insufficiency was present in 16 patients within 2 years after irradiation within 2 years after irradiation. 23/49 patients (47%) after 5 years and 27/45 (60%) after 10 years and 31/35 patients (89%) after 15 years, respectively.

Conclusion: Pituitary insufficiency is highly prevalent in adult patients treated with cranial radiotherapy for head and nasopharyngeal tumours. These prevalence rates are comparable to those observed after radiotherapy for pituitary tumours. Because hormone replacement of endocrine deficits improves quality of life and prevents potential severe complications, such as Addisonian crises, periodical evaluation of pituitary function is advocated.

INTRODUCTION

Radiation-induced pituitary insufficiency is a well-known dose-dependent late sequel of pituitary irradiation for pituitary tumours with prevalence rates of any pituitary insufficiency of approximately 50% after 5 years, and up to 75 % after 10 years following a total dose of 40-45Gy (1-3). In accordance, when the hypothalamic-pituitary region is within the radiation field, cranial irradiation for non-pituitary tumours may also induce pituitary insufficiency (4). In children, the high incidence of pituitary insufficiency after cranial irradiation for cerebral or nasopharyngeal tumours, including total body irradiation (TBI) for hematological malignancies, is well established (5-9). The Childhood Cancer Survivor Study (CCSS) reported one or more endocrinopathies to be present in 43% of children treated for cerebral tumours. Consequently, these children are subjected to structural endocrine surveillance also when reaching adulthood (10).

Currently, guidelines on endocrine surveillance in adult patients are not available. Survival rates for e.g. cerebral and nasopharyngeal tumours have improved substantially by new treatment modalities (11,12). Therefore, it is likely that an increasing number of adult patients will also be affected by endocrine complications of cranial irradiation. Since complaints of hypopituitarism are generally non-specific, endocrine tests are required for an accurate diagnose of pituitary failure. Endocrine function tests are necessary for diagnosing hypocortisolism or growth hormone deficiency. Growth hormone deficiency however might not be clinically relevant for a patient treated for a malignant tumour since cancer patients generally will not be substituted with growth hormone, although in childhood cancer survivors no there was no statistically significant increased overall risk of the occurrence of neoplasms associated with rh-GH exposure (13). But diagnosing growth hormone deficiency will still be useful since it may serve as an indicator of radiation induced hypothalamic/pituitary damage. In a recent meta-analysis, we have concluded that the low number of adult patient cohorts followed after cranial radiotherapy for non-pituitary tumours with sufficient long-term data and proper dynamic endocrine evaluation precludes strong conclusions on the incidence and prevalence rates of pituitary insufficiency. However, the meta-analysis suggested a high prevalence of any form of pituitary insufficiency, like in children, of 0.66 (95% CI, 0.55–0.76) after cranial radiotherapy for both nasopharyngeal and cerebral tumours (14). In addition, the time of onset of pituitary failure was documented in only 3 studies (15-17). The aim of this cohort study was to evaluate the prevalence, and the time of onset, of pituitary insufficiency in adult patients after cranial irradiation for non-pituitary tumours in our center.

SUBJECTS AND METHODS

The patient registry of the department of Radiotherapy was checked for patients who underwent cranial radiotherapy for non-pituitary tumours from 1990-2010 with the hypothalamus and/or the pituitary within the radiation field and whom received >20Gy to the hypothalamus-pituitary region (n=1504). We selected a threshold of 20 Gy based on data from historical cohorts indicating that a total dose of 7-24 Gy delivered to the pituitary/hypothalamus region, may cause growth hormone deficiency only, whereas dosages as high as 50-60 Gy will most certainly cause multiple pituitary hormone deficiencies (18). When alive and not already known to the outpatient clinic of the department of Endocrinology, patients were invited for endocrine testing. Patients were excluded if: 1) radiotherapy was given for pituitary or parasellar tumours 2) radiotherapy was applied as TBI, 3) pituitary insufficiency was already present before radiotherapy 4) was a life expectancy of less than 12 months at time of screening. Pituitary functions were checked at first outpatient clinic visit with basal hormone samples and endocrine function tests, afterwards patients were monitored by a standardized protocol (vide infra). In addition we used clinical and anamnestic information on their condition prior to radiation. In case of pituitary insufficiency medication was started at the discretion of the treating physician. This study represents a combined analysis of the patients already known at the department of endocrinology and patients from the screening of records of radiotherapy.

Mean applied radiation dose:

All files were screened for a calculated/estimated dose to the pituitary/hypothalamic region. For patients irradiated before 2004, the isodose lines plotted on 2D images and on plain x-rays of the skull were used to estimate the pituitary dose. After the introduction of CT based treatment planning in our department CT images were used to read the plotted dose. Since 2007 the planning software gives a calculated dose to the hypothalamic/pituitary region, and mean doses to the pituitary were collected.

Parameters

At baseline disease specific information was extracted from the medical files.

The following parameters were assessed:

Anthropometric parameters: body weight and height were measured. Body weight was measured to the nearest 0.1 kg, and body height was measured barefoot to the nearest 0.001 m. Additional information on medication use, Karnofsky score, IADL score, and co-morbidity was gathered.

Endocrine assessment

Biochemical parameters: IGF-1, GH, TSH, fT₄, ACTH, cortisol, LH, FSH, estradiol, testosterone, Sex Hormone Binding Globulin (SHBG), and prolactin concentrations were measured, furthermore general laboratory parameters including renal and liver function and cardiovascular parameters were obtained. Blood samples were taken for laboratory measurements after an overnight fast.

For diagnosing cortisol deficiency we used the following stepwise approach. First a basal cortisol level was performed. When basal cortisol concentrations were <80 nmol/L, in the absence of glucocorticoid use, the diagnosis of hypocortisolism was considered evident and no additional tests were performed (19). To date, the insulin tolerance test (ITT) remains the golden standard for the evaluation of the HPA-axis (19). In case of contraindications for the ITT, such as epilepsy or coronary artery disease, alternative dynamic tests such as the corticotrophin releasing hormone (CRH) test (n=10), the metyrapone test (n=4), or the ACTH stimulation test were used as to assess adrenal function (19-23). The choice for a specific test was made by the treating physician on an individual basis depending on the patient's clinical condition. Cortisol deficiency was defined by a peak cortisol below 0.55 $\mu\text{mol/L}$, either after insulin-induced hypoglycemia (glucose nadir <2.2 mmol/L) or after stimulation with 100 mcg CRH. A limited number of patients were tested using metyrapone (n=4) since in the past CRH was not available for some time, two of them were retested with the insulin tolerance test when possible. Metyrapone (30 mg/kg, Metopiron, Novartis Pharma B.V., Arnhem, the Netherlands) was administered orally at midnight. The next morning post absorptive blood samples were obtained for measurement of 11-deoxycortisol, cortisol and ACTH levels. A cut-off value for 11-deoxycortisol of 200 nmol/L was used to define normal adrenal function (20-22). Growth hormone deficiency was defined by a GH peak response to the insulin induced hypoglycemia of <3 $\mu\text{g/l}$ or by a GH peak after combined Growth Hormone Releasing Hormone + Arginine-test (GHRH/Arg test) using BMI-adjusted GH cut-offs. (24,25). When secondary amenorrhea was present for >1 year in the presence of a low serum estradiol (estradiol 0 - 200 pmol/L) with normal or low serum levels of FSH and LH, premenopausal women were classified as gonadotropin-deficient. In men, gonadotropin deficiency was defined as a testosterone level <8.0 l with and normal or low serum levels of FSH and LH (FSH 1.5 - 12.5 U/L; LH 2.0 - 9.0 U/L). Thyroid-stimulating hormone (TSH) deficiency was defined as free T₄ level below the reference range (<12 pmol/L). Hyperprolactinemia was defined by a basal serum prolactin level above the reference range (15.0 and 23 $\mu\text{g/L}$, for men and women, respectively).

Assays

In patients, serum IGF-1 concentrations were measured. From 1986 to 2005, serum IGF-1 concentrations were determined by RIA (Incstar, Stillwater, MN) with a detection limit of 1.5 nmol/l and an interassay CV less than 11%. IGF-1 was expressed as SD score for age- and gender-related normal levels determined in the same laboratory. Since 2005, serum IGF-1 concentrations (nmol/l) were measured using an immunometric technique on an Immulite 2500 system (Siemens Healthcare Diagnostics, Deerfield, IL, USA). The intra-assay variations at mean plasma levels of 8 and 75nmol/l were 5.0 and 7.5%, respectively. IGF-1 levels were expressed as SDS, using lambda-mu-sigma smoothed reference curves based on 906 controls (26,27).

FT4, TSH, LH, FSH, and PRL concentrations were measured by electrochemiluminescence immunoassay (ECLIA), using a Modular E170 (Roche Diagnostics). The maximal inter-assay CV was 5.0%. ACTH was determined by immunoluminometric assay using an Immulite 2500 (Siemens Healthcare Diagnostics, Deerfield, IL, USA). The maximal inter-assay CV was between 5.0 and 10.0%. For the measurement of estradiol, a RIA (Orion Diagnostica, Espoo, Finland) was used (CV was 6% at 70 pmol/l) with a detection limit of 20 pmol/l. Testosterone was measured using an RIA (Siemens Healthcare Diagnostics; CV was 20% at 1.0 nmol/l and 12% at 14 nmol/l). The detection limit was 0.2 nmol/l.

Statistical analysis

SPSS for Windows, Version 17.0 (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. Results are presented as mean, age and follow up are stated as median, unless stated otherwise.

RESULTS

We identified 1504 patients from the records of the radiotherapy department. We excluded 426 patients treated with TBI for hematological malignancies. Of the 1078 remaining patients, 243 patients were still alive at screening (23%). Another 130 patients did not fulfill inclusion criteria: 102 patients (9%) had progressive disease at the time of the study, 28 had other exclusion criteria. Finally, 8 patients were lost to follow up. 105 patients were enrolled in the current study.

Of this total of 105 patients, 59 patients had been assessed at the endocrine department since the beginning of their follow up period. The remaining 45 patients were invited for endocrine evaluation, of whom 24 declined, and therefore 21 new patients underwent a complete endocrine work-up (Figure 1).

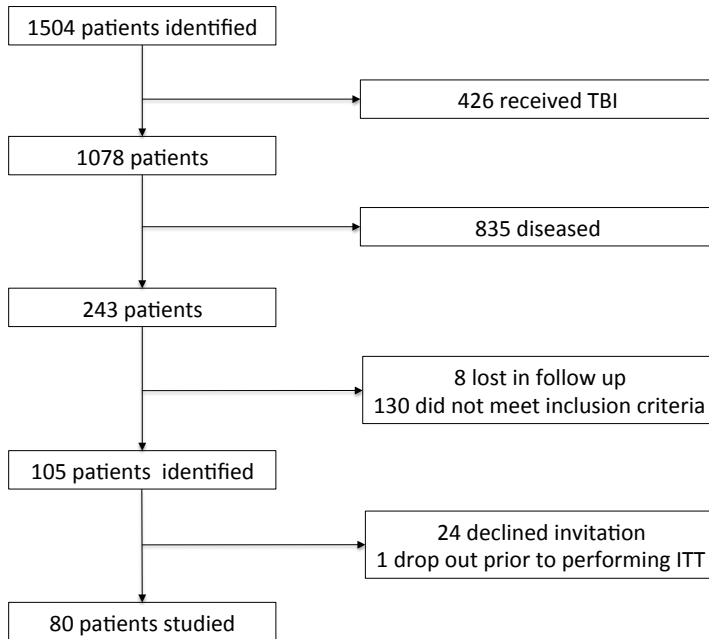


FIGURE 1.

Flowchart patient selection

TBI: total body irradiation, ITT : Insulin Tolerance Test

Patient characteristics

A total of 80 patients were enrolled in the study. Forty were treated for cerebral tumours, 15 for nasopharyngeal tumours, 25 for different tumours like meningioma, or metastasis. Median age was 47.5 years and median time of follow-up was 6 years (range 0.5-35) (Table 1.)

General assessment of Karnofsky score and ADL in general showed a normal score, in agreement with the inclusion criteria and outpatient clinic setting of this study.

For 39 patients, treated after 2007, the planning software calculated a estimated dose to the pituitary, from all other patients, if possible, retrospective dose calculations were made from the the isodose lines plotted on 2D images and on plain x-rays of the skull or from 2004 onwards CT images were used. Mean radiation dose was 56.27 Gy (range 40-70).

For 39 patients, treated after 2007, the planning software calculated an estimated dose to the pituitary, mean 31.7 Gy. Stereotactic radiotherapy was fractionated and performed elsewhere, it was not possible to retrieve the radiation plans.

TABLE 1 Patient characteristics

Baseline characteristics	Number of patients (n=80)
Diagnosis (n):	
Cerebral tumor	40
Nasopharyngeal tumor	15
Metastasis	2
Meningioma	14
Other	9
Radiotherapy (n):	
Conventional	77
Stereotactic	3
Mean Dose Rtx (Gy)	56.3 (40.0-70.0)
Median Age (years)	47.5 (18.6-89.7)
Follow up	6.0 (0.5-35.0)

Other tumours: Chondrosarcoma n=2, Ethmoidcarcinoma n=1, Arachnoidsarcoma n=1, Osteosarcoma n=1, Parachordoma n=1, Haemangiopericytoma n=1, Non-Hodgkin Lymphoma n=1. Gy; Grey, Rtx; Radiotherapy

Endocrine assessment

No adverse events occurred during the insulin tolerance test.

Of the total of 80 patients, fifty patients (62%) were diagnosed with any form of hypothalamic-pituitary insufficiency. When patients with isolated hyperprolactinemia (n=9) were excluded, the prevalence of any pituitary insufficiency was 51%. Pituitary insufficiency was present in 16 patients within 2 years after irradiation. This number increased to 23/49 patients (47%) after 5 years and 27/45 (60%) after 10 years. Pituitary insufficiency was present in 31/35 patients (89%) with a follow-up duration of at least 15 years.

Of the 21 patients first tested during this cross-sectional study, 9 (43%) were found to have any form of pituitary insufficiency; including previously undiagnosed symptomatic pituitary insufficiency.

Growth hormone- IGF-1 axis:

Severe GH deficiency (GHD) was documented in 27 patients (33%).

In 70% IIT was performed, 18 patients did not undergo dynamic testing and were diagnosed with GHD using serum IGF-1 followed by calculating the standard deviation

of the value in the age- and sex-specific reference range $<-2SD$ in addition of 2 other failing pituitary hormones. Duration of follow up before diagnosing GHD was 4,5 years after irradiation (0,5-35 years) in the 59 patients known on the outpatient clinic of the endocrinology department

Hypothalamic-Pituitary-Adrenal-axis:

Secondary adrenal insufficiency was diagnosed in 25 patients (31%). In 73% (n=59) of the patients tested for HPA-axis IIT was performed, 7 (12%) were diagnosed with secondary hypocortisolism with IIT. Secondary adrenal insufficiency was diagnosed in the other patients with the ACTH test (n=4), the CRH test (2), the Metyrapon test (n=4). Duration of follow up before diagnosing cortisol deficiency was after 6 years (range 0.5- 24 yrs) in the 59 patients known on the outpatient clinic of the endocrinology department.

Gonadal axis

Hypogonadotropic hypogonadism was present in 20 patients (25%) of the 59 patients known and the duration of follow up before diagnosis was 7 years (range 0,5-16). Hypogonadotropic hypogonadism in the presence of hyperprolactinemia was transient and resolved after initiation of anti-dopaminergic treatment and these patients were not classified as having gonadal deficiency.

Pituitary-Thyroid axis

Central hypothyroidism was observed in 11 patients (14%), as defined by a low Ft4 and and inappropriate TSH. TSH deficiency was seen after a duration of follow up of 5.1 (1.5-10.3) years after irradiation in the 59 patients known on the outpatient clinic of the endocrinology department.

Prolactin

Hyperprolactinemia was seen in 17 patients (21%) of the patients known to the outpatient clinic after a follow up of 2,5 (0,5-21) years, but was symptomatic in only 2 patients (females).

Disease specific pituitary insufficiency.

Cerebral tumours

40 patients (22 males) were treated for primary cerebral tumours with a mean dose of 55.8 Gy \pm 4.4 Gy, range 46-61 Gy. Eleven patients (28%) were GHD, 9 (27%) suffered

from hypocortisolism, 13% were TSH deficient, and 13% had hypogonadotropic hypogonadism. Hyperprolactinemia was seen in 27% of patients, none were symptomatic.

Nasopharyngeal carcinoma

Fifteen patients (11 males) were treated for nasopharyngeal carcinoma. Mean radiation dose was 63 Gy \pm 9.8 range 40-70 Gy. 2 patients from the group never tested prior to this study turned out to have symptomatic pituitary insufficiency. In the total of 15 patients treated for nasopharyngeal carcinoma 3 (21%) were GHD, 5 (33%) were HPA deficient. TSH deficiency was seen in 20%, whereas 40% of patients were hypogonadal and 40% suffered from hyperprolactinemia. Two patients (females) were symptomatic and were subsequently treated with cabergoline with reinstatement of the gonadotroph function.

Other tumours

Twenty-five patients were treated for various other tumours with a mean dose of 53 Gy \pm 7 with a range of 40-69 Gy. In patients treated for cerebral metastases or other tumours 52% were GHD, 40% HPA deficient, 28% TSH deficient, 36% were hypogonadal and 28% of patients had hyperprolactinemia.

DISCUSSION

This study, using optimal endocrine testing to evaluate pituitary function in a group of adult patients after cranial radiotherapy for head and neck tumours with the pituitary within the radiation field, showed that pituitary insufficiency was highly prevalent, since 62% of the patients were diagnosed with any form of hormone deficiency. These findings add up to the presently available reports (14,17,28). The additional value of the present study is the standardized approach of stringent endocrine testing and long-term follow up in the majority of patients. In addition, the long-term follow-up enabled to produce an overall timeframe showing that pituitary insufficiency of any form was present in 55% of the cases within 5 years after radiotherapy, and amounted to 75% and 90% of the patients after 10 and 15 years, respectively. Another study following the same testing protocol reported a slightly lower rate of pituitary deficiencies in patients irradiated for non-pituitary brain tumours in adulthood (28). The lower rate of deficiencies was mainly driven by the approximately 20% of patients with diagnosed as adrenal insufficient, which can be explained, at least in part, by the use of different cut of values for the ITT (500 nmol/L *vs* 550 nmol/L in our hospital). A similar pattern of

radiation-induced pituitary insufficiency with a prevalence of 38% within 32 months of cranial irradiation was reported by Madaschi and colleagues (17).

This retrospective study, as others, suffers from several limitations. We fully acknowledge the fact that the patients from the Endocrinology department (n=59) studied in the present study reflect a very selected cohort since they were actively referred. A large number of patients from our registry were deceased, due to their malignancies or had progressive disease and were not tested at time of the study, which largely influences the population at risk to develop pituitary insufficiency. In addition, concurrent medication use like corticosteroids for the treatment of cerebral edema or already diagnosed and treated primary thyroidal or gonadal failure precludes complete testing of pituitary function in a significant number of cases (29). We acknowledge the fact that the patients studied in the long-term in the present study reflect a selected cohort since they were actively referred. Although we screened the files of all eligible patients treated with cranial radiation (Figure 1) and invited all patients alive with reasonable life expectancy, we were only able to study a minority of all irradiated patients (n=80). Of note, 59 patients treated with cranial radiotherapy at our center was actively referred for endocrine testing. However these patients did not differ from the patients actively recruited in terms of pituitary deficiencies, since pituitary insufficiency was present in 43% of cases after a mean follow up of 4.8 ± 3.2 years after radiotherapy (range 1-10 years). However, despite the high level of heterogeneity in this study, as in the other available studies on this subject, and the methodological flaws, the prevalence of pituitary insufficiencies is significant and clinically relevant. Despite the lack of prospective data, this condition merits a much greater awareness of all health care providers involved, including the development of recommendations or guidelines.

Lastly, the use of different radiation schemes and patient cohorts, creating a very diverse cohort. The degree of pituitary deficiencies depends on the radiation dose delivered to the hypothalamic/pituitary region. Previous studies have shown that 7- 24 Gy as used for the treatment of haematological malignancies result in growth hormone deficiency only (18,30). The incidence of multiple deficiencies increases in time and with higher dosages due to the radiation induced changes to the DNA as well as indirectly by production of free radicals from intracellular water molecules (31,32). These radiation-induced changes can cause direct lethal effects or will accumulate to sublethal effects that will restrict potential cell replication. Cell death after radiation occurs in the mitotic phase of the cell cycle providing the explanation for the delayed onset of hormonal failure in slowly replicating tissue, like neuroendocrine tissues of the hypothalamic and pituitary (33). Furthermore, radiation may also induce tissue damage and dysfunction through chronic inflammation and release of pro-inflammatory cytokines, compromising endothelial function by increasing endothelial proliferation and collagen synthesis (31-34). We selected a threshold of 20 Gy based on data from historical cohorts indicating that a total dose of 7- 24 Gy delivered to the pituitary/hypothalamus region, may

cause growth hormone deficiency only, whereas dosages as high as 50-60 Gy will most certainly cause multiple pituitary hormone deficiencies (30). On the basis of the current data and other studies we consider the chance of developing hypopituitarism with pituitary doses > 20 Gy high enough to justify endocrine follow-up.

The presence of pituitary insufficiency *per se* is associated with a decrease in quality of life as well as an increase in morbidity and mortality (35,36). Although available studies have some limitations, because studies are small sized, retrospective nature and use different diagnostic criteria to study pituitary function, it is clear that patients treated with cranial irradiation are at increased risk to develop pituitary insufficiency and that this easily treatable side effect can not be neglected. Therefore, although we advocate routine endocrine testing in every patient after cranial radiotherapy, the decision to proceed to pituitary testing with stimulation tests should be individually based. Diagnosing hypopituitarism can be challenging since it might be difficult to distinguish between symptoms of hypopituitarism or radiation/chemotherapy induced changes. Furthermore biochemical findings might not be that clear e.g the finding of low FT4 combined with an abnormally low TSH makes a diagnosis of central hypothyroidism obvious. However milder defects, characterized by FT4 levels still within the normal range, but decreasing following radiotherapy may be also clinically relevant and remain undiagnosed (37). Rose et al. reported on the fact that in childhood cancer survivors many patients with mild thyrotrope insufficiency were not diagnosed on the basis of basal thyroid function screening (38). Patients treated for malignancies often complain of irritability, anxiety and depression as well as fatigue (39-41). In patients with hypopituitarism, for example with growth hormone deficiency, the psychological symptoms include decreased energy levels, social isolation, and lack of positive well being, depressed mood and increased anxiety (42). Whereas physical complaints like fatigue and decreased libido can be seen due to hormonal dysfunction as well. Even for endocrinologists, it remains very difficult to distinguish between hypopituitarism and general complaints after radiation or chemotherapy. Nevertheless, endocrine replacement is able to improve complaints caused by hypopituitarism. For example 2 of the 21 patients who were invited for endocrinological screening were already under long-term treatment for depression and their decrease libido was considered secondary to depression instead of hypogonadism and 2 patients cured from nasopharyngeal carcinoma even presented in the past with unexplained hypotension before the diagnosis of panhypopituitarism was made. This exemplifies the need for endocrine testing in any of these patients since detection purely based on anamnesis will not be sufficient.

We propose a follow up schedule according to both the total radiation dosage delivered to the pituitary and the expected life expectancy that is currently incorporated in our standard protocols in the follow up postcranial radiation (Figure 2). For all patients treated by cranial radiotherapy an estimated dose to the pituitary should be calculated. If this estimated dose to the pituitary is > 20 Gy, depending on the physical condition

of the patient endocrine follow up is mandatory. How to proceed within the first years after radiation has to be tailored for each patient personally, since this is a very complex and fragile patient cohort. A follow up protocol as proposed needs to be validated prospectively, but this matter should be addressed since pituitary insufficiency is highly prevalent in adult patients treated with cranial radiotherapy with the pituitary within the radiation field. Replacement of endocrine deficits is associated with improvement of quality of life and prevents severe complications such as Addisonian crises. Therefore, we advocate that all patients with a life expectancy of more than 1 year should be referred and followed for the development of pituitary insufficiencies.

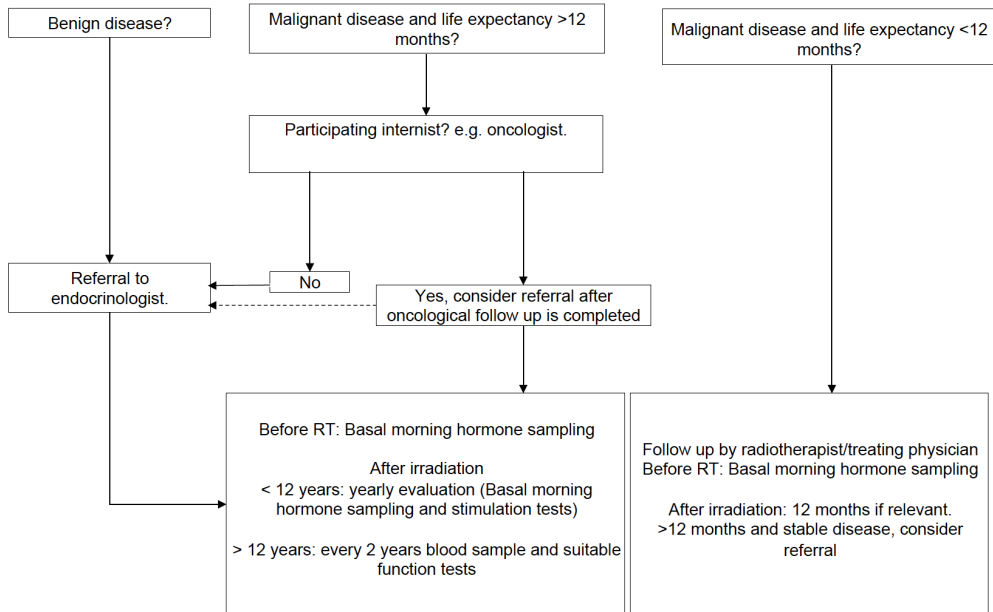


FIGURE 2.
Proposed follow up

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