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Occurrence of pituitary hormone deficits in relation to both pituitary and hypothalamic doses after radiotherapy for skull base meningioma

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Abstract

Context: Little accurate information is available regarding the risk of hypopituitarism after irradiation of skull base meningiomas.

Design: Retrospective study in a single centre.

Patients: 48 patients with a skull base meningioma and normal pituitary function at diagnosis, treated with radiotherapy (RXT) between 1998 and 2017 (median follow-up of 90 months).

Measurements: The GH, TSH, LH/FSH and ACTH hormonal axes were evaluated yearly for the entire follow-up period. Mean doses delivered to the pituitary gland (PitD) and the hypothalamus (HypoD) were calculated, as well as the doses responsible for the development of deficits in 50% of patients after 5 years (TD50).

Results: At least one hormone deficit was observed in 38% of irradiated patients and complete hypopituitarism in 13%. The GH (35%), TSH (32%) and LH/FSH axes (28%) were the most frequently affected, while ACTH secretion axis was less altered (13%). The risk of hypopituitarism was independently related to planning target volume (PTV) and to the PitD (threshold dose 45 Gy; TD50 between 50 and 54 Gy). In this series, the risk was less influenced by the HypoD, increasing steadily between doses of 15 and 70 Gy with no clear-cut dose threshold.

Conclusions: Over a median follow-up period of 7.5 years, hypopituitarism occurred in more than one third of patients irradiated for a skull base meningioma, and this prevalence was time- and dose-dependent. In this setting, the risk of developing hypopituitarism was mainly determined by the irradiated target volume and by the dose delivered to the pituitary gland.

KEYWORDS
brain tumour, endocrine deficit, hypopituitarism, hypothalamus, pituitary, radiotherapy, skull base meningioma

1 | INTRODUCTION

The hypothalamic-pituitary (HP) hormonal axis plays a crucial role in the regulation of endocrine functions. HP insufficiency can occur after cranial radiotherapy treatment (CRT) when the HP region falls within the radiation field. Several studies have been published on childhood patients treated by radiation therapy (RT) for a brain tumour who subsequently developed deficiency of growth hormone

(GH) or of all other HP hormonal axes.[1-3] Hormonal deficiencies were also reported after high-dose irradiation (>60 Gy) of head and neck cancers such as nasopharyngeal tumours,[4] as well as in patients with a pituitary tumour or craniopharyngioma treated with radiotherapy.[5-8] Despite the well-recognized risk of pituitary hormone deficits following CRT, little accurate information is available regarding their prevalence and the threshold radiation doses, which are critical at the hypothalamic and pituitary levels,[9] especially in the case of skull base meningioma. Thus, current recommendations propose a yearly monitoring of endocrine functions, whatever dose levels received by HP structures.

In this monocentric study, we analysed the endocrine outcome of patients irradiated for a skull base meningioma, with the aim to provide new information about the dose- and time-dependant relationships between hypothalamic and pituitary irradiation and the risk of developing pituitary hormone deficits.

2 | MATERIAL AND METHODS

2.1 | Patients

Between 1998 and 2017, 64 adult patients were treated by fractionated radiotherapy in our institution for a skull base meningioma (including optic nerve sheath, cavernous sinus, anterior clinoid and spheno-orbitar localizations). Twelve patients with insufficient follow-up data were excluded, as well as four patients with hypopituitarism already present at diagnosis. The study therefore included 48 patients. Not all patients had interpretable data for all hypothalamic-pituitary hormone axes, mainly because of an interfering condition or treatment (ie 8 patients with primary hypothyroidism, two patients with a previous thyroidectomy, 6 women taking oestrogen-progestin treatment and one treated with tamoxifen). Thus, the number of evaluable patients was as follows: thyroid-stimulating hormone (TSH) axis: $n = 38$, growth hormone (GH) axis: $n = 46$, gonadotrophins (LH/FSH) axis: $n = 39$ and adrenocorticotrophic hormone (ACTH) axis: $n = 48$. Hormonal and radiological data were recorded at the time of diagnosis and then yearly for the entire period of follow-up (median: 90 months; range: 17-217 months).

2.2 | Endocrine assessment

Blood samples were taken between 08:00 and 9:00AM in a fasting state. Serum or plasma hormonal concentrations (TSH, free thyroxine (fT_4), morning cortisol and ACTH, insulin-like growth factor 1 (IGF-1), LH, FSH, prolactin, oestradiol in women, total testosterone in men) were assessed by classical assays routinely used in the biochemistry laboratory of the hospital. To correct for the variations in assay techniques and standards used over time, all hormonal results were expressed relative to the normal range. Table 1 outlines the criteria used to define the presence of a deficit in each of the evaluated pituitary hormonal axes. A clinically significant ACTH deficit was diagnosed when morning serum cortisol value was below the value of 138 nmol/L, as previously proposed,[10] while the diagnosis of GH deficiency relied on serial IGF-1 measurements. In some patients ($n = 16$), an insulin stimulation test (ITT) was also performed and confirmed GH deficiency in 10 and ACTH deficiency in 6 patients. In our real-life practice, GH dynamic testing is performed only in patients with at least one other pituitary deficit and who would be candidates for GH treatment. When fT4 and cortisol concentrations were judged as significantly low and indicative of deficit, the value

TABLE 1 Criteria used to define pituitary hormone deficits

Hormonal deficit	Hormonal testing	Criteria
TSH deficit	*TSH and fT4*	Low fT4 with low/normal TSH or a more than 20% decrease in fT4 during follow-up compared to baseline (based on ETA criteria of central hypothyroidism)[16]
GH deficit	*IGF-1*, *ITT*	GH peak response <3.0 μg/L to ITT or IGF-1 falling below the lower limit of normal range with at least one other deficit
LH/FSH deficits		
Men	*LH*, *FSH*, *Testosterone*	Low morning total testosterone with low LH/FSH values and symptoms of hypogonadism
Premenopausal women	*LH*, *FSH*, *oestradiol*	Amenorrhoea and low LH/FSH/oestradiol values
Postmenopausal women	*LH*, *FSH*	LH/FSH values below the normal postmenopausal range
ACTH deficit	*cortisol*, *ACTH*, *ITT*	Morning cortisol below 138 nmol/L[10] with low/normal ACTH; cortisol peak response <450 nmol/L at ITT

Abbreviations: ACTH, adrenocorticotrophic hormone; FSH, follicle stimulating hormone; fT4, free thyroxine; GH, growth hormone; IGF-1, insulin-like growth factor 1; ITT, insulin tolerance test; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

was first confirmed in a separate blood sample before starting hormonal replacement therapy. The time between the end of irradiation and the first appearance of each deficiency was reported in months. No patient was taking drugs (such as opioids or neuroleptics) that may have significantly affected the hormonal evaluation.

2.3 | Cranial radiation therapy

Among the 48 patients, 15 had been treated between 1998 and 2004 by a three-dimensional technique on a linear accelerator (3D-RT), while 33 were treated between 2005 and 2017 by intensity-modulated radiation therapy (IMRT) on a Tomotherapy machine using a helicoidal treatment delivery. Patients were immobilized with a thermoplastic 3 point mask. Contrast-enhanced computed tomography (CT) scan and magnetic resonance imaging (MRI) were performed on all patients to delineate the meningioma and the organs at risk. The gross tumour volume (GTV)[9] encompassed the meningioma itself, while compensation for geometrical uncertainties was ensured by an isotropic GTV expansion of 3 mm defining the planning target volume. (PTV). CRT was optimized using dedicated treatment planning systems (TPS) such as HELAX or Tomotherapy TPS for 3D and IMRT treatments, respectively. The total radiation dose ranged from 50.4 to 61.2 Gy delivered in daily fractions of 1.8 Gy. The following data were collected: GTV (mm^3), PTV (mm^3), minimal dose received by 95% of the PTV (D95 PTV in Gy), mean dose given to the pituitary (PitD in Gy), mean dose given to the hypothalamic area (HypoD in Gy) and treatment duration (days). We also subdivided patients according to the PitD being <or ≥45 Gy (cut-off based on a consensus of the European Particle Therapy Network[11]) or according to the HypoD being <or ≥20 Gy (cut-off defined according to the study by Vatner et al.[9]).

2.4 | Statistical analyses

Statistical analyses were performed using the IBM SPSS Statistics version 25.0 software. Continuous variables were reported as mean ± standard deviation, or as median and range between percentiles 5 and 95 (P5-P95) when the distribution was not symmetric. Normality was however usually assumed for a sample size ≥30 according to the central limit theorem. Continuous variables were compared using unpaired the Student t tests or ANOVA with multiple comparison tests. Discrete variables were compared using the chi-square test. Correlations were performed by Pearson's test, while cumulative incidence curves of hormonal deficits over time were calculated by the Kaplan-Meier method and comparisons of median incidence estimates between groups were performed using the log-rank test.

We also computed normal tissue complication probability (NTCP) curves for the occurrence of the different hormonal deficits at 5 years as a function of the PitD and HypoD, using univariate Cox regression analyses. These NTCP curves allowed us to calculate the radiation doses to the pituitary or the hypothalamus, which were responsible for the development of a particular deficit 5 years after RT in 50% of patients (TD50 in Gy). The NTCP curve for ACTH deficit as a function of PitD was approximated by a univariate logistic regression. Aberrant results were indeed obtained with Cox regression probably due to low event per variable ratio in this category.[12] Finally, a multivariate Cox regression analysis was carried out to investigate clinical and dosimetric predictors of hypopituitarism. Variables with a p-value <.20 in univariate analysis were included in the final multivariate model. In the case of strong correlation between two variables (Pearson's coefficient >0.8), the less significant one was excluded. Proportional hazards assumption was verified by analysing Schoenfeld residuals as a function of Napierian logarithm of time. A p value <.05 was considered statistically significant.

3 | RESULTS

3.1 | General characteristics of the patients

Patient characteristics at diagnosis are shown in Table 2 (n = 48; mean age: 49.2 years; three men and 45 women; sex ratio 1:15). Mean body mass index (BMI) was 28, and there was no difference between patients who developed or not a pituitary deficit (data not shown). Among the 45 women, 22 (46%) were postmenopausal. Five premenopausal and one postmenopausal woman were on oral oestrogen-progestin treatment, which was discontinued at the time of the diagnosis. One patient received adjuvant tamoxifen for breast cancer in complete remission. Mean D95 PTV dose was 51.7 ± 1.8 Gy (extreme values: 47.7–58.8 Gy), and mean duration of treatment was 46 days [36-69 days]. The median PitD was 48.9 Gy (range: 6.0–55.1 Gy) while the median HypoD was 15.8 Gy (range: 2.0-51.1 Gy). Of the 48 patients, 10 (21%) had a partial response to radiotherapy, 37 (77%) remained stable and only one progressed.

3.2 | Cumulative overall incidence of pituitary hormonal deficits over time

We observed that 30 patients (62%) did not present any deficit during a median follow-up period of 90 months (range: 17-217 months), while 18 (38%) developed at least one deficit. Four patients had only one deficit, six patients had two deficits, two patients had three deficits and six patients (13%) had a complete anterior hypopituitarism. When considering each hormonal axis individually, at least 16/46 patients (35%) developed GH deficiency after a median follow-up period of 23 months (4–78), 12/38 patients (32%) developed TSH deficiency after a median period of 23 months (4–58), 11/39 patients (28%) had gonadotrophin deficiency after a median period of 26 months (11–72), and only 7/48 patients (15%) were diagnosed with severe ACTH deficiency after a longer median period of 60 months (12–110). Hyperprolactinaemia was observed in 5/39 (11%) patients and persisted throughout the follow-up period.

TABLE 2 General characteristics of the study population at diagnosis and characteristics of irradiation

	All patients ($n = 48$)
Age (years)	49.2 ± 12.0
Sex ratio (men/women)	3/45
Body mass index (kg/m²) ($n = 37$)	28.0 ± 5.9
Meningioma localization	
Optic nerve sheath	15/48 (31%)
Cavernous sinus	10/48 (21%)
Spheno-orbitar	12/48 (25%)
Anterior clinoid	11/48 (23%)
Irradiation procedure	
3D-RT	15/48 (31%)
IMRT	33/48 (69%)
GTV (mm³)	8.0 (1.0–70.0)
PTV (mm³)	24.4 (4.3–118.5)
PitD (Gy)	48.9 (11.7–54.5)
HypoD (Gy)	15.8 (3.1–50.5)
D95 PTV dose (Gy)	51.7 ± 1.8

Note: Abbreviations: 3D-RT, three-dimensional irradiation; D95 PTV, dose received by 95% of the PTV (see Material and methods section for definition); GTV, gross tumour volume; HypoD, mean dose delivered to the hypothalamic area; IMRT, intensity-modulated radiation therapy; PitD, mean dose delivered to the pituitary gland; PTV, planning target volume.

Values are expressed as proportions or as medians and [P5-P95] ranges.

Figure 1 shows the cumulative incidence curves for each pituitary hormone deficit as a function of time. Three years after irradiation, the probabilities of having developed GH (25%), TSH (23%) and LH/FSH (24%) deficiencies were similar but greater than for ACTH insufficiency (7%, $p < .05$). After 5 years, the probability of deficit appears to be slightly higher for TSH (40%) than for GH (35%) and LH/FSH (33%), while it remained lower for ACTH (10%). After a period of 10 years, GH deficiency became the most frequent deficit (49%) followed by TSH (40%) and LH/FSH deficits (39%), while the cumulated incidence of ACTH deficiency had continued to increase steadily but still remained less frequent than other hormonal deficits (22%; $P < .05$).

3.3 | Hormonal deficits according to meningioma localization and irradiation procedure

As expected from differences observed in size and vicinity to the HP axis, meningioma localization influenced the risk of developing pituitary hormonal deficits, with optic nerve sheath meningiomas exposing to a much lower risk (3/15 patients with at least one deficit over the median period of 90 months) than spheno-orbitar (5/13), clinoid (5/11) and cavernous sinus meningiomas (5/9; $p < .01$).

The proportion of patients developing any deficit was significantly higher after 3D-RT (9/15) than after IMRT (9/33; $p < .05$),

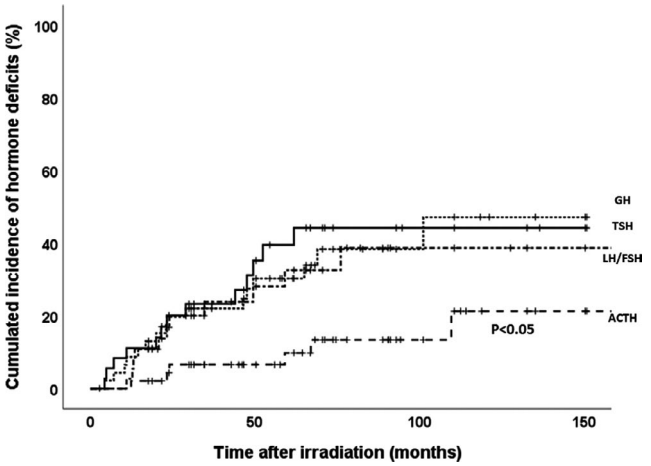

FIGURE 1 Cumulative incidence of individual pituitary hormone deficits after irradiation for a skull base meningioma in all patients ($n = 48$). $p < .05$ relates to a difference between the ACTH axis and the three other hormonal axes. ACTH, adrenocorticotrophic hormone; FSH, follicle stimulating hormone; GH, growth hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone

and this was largely explained by higher PitD and HypoD observed with the 3D-RT technique compared to the local doses delivered by the IMRT procedure, independent of the localization and size of the meningiomas.

3.4 | Hormonal deficits according to doses delivered to pituitary gland and hypothalamus

The median PitD in our cohort was 48.9 Gy (range: 6.0–55.1), and the median HypoD was 15.8 Gy (range: 2.0–52.1). As expected, a significant correlation was observed between these two parameters ($R = 0.579$; $n = 48$; $p < .001$). Among patients developing at least one hormonal deficiency, median PitD was 53.5 Gy (P5-P95: 44.4-54.5 Gy), whereas it was only 42.6 Gy [8.9–54.0] in non-deficient patients ($p < .001$). Similar values and differences were observed for each individual hormonal axis (data not shown). On the other hand, nearly half of the patients who received a PitD ≥45 Gy developed a deficiency in every evaluated hormonal axis over the study period, with the exception of the corticotrope axis (deficient in 25%), while these proportions remained much lower (0%-7%, $p < .01$) for patients receiving a lower PitD (Table 3). The probability to develop at least one deficiency over time was also significantly higher for patients with PitD ≥45 Gy than for patients having received a lower dose (Figure 2A). Similar findings were found for each axis considered separately (Figure S1).

The median HypoD was also higher in patients with at least one deficit (23.9 Gy [7.5–50.0]) than in the non-deficient patients (14.9 Gy [2.1-46.5]), although this difference did not reach statistical significance ($p = .072$). In addition, a higher proportion of patients who received a HypoD ≥20 Gy developed TSH, GH and LH/FSH deficiencies during follow-up, while the difference was not significant for ACTH (Table 3). Differences in deficit-free survival rates were

TABLE 3 Proportions of patients having developed pituitary hormonal deficits during the indicated follow-up time, according to the mean dose of radiations delivered to the pituitary gland (PitD) or to the hypothalamus (HypoD)

	PitD <45 Gy (*n* = 20)	PitD ≥45 Gy (*n* = 28)	HypoD <20 Gy (*n* = 29)	HypoD ≥20 Gy (*n* = 19)
Nb with GH deficit (%)	1/19 (5%)	15/27 (56%)[b]	6/27 (23%)	10/19 (53%)[a]
Nb with TSH deficit (%)	1/14 (7%)	11/24 (46%)[a]	4/23 (17%)	8/15 (53%)[a]
Nb with LH/FSH deficit (%)	0/15 (0%)	11/24 (46%)[b]	4/25 (16%)	7/14 (50%)[a]
Nb with ACTH deficit (%)	0/20 (0%)	7/28 (25%)[a]	2/29 (7%)	5/19 (26%)
Nb with any deficit (%)	1/20 (5%)	17/28 (61%)[b]	8/29 (28%)	10/19 (53%)[a]
Duration of follow-up (months)	73.8 [30.4-118.2]	97.2 [17.6-216.2]	83.1 [17.9-190.0]	90.4 [17.8-216.9]

Note: Values are shown as proportions or as medians and ranges.

Abbreviations: ACTH, adrenocorticotrophic hormone; FSH, follicle stimulating hormone; GH, growth hormone; Gy, Gray; HypoD, mean dose delivered to the hypothalamus; LH, luteinizing hormone; Nb, number; PitD, mean dose delivered to the pituitary gland; TSH, thyroid-stimulating hormone.

[a]$p < .05$

[b]$p < .01$, respectively, vs. the corresponding lower dose subgroup.

also observed when comparing patients who received a HypoD <or ≥ 20 Gy, whether analysing patients with any deficiency (Figure 2B) or each individual hormone deficit (Figure S2). Overall, these differences were–less significant than those observed according to the pituitary dose.

Lastly, pituitary TD50 doses at 5 years were relatively similar for the GH and TSH axes and slightly higher for the LH/FSH and ACTH axes, ranging between 50.0 and 55 Gy (Table 4 and Figure 3A). On the other hand, hypothalamic TD50 doses at 5 years were lower for the GH, TSH and LH/FSH axes (ranging between 29.2 and 31.9 Gy) but clearly higher for the corticotropic axis (54.7 Gy) (Table 4 and Figure 3B).

3.5 | Factors predicting hormone deficiency

Several factors were significantly associated with an increased risk of developing hypopituitarism in univariate analyses. These included localizations of the meningioma, regression in meningioma size after irradiation, treatment duration, PTV, PitD and HypoD. (Table 5). Age, gender and BMI had no significant influence (p value >.200). Although not statistically significant ($p = .152$), the radiotherapy technique (3D vs IMRT) was included in the final multivariate model. This analysis showed that only PitD and PTV were independent factors predicting the occurrence of hypopituitarism after CRT. Similar results were found for each hormonal axis considered individually, with the exception of gonadotrophin deficiency, which was also independently influenced by the localization of the meningioma (data not shown).

4 | DISCUSSION

The present study shows that more than one third of patients (38%) develop at least one pituitary deficit during the years following CRT for a skull base meningioma, and 13% develop complete anterior hypopituitarism. These results are similar to those reported by Madaschi et al.[6] in a series of 56 patients treated by CRT for extrasellar brain tumours, although in this study a few patients were also treated by chemotherapy. Likewise, out of 56 adult patients receiving radiotherapy for various non-pituitary brain tumours, Agha et al.[7] observed that 41% presented some degree of hypopituitarism during a median follow-up of 12 years and 7% had complete anterior hypopituitarism.

A higher overall prevalence of pituitary dysfunction was observed in a large study of 107 adult patients having received CRT for various non-pituitary brain tumours (89% after a median follow-up of 8 years),[13] as well as in a recent study of patients irradiated for a brain glioma with a mean dose of 36 Gy, mainly given to the hypothalamic area (85% after a mean follow-up of 8.2 years).[5] However, this higher frequency of deficit was only observed for GH (83%–87%) and not for the other pituitary hormones, which were deficient in only 10%-30% of the patients, as observed in our study. This discordance may be explained by several factors. First, we likely underestimated the prevalence of GH deficiency (GHD) as we did not frequently perform GH provocative testing in our patients and relied on IGF-1 which is not a sensitive marker of GHD in adults. In addition, in both studies reported by Kyriakakis et al,[5,13] many or all patients were treated for a deep brain malignant tumour by a multimodal treatment combining surgery, radiotherapy and chemotherapy which may have affected the occurrence of pituitary deficits. Moreover, striking differences in irradiation procedures do not allow a valid comparison of the biological equivalent doses given to the pituitary and hypothalamic regions, respectively, between our cohorts. It is much likely, however, that the hypothalamic area was more exposed than the pituitary gland in the two previous reports.

As also reported in most studies,[5,7,13-15] GH secretion is usually the most sensitive to the deleterious effects of irradiation on

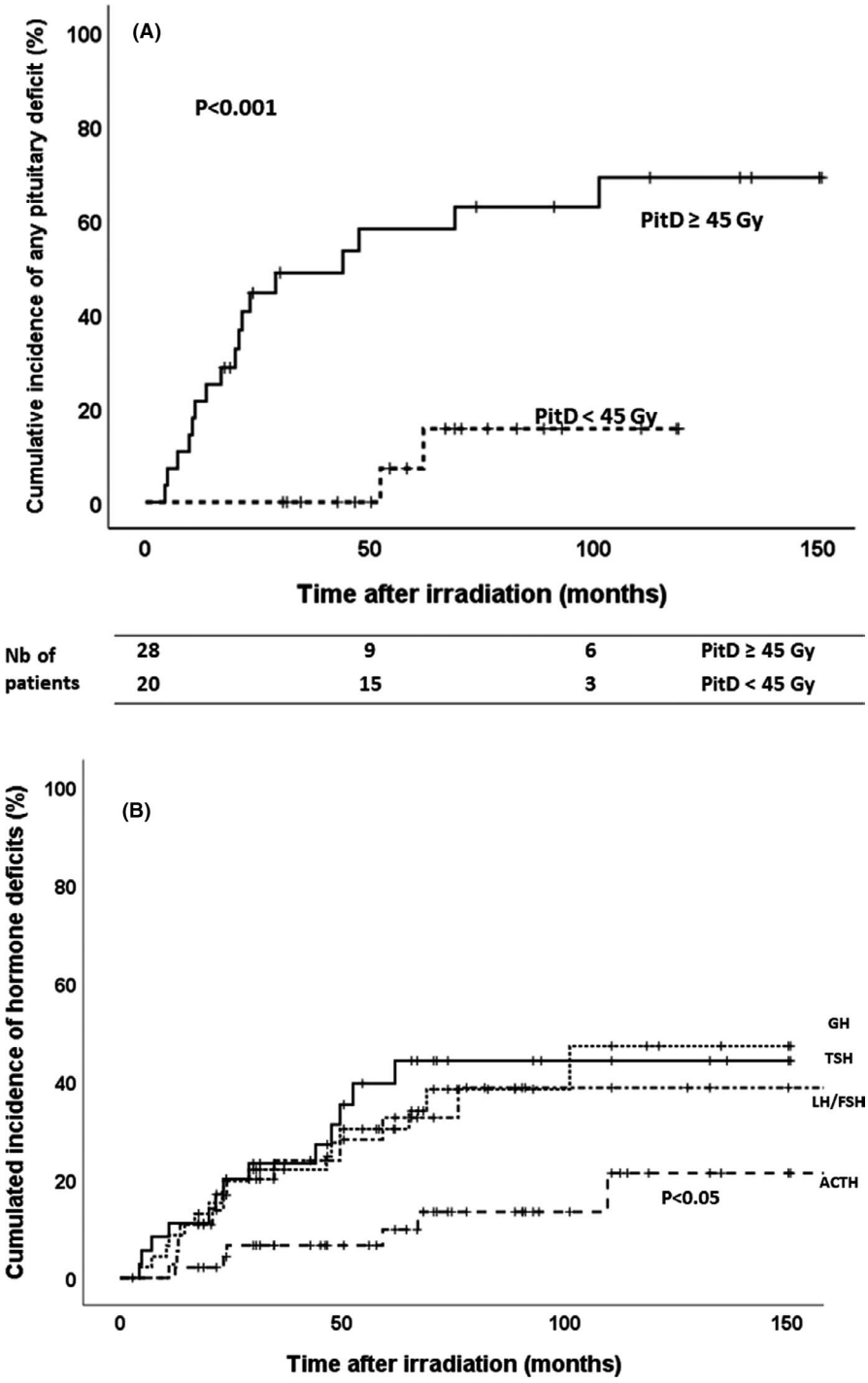

FIGURE 2 (A) Cumulative incidence of any pituitary hormone deficit after irradiation for a meningioma of the skull base according to a mean dose delivered to the pituitary gland (PitD) below 45 grays (Gy) or not. (B) Cumulative incidence of any pituitary hormone deficit after irradiation for a meningioma of the skull base according to a mean dose delivered to the hypothalamic area (HypoD) below 20 grays (Gy) or not

the HP axis and thus the first deficit to appear over time. Our results also confirm a rapid and steady increase in the proportion of GH-deficient patients during the first years after irradiation. However, as opposed to most previous reports, we also observed similar time-courses of TSH and LH/FSH deficits after skull base meningioma irradiation and similar pituitary TD50 doses, thus suggesting that these hormonal axes might be just as sensitive as the somatotropic axis at the pituitary level. Again, we must acknowledge, however, that the prevalence of GH deficiency might have been underestimated in our study for the above-discussed reasons.

In contrast, we believe that our criteria to diagnose TSH deficiency might have been more sensitive than in other studies. Indeed, we did not request the finding of a free T4 concentration below the normal range to establish the diagnosis, but also considered as hypothyroid patients with a more than 20% decrease in fT4 during follow-up compared to baseline, as recommended by the recent ETA guidelines.[16] This may explain why the prevalence of TSH deficit was high in our study compared to previously reported data.[5,6,15] Agha et al.[7] have also found similar figures, and it is well known that TSH deficiency is often underestimated, especially in the presence of a concomitant GH deficit, which reduces the conversion of T4 into T3.[17]

The corticotropic axis is clearly more radio-resistant than the other axes, and higher hypothalamic or pituitary doses (with TD50 above 50 Gy) are needed to induce a clinically significant deficit in ACTH secretion. This likely explains why no severe ACTH deficit is usually observed after low-dose irradiation of brain tumours or TBI in a children populations.[1,18]

TABLE 4 Estimates of the radiation doses delivered to the pituitary or to the hypothalamic area which induce a deficiency in each specific pituitary hormonal axis separately or in any hormonal axis, in 50% of the patients (TD50) after a follow-up period of 5 years (data derived from the Cox regression analyses performed on cumulative incidence curves)

Hormonal axis	TD50 pituitary (Gy)	TD50 hypothalamus (Gy)
GH ($n = 46$)	51.1	31.9
TSH ($n = 38$)	50.4	30.9
LH/FSH ($n = 39$)	53.0	29.2
ACTH ($n = 48$)	54.5	54.7
Any hormone ($n = 48$)	50.6	31.2

Abbreviations: ACTH, adrenocorticotrophic hormone; FSH, follicle stimulating hormone; GH, growth hormone; Gy, Grays; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

The dose thresholds used for PitD (45 Gy) and HypoD (20 Gy) were selected based on current literature.[8,9,11,19] We could indeed confirm in the present study that below an average cut-off dose of 45 Gy given to the pituitary gland, the risk of developing any pituitary deficit is very low, while it increases markedly with higher doses. Madaschi et al.[6] also observed a higher prevalence of deficits at a mean dose to pituitary above 43 Gy.

In contrast, the so-considered dose threshold of 20 Gy given to the hypothalamus was not so accurate and determinant in our study. Although we observed indeed a higher prevalence of hormone deficits when the dose received by the hypothalamic area was above this value, a substantial proportion of patients were also deficient with lower doses. Moreover, analysis of the NCTP curves, albeit performed on a limited number of patients and events, also showed that the risk of developing any hormonal deficit gradually increased for hypothalamic doses between 10 and 60 Gy, and TD50 doses are close to 30 Gy for GH, TSH and LH/FSH axes and higher, around 55 Gy, for ACTH secretion.

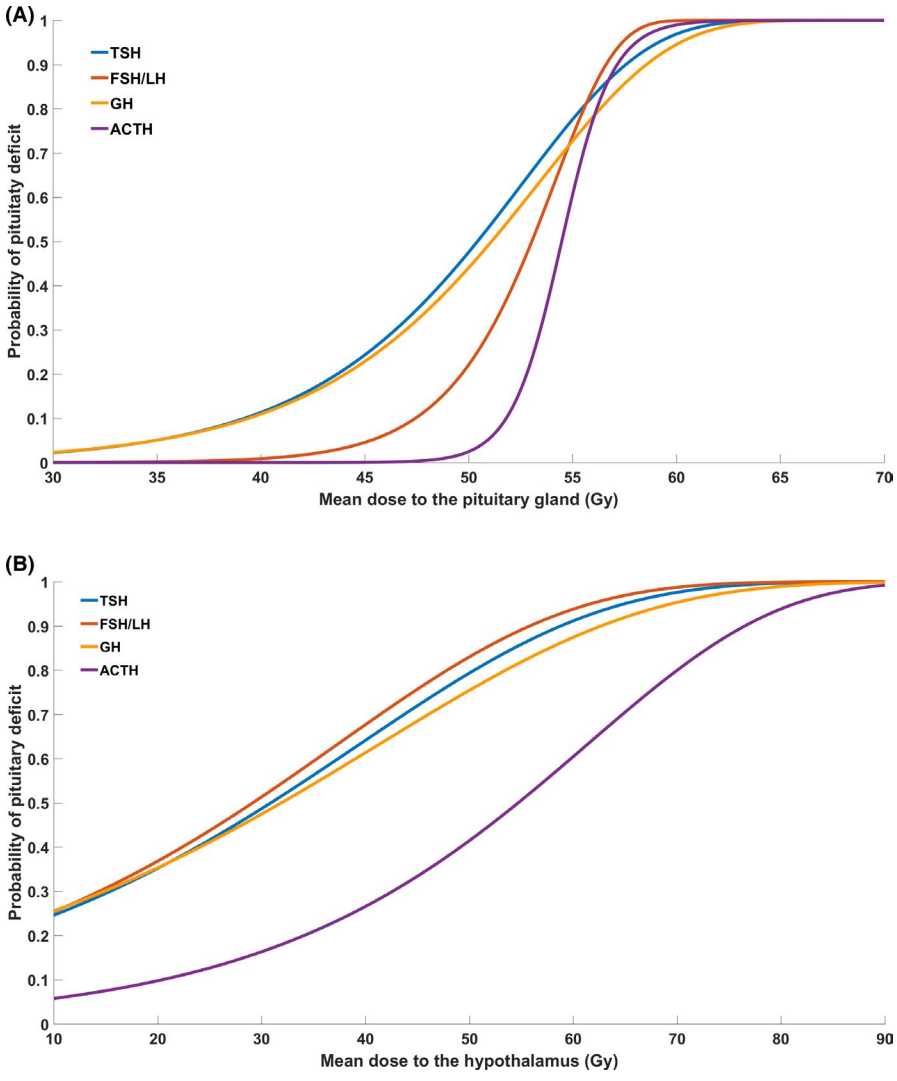

FIGURE 3 (A) NCTP modelling of the mean dose to the pituitary (PitD) according to the hormonal deficits appearance at 5 years. ACTH, adrenocorticotrophic hormone; FSH, follicle stimulating hormone; GH, growth hormone; LH, luteinizing hormone; NTCP, normal tissue complication probability; TSH, thyroid-stimulating hormone. (B) NCTP modelling of the mean dose to the hypothalamus (HypoD) according to the hormonal deficits appearance at 5 years. ACTH, adrenocorticotrophic hormone; FSH, follicle stimulating hormone; GH, growth hormone; LH, luteinizing hormone; NTCP, normal tissue complication probability; TSH, thyroid-stimulating hormone

TABLE 5 Uni- and multivariate regression analyses of factors predicting the occurrence of hypopituitarism (any deficit) after radiotherapy for a skull base meningioma

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Meningioma localization[a]	4.012	(0.948–16.98)	.059	-	-	NS
Duration of RT (days)	1.101	(1.017–1.193)	.018	-	-	NS
PTV (cm^3)	1.013	(1.002–1.023)	.018	1.013	(1.001–1.026)	0.038
PitD (Gy)	1.170	(1.034–1.324)	.013	1.136	(1.012–1.275)	0.031
HypoD (Gy)	1.035	(1.002–1.068)	.037	-	-	NS
Regression of the meningioma	3.019	(1.166–7.814)	.023	-	-	NS
3D-RT vs. IMRT	0.507	(0.2–1.285)	.152	-	-	NS

Abbreviations: 3D-RT, three-dimensional radiation therapy; CI, confidence interval of the hazard ratio; Gy, Grays; HR, ratio; HypoD, mean dose delivered to the hypothalamus; IMRT, intensity-modulated radiation therapy; PitD, mean dose delivered to the pituitary; PTV, planning target volume; RT, radiotherapy.

The indicated HR is calculated for a localization in the cavernous sinus by comparison with optic nerve sheath meningioma; spheno-orbitar localization had a HR of 2.287 and clinoid localization had a HR of 2.412 relative to the optic site.

It is hard to compare the TD50 values estimated in this study for the pituitary and hypothalamic area with similar data from the literature, as they are very scarce. De Marzi et al.[19] reported a higher pituitary dose of 65 Gy to be predictive of hormonal deficits as compared to the 50.6 Gy dose observed here. One needs to reemphasize here the fact that such numbers are rough estimates calculated on a limited number of patients with a short follow-up. There is even less data concerning the dose to the hypothalamus. Nevertheless, our results confirm that doses necessary to generate one or more deficits are lower at the level of the hypothalamus than the pituitary gland, which supports the classical view that hypothalamus is more radiosensitive than the pituitary gland.[19,20] It is also worth mentioning here that additional caution needs to be taken regarding cut-off doses as we could not separate in our patients the respective effects of pituitary vs hypothalamic irradiation given their close vicinity and a PTV usually encompassing both anatomic structures. We could indeed observe a significant correlation between the PitD and the HypoD given in our patients. This correlation might be less obvious for other tumours such as deep brain gliomas, which may be more distant from the pituitary gland and will mainly expose the hypothalamic area, as in the study reported by Kyriakakis and colleagues.[5]

The time interval between CRT and the hormonal assessment is also essential in the evaluation of pituitary deficits, and the follow-up should be continued for a very long period of time, at least 10 years, as new insufficiencies may still appear at that time. Of note, a long follow-up was obtained only in a minority of our patients and our results are mainly valid for the first five years following irradiation. During this period, the time-courses seem however to differ between the somatotropic, thyrotropic and gonadotrophic axes on one side whose deficits appear rather quickly during the first three years after irradiation, continue to develop until year 6 and then remain stable, and the corticotropic axis on the other side, whose deficiency continues to progress over the entire follow-up period.

The PTV was an independent factor predicting the appearance of any hormone deficit. As we collected data only from patients with a meningioma located near to the pituitary and the hypothalamus, we can postulate that the larger the meningioma size is, the higher will be the risk to deliver a high dose to the HP axis. We also observed that meningioma regression after RT is also a risk factor for the appearance of hormonal deficits. A radiosensitive individual pattern could be similarly expressed in meningioma cells and hypothalamic neurons or pituitary cells of patients who have a good tumoural response to RT. Genetic pathways which are linked to the development and treatment resistance of meningiomas are still currently under investigation.[21]

In conclusions, over a median period of 7.5 years, hypopituitarism occurs in more than one third of patients irradiated for a skull base meningioma, and this prevalence is time- and dose-dependent. The risk is however lower with more recent techniques (such as IMRT) allowing to spare the HP axis. The GH, TSH and gonadotrophic axes appear to be equally sensitive to the effects of irradiation at the pituitary level, while the corticotropic axis is more resistant. In such patient population, the mean dose delivered to the pituitary gland and the time after radiotherapy are the two major factors independently predicting the incidence and severity of hypopituitarism. The hypothalamic area, although highly radiosensitive, seems to be less exposed in patients with skull base meningioma and was therefore a less determinant factor in this setting.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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