Hypopituitarism : clinical assessment in different conditions

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Chapter 6

Pituitary dysfunction in adult patients after cranial radiotherapy: a systematic review and meta-analysis

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J Clin Endocrinol Metab. 2011 Aug;96(8):2330–40

Abstract

Context: Cranial radiotherapy is an important cause of hypopituitarism. The prevalence of hypopituitarism varies considerably between studies.

Objective: We conducted a systematic review and meta-analysis of reported prevalences of hypopituitarism in adults radiated for nonpituitary tumors.

Data sources: We searched PubMed, EMBASE, Web of Science and the Cochrane Library to identify potentially relevant studies.

Study selection: Studies were eligible for inclusion with following criteria: 1) cranial radiotherapy for nonpituitary tumors and/or total body irradiation for haematological malignancies 2) adult population (>18 yr old) 3) report on endocrine evaluation.

Data extraction: Data review was done by two independent reviewers. Besides extraction of baseline and treatment characteristics, also endocrine tests; definitions and cut-off values used to define pituitary insufficiency, were extracted.

Results: Eighteen studies with a total of 813 patients were included. These included 608 patients treated for nasopharyngeal cancer (75%) and 205 for intracerebral tumors. The total radiation dose ranged from 14 to 83 and 40 to 97 Gy for nasopharyngeal and intracerebral tumors, respectively. The point prevalence of any degree of hypopituitarism was 0.66 [98% confidence interval (CI), 0.55–0.76]. The prevalence of GH deficiency was 0.45 (95% CI, 0.33–0.57), of LH and FSH 0.3 (95% CI, 0.23–0.37), of TSH 0.25 (95% CI, 0.16–0.37), and of ACTH 0.22 (95% CI, 0.15–0.3), respectively. The prevalence of hyperprolactinemia

was 0.34 (CI 0.15–0.6) There were no differences between the effects of radiotherapy for nasopharyngeal *vs.* intracerebral tumors.

Conclusion: Hypopituitarism is prevalent in adult patients after cranial radiotherapy for nonpituitary tumors. Therefore, all patients treated by cranial radiotherapy should have structured periodical assessment of pituitary functions.

Introduction

Pituitary insufficiency is a late onset sequel of cranial irradiation for intracerebral and nasopharyngeal tumors or total body radiotherapy for hematological malignancies in children (1–9). In the Childhood Cancer Survivor Study (CCSS) 43% of children treated for cerebral tumors had one or more endocrinopathies (10). Consequently, structured follow-up programs for childhood cancer survivors include endocrine assessments. In the last decades, survival rates of patients treated with cranial radiotherapy for various malignancies as well as for benign tumors have improved substantially by introduction of new surgical, radiotherapeutical, and chemotherapeutical options. In contrast to the long-term survivors of cranial radiotherapy in childhood, endocrine surveillance programs have not been routinely incorporated in adults treated with cranial radiotherapy. The prevalence of hypopituitarism after cranial radiotherapy is affected by several factors. First, the time interval between radiotherapy and the assessment of pituitary function is important because the development of pituitary failure is likely to increase in time after radiotherapy (11–13). Second, hypothalamic and pituitary insufficiencies are more likely to develop with increasing radiation exposure (10;14). Finally, methodological differences between the studies with respect to endocrine evaluation, like the use of different endocrine tests with different criteria for pituitary insufficiency, will also affect the prevalence of hypopituitarism.

The aim of this study was to systematically assess the reported prevalence of pituitary insufficiency after cranial or total body radiotherapy for intracerebral tumors, nasopharyngeal tumors or haematological malignancies at the adult age.

Design

Search strategy and eligibility criteria

We searched the following databases for studies on cranial radiotherapy and pituitary failure: PubMed, Cochrane Library, Web of Science, EMBASE, CINAHL database, Academic Search Premier, and Science Direct. The search was performed on August 14, 2010.

In collaboration with a trained clinical librarian, we composed a search strategy for the above mentioned databases, focusing on radiotherapy, pituitary function, cerebral tumors and nasopharyngeal tumors. We used all relevant keyword variations, including free text words. The complete strategy is provided in the Appendix 1. Furthermore, the references of relevant articles were checked for additional articles.

Only original articles in English were included. Studies were eligible for inclusion in this review if they fulfilled the following criteria: 1) cranial radiotherapy for nonpituitary tumors and/or total body irradiation for hematological malignancies 2) >18 yr old at the time of radiotherapy 3) report on endocrine evaluation.

In case of mixed cohorts (*i.e.* including both paediatric and adult patients), patients younger than 18 yr were filtered from the results. In case of duplication of reports involving the same patient cohort the results on the different axes were combined in the analyses and tables, and only the paper with the longest duration of follow-up was included.

Data review and analysis

Initial selection of studies by title and abstract was performed by two reviewers (N.M.A-D en N.E.K.). These studies were retrieved for full assessment. All studies were evaluated by the two reviewers independently. Disagreements were resolved by consensus. Data extraction was based on data from each study provided at the population level. The definition of hypopituitarism had to be stated in the paper, including the endocrine tests used for the evaluation, definitions and cut-off values used to define

pituitary insufficiency for each axis, hormone assays and reference values provided by the authors.

Statistical analysis

The main outcome of the present meta-analysis was the pooled proportion of patients with pituitary insufficiency after cranial radiotherapy. For all studies, the proportion of patients with hypopituitarism was calculated as the number of patients with the pituitary insufficiency divided by the total number of tested patients.

Meta-analysis was performed using an exact likelihood approach. The method used was a logistic regression with a random effect at the study level (15). Given the expected clinical heterogeneity, a random effects model was performed by default, and no fixed effects analyses were performed. For meta-analysis of proportions, the exact likelihood approach based on a binomial distribution has advantages compared to a standard (DerSimonian and Laird) random effects model that is based on a normal distribution. First, estimates from a binomial model are less biased than estimates from models based on a normal approximation (15;16). This is especially the case for proportions that are close to 0 or 1. Secondly, no assumptions are needed for the exact approximation when dealing with zero-cells, whereas the standard approach needs to add an arbitrary value (often 0.5) when dealing with zero-cells. Adding values to zero-cells is known to contribute to the biased estimate of the model (17;18).

Meta-regression analyses were also performed with an exact likelihood approach. A random effects meta-regression was performed to address the question whether the tumor site (nasopharyngeal *vs* intracerebral) influences the prevalence of pituitary insufficiency. All analyses were performed with STATA 10.0 (Stata Corp, College Station, TX, USA).

Risk of bias assessment

An additional evaluation of the risk of bias was performed to identify components that could potentially bias an association between cranial radiotherapy and hypopituitarism. The following study characteristics were evaluated: 1) adequacy of exposure determination, 2) adequacy of inclusion and follow-up, and 3) adequacy of outcome determination. For exposure determination, one point was given if it was stated clearly that

the pituitary was involved in the radiation field, and one point was given if the estimated dose at the pituitary was reported. For the evaluation of inclusion of patients, one point was given for each study that included (consecutive) non-selected patients. For outcome determination, one point was given when the hormonal evaluation also included dynamic tests, and one point was given if all patients in the study were tested. Consequently, each study could attain a maximum score of 5 points. Studies that scored 0–2 points were considered to have a high risk of bias, studies with 2–3 points as intermediate risk, and studies with 4–5 points as studies with a low risk of bias.

Results

Systematic literature search

The initial search resulted in a total of 849 articles (301 in PubMed, four in Cochrane Library, 131 in Web of Science, 353 in EMBASE, 16 in CINAHL database, 27 in Academic Search Premier, and 17 in Science Direct). Of these articles, 616 were unique without duplications (Figure 1). We excluded 378 papers based on title and abstract or language, 157 studies that evaluated patients younger than 16 yr, and seven papers which were not available for evaluation. Consequently, a total of 74 potentially relevant papers were retrieved for full assessment. Of these 74 publications, 51 papers were excluded from further analysis because the studies did not fulfill one or more of the eligibility criteria.

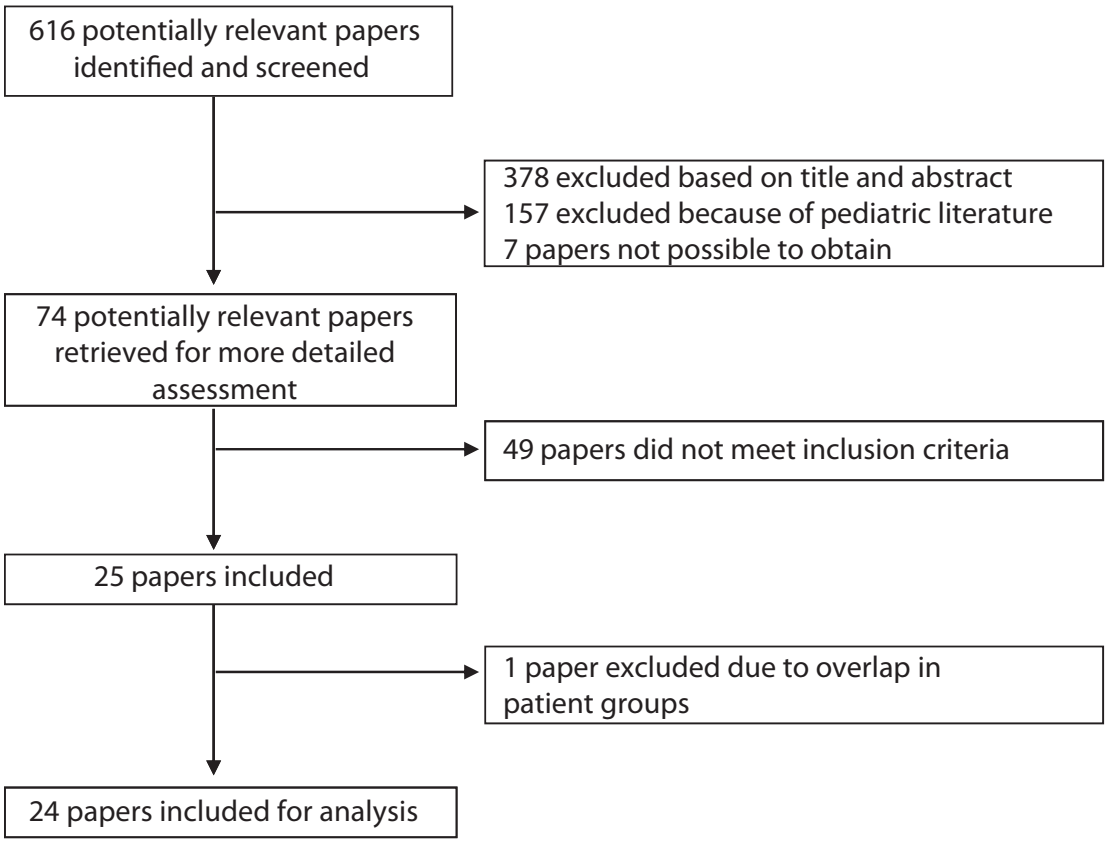

Figure 1. Flowchart of study assessment and exclusion stages

Therefore, ultimately, our search strategy resulted in 23 manuscripts meeting the inclusion criteria. However, some reports described data from the same patient cohort (19–26). In these cases, the results were combined as one study in the analysis, or the study with the longest follow-up was included. Consequently, a total of 18 studies were included in the present review, comprising 813 patients. The number of included patients per study ranged from only six (27) to 312 (20). Five studies included patients younger than 18 yr (26–30). However, in only three of these five studies (27;28;30) it was possible to obtain the numbers of patients treated after the age of 18 yr. The remaining two were included because of the low number of patients younger than 18 yr, or sub-analysis on the patient group younger than 18 yr was performed with no different outcome then the older group (Table 1).

Study characteristics

Details of the 18 included studies are summarized in Table 1 and 2. The studies were published between 1975 and 2009. Seventy-five percent of the patients (608 of 813) were treated for nasopharyngeal cancer (Table 1). The remaining 25% were treated for intracerebral tumors (Table 2). The majority of studies were cross-sectional studies with time after irradiation ranging from 4 months to 30 yr. However, the time after radiation varied considerably between individuals, even within one single study. Two studies did not report the time interval between irradiation and endocrine evaluation (28;31). None of the included papers evaluated patients treated with prophylactic body irradiation in the course of stem cell transplantation for haematological malignancies. In three reports, patient selection criteria were not stated (20;28;31), whereas four studies selected symptomatic patients by recruiting from a radiotherapy complication outpatient clinic or by inclusion of only patients suspected for any degree of hypopituitarism (21;30;32;33). For example, two studies used questionnaires on fatigue or diminished libido in combination with basal hormone samples to select patients for further endocrinological evaluation (22;28).

Table 1. Head and neck tumors

Author	Number of patients, age and gender	Tumor characteristics	Cranial irradiation (Gy)	Time since Rtx (months)	Endocrine evaluation	Bias assessment	Pituitary insufficiency per axis (%)					
							Any	*GH*	*HPA*	*TSH*	*LH/FSH*	*PRL*
Snyers, 2009(37)	Total n=32 [a] n=21 endocrine evaluation 56 (28–74) yr	Sinonasal cancer	44–66 Mean dose pituitary = 51–56 Mean dose hypothalamus = 44–52 Chemo n= 23	107 (11–253)	Basal morning serum samples, if abnormal : ITT, ACTH stim test or GHRH-arg	4	62% (13/21)	24% (5/21)	19% (4/21)	14% (3/21)	19% (4/21)	10% (2/21)
Bhandare, 2008(19)[b]	Total n=312 200M/112F n= 112 endocrine evaluation No age mentioned	Nasal cavity n=56 Nasopharynx n=119 Frontal sinus n=2 Etmoid sinus n=5 Sphenoid sinus n=34 Maxillary sinus n=59 Other n=37	Broad range: < 40 – >70 Chemo n= 40	63 (6–365)	Basal serum samples: TSH, fT_4, PRL, GH, Cortisol, LH, FSH, T If abnormal: ACTH-test, metyrapone, CRH test, ITT + vasopressin, GST, GHRH-test, Arginine-test, TRH test	2	60% (67/112)	36% (16/44)	32% (14/44)	70% (31/44)	27% (12/44)	15% (10/68)

Author	Number of patients, age and gender	Tumor characteristics	Cranial irradiation (Gy)	Time since Rtx (months)	Endocrine evaluation	Bias assessment	Pituitary insufficiency per axis (%)					
							Any	*GH*	*HPA*	*TSH*	*LH/FSH*	*PRL*
Lam, 1991(22)[c]	n=20 22M/9F M: 43.7±8.4 yr F: 36.8±9.0 yr	Nasopharyngeal	Total dose: 60 Estimated dose pituitary: 62	60	Basal serum samples: LH, FSH, PRL, TSH, T_4, T, E_2 ITT, LHRH 100 µg, TRH 200 µg	5	75% (15/20)	55% (11/20)	25% (5/20)	15% (3/20)	35% (7/20)	30% (6/20)
Woo, 1988(31)	n=11 8M/3F Age: 48(33–64) yr	Nasopharyngeal	Estimated dose pituitary: 62–67	72–240	Basal serum samples: LH, FSH, THS, T_4, cortisol, PRL, T, E_2 ITT, LHRH 100 µg, TRH 200 µg	4	82% (9/11)	90% (9/10)	18% (2/11)	45% (5/11)	55% (6/11)	27% (3 /11)
Samaan, 1987(25)[d]	Total n=166 98M/68F Age: 47(6–80) yr	Nasopharyngeal n=114 Paranasal sinus tumors n=29 Optic nerve/ eye tumors n=23	Estimated dose anterior pituitary: 57 (4–75) Estimated dose hypothalamus: 50 (11–75)	12–312	ITT, TRH 500 µg, LHRH 100 µg; Total T_4, T_3 resin uptake	5	75% (124/166)	75% (124/166)	18% (30/166)	20% (33/166)	35%/20% (58/166 FSH) (33/166 LH)	36% (60/166)

Table 1. Continued

Author	Number of patients, age and gender	Tumor characteristics	Cranial irradiation (Gy)	Time since Rtx (months)	Endocrine evaluation	Bias assessment	Pituitary insufficiency per axis (%)					
							Any	*GH*	*HPA*	*TSH*	*LH/FSH*	*PRL*
Lam, 1987(21)[e]	n=32 21M/11F n=14 dynamic testing Age: 27–50 yr	Nasopharyngeal	46–60	60–204	n=32 Questionnaires on sexual impairement, galctorroea Basal serum samples: PRL, T_4, FTI, TSH, T If abnormal: E_2, T, ITT, LHRH-test, TRH test	3	25% (8/32)	19% (6/32)	6% (2/32)	13% (4/32)	16% (5/32)	19% (6/32F)
Lam, 1986(20)[f]	n=8 1M/7F Age: 27–52 yr	Nasopharyngeal	46–61 Estimated dose to pituitary: 55–67	>60	Basal serum samples: LH, FSH, TSH, PRL, fT4, E_2, T ITT (n=2), LHRH test, TRH test, GHRH-test (n=6), CRH test (n=4)	5	100% (8/8)	50% (4/8)	50% (4/8)	50% (4/8)	25% (2/8)	88% (7/8)
Huang, 1979(33)	n=11 All females Age: 19–40 yr	Nasopharyngeal	Nasopharyngeal area: 70 Estimated dose HP area: 60–65	12–156	LHRH 25 µg	3	82% (9/11)	NR	NR	NR	82%/64% (9/11 LH) (7/11 FSH)	100% (8/8)

Author	Number of patients, age and gender	Tumor characteristics	Cranial irradiation (Gy)	Time since Rtx (months)	Endocrine evaluation	Bias assessment	Pituitary insufficiency per axis (%)					
							Any	*GH*	*HPA*	*TSH*	*LH/FSH*	*PRL*
Rosenthal, 1976(34)	n=6 All Male Age: 35–66 yr	Nasopharyngeal	55–65	12–96	Basal serum samples: T_4, TSH, FTI, T_3, cortisol, LH, FSH, GH TRH test, ITT (n=2)	3	67% (4/6)	100% (2/2)	50% (1/2)	67% (4/6)	NR	NR
Samaan, 1975(36)	n=10 7M/3F Age: 26–55 Age Rtx: 41 (8–58 yr)[g]	Nasopharyngeal	Estimated dose HP area: 50–83 50–65 to thyroid lobes (n=12)	60–240	ITT, Chlorpromazin: 25 mg, TRH test 500 µg, LHRH 100 µg, T_4, T_3 resin uptake, 24 hour 131-I thyroid uptake	4	100%	60% (6/10)	50% (5/10)	40% (4/10)	30% (3/10)	50% (5/10)

ACTH, adrenocorticotrope hormone; E_2, estrogens; F, female; FSH, follicle stimulation hormone; GH, growth hormone; GHRH, growth hormone releasing hormone; GST, glucagon stimulation test; Gy, Gray; HPA, hypothalamus pituitary axis; ITT, insulin tolerance test; LH, luteinizing hormone; LHRH, luteinizing hormone releasing hormone; N, number; NR, not reported; M, male; PRL, prolactin; Rtx, radiotherapy; T, testosterone; T_4, thyroxine; T_3, triiodothyronine;TRH, thyreotropin releasing hormone, TSH, thyroid stimulating hormone;

[a] Total population n=168, however only n=32 long term follow-up in late morbidity clinic and n=21 endocrine evaluation

[b] Same patient group as (18): Clinical hypopituitarism: 14.1% (44/312), n=68 had dynamic testing and n=23 (33.8%) had subclinical hypopituitarism

[c] Combination of results with (44) which described follow-up after 2 yrs of same cohort

[d] Part of the results were reported previously in (24). Patients were divided into 2 groups >15 yrs and <15. There was no difference between both groups in pituitary failure after 4 yrs.

[e] All patients received questionnaires; only those with suggested hypopituitarism had detailed endocrine assessment (n=14)

[f] All patients referred because of symptoms of hypopituitarism

[g] n=5 < 16 years during radiotherapy

Table 2. Primary intracerebral tumors

Author	Number of patients, age and gender	Tumor characteristics	Cranial irradiation (Gy)	Time since RTx (years)	Endocrine Evaluation	Bias assessment	Pituitary insufficiency per axis (%)					
							Any	*GH*	*HPA*	*TSH*	*LH/FSH*	*PRL*
Schneider, 2006(30)	n= 44 28 M/40 F Age: 45 (20–79) yr	Glioma n= 40 Neuroblastoma n= 1 Menigeoma n= 18 Schwanoma n= 5 Dysgerminoma n= 2 Neuroblastoma n= 1 Chondrosarcoma n= 1 Hemangiopericytoma n= 1 Oesteosarcoma n= 1	NR Chemo n=27	NR	Basal serum samples: cortisol, 24-h urinary cortisol, T_3, T_4, TSH, PRL, FSH, LH, test, E_2 GHRH-arg	2	37% (17/44)	27% (12/44)	18% (8/44)	16% (7/44)	29.5% (13/44)	7% (3/44)
Agha, 2005(35)	n= 56 28 M/28 F Age: 39.3±11.9 yr	Glioma n= 43 Meningeoma n= 5 Pinealoma n= 3 Medulloblastoma n= 2 Other n= 3	Estimated dose pituitary: 54(4–97) Chemo n=7	6	Basal serum samples: FSH, LH, TSH, T_4, PRL, IGF-I, T, E_2 ITT (n=25), Arginine stim test, ACTH stim test	5	41% (23/56)	32% (18/56)	21% (12/56)	9% (5/56)	27% (15/56)	32% (18/56)

Author	Number of patients, age and gender	Tumor characteristics	Cranial irraidiation (Gy)	Time since RTx (years)	Endocrine Evaluation	Bias assessment	Pituitary insufficiency per axis (%)					
							Any	*GH*	*HPA*	*TSH*	*LH/FSH*	*PRL*
Johannesen, 2003(28)	n= 33 18M/15F n= 25 endocrine evaluation Age Rtx: 38 (14–68) yr	Low grade glioma n= 27 High grade glioma n= 5 Anaplastic glioma n= 1	54 (45–59)	13.1 (6–25.6)	Basal serum levels If abnormal: TRH test, CRH test	3	64% (16/25)	NR	4% (1/25)	56% (14/25)	16% (4/25)	0
Popovic, 2002(29)	Total n= 22 n= 6 >18 yr	Medulloblastoma n= 4 Pinealoma n= 2	56 Estimated dose pituitary: 25–30	7.6 ± 0.7 (2–13)	ITT, GHRH-GHRP6	3	67% (4/6)	ITT: 67% (4/6) GHRH-GHRP6: 33% (2/6)	NR	NR	NR	NR
Taphoorn, 1995(38)	n= 13 9M/4F Age: 24–66 yr	Low grade astrocytoma n= 7 Low grade oligodendroma n= 6	45–61 Mean calculated dose pituitary 36(0–50)	3 (1–11.5)	Basal serum levels TRH test 200 µg GnRH test 100 µg hCRF test 100 µg GHRH 50 µg	5	77% (10/13)	31% (4/13)	62% (8/13)	0%	15% (2/13)	23% (3/13)

Table 2. Continued

Author	Number of patients, age and gender	Tumor characteristics	Cranial irradiation (Gy)	Time since RTx (years)	Endocrine Evaluation	Bias assessment	Pituitary insufficiency per axis (%)					
							Any	*GH*	*HPA*	*TSH*	*LH/FSH*	*PRL*
Constine, 1987(27) [a]	Total n=65 n=30 (>18 yr) Age: 36.5(19–65) yr	Glioma n= 43 Medulloblas n= 7 Meningioma n= 5 Ependymoma n= 4 Others n= 5 No biopsy n= 2	Various amounts n = 47 cranial Rtx n= 18 craniospinal Rtx Chemo n=8	NR	T_4 and TSH n= 65 PRL n= 47 No dynamic tests n= 35 cranial Rtx	1	NR	NR	NR	25% (7/28)	Only measured in 9 people	29% (7/24)
Mechanick, 1986(32)	n= 15 5M/10F Age: 22–59 yr	Astrocytomas n= 14 Medulloblast n= 1	40–50 to whole brain 1–22 local boost Chemo n=13	2–9	PRL n=9,T_4, T_3, T_3-resin uptake TRH 200 µg	2	60% (9/15)	NR	NR	14.3% (1/7)	NR	100% (9/9)

Author	Number of patients, age and gender	Tumor characteristics	Cranial irraidiation (Gy)	Time since RTx (years)	Endocrine Evaluation	Bias assessment	Pituitary insufficiency per axis (%)					
							Any	*GH*	*HPA*	*TSH*	*LH/FSH*	*PRL*
Harrop, 1976(26)	Total n=17 n= 8 > 18 yr Group 1 : tumors remote from the HP-area n= 5 3M/2F Group 2: tumors in hypothalamic area n= 3 1M/2F	Astrocytoma: n= 2 Meningeoma: n= 3 Angioma: n= 1 No biopsy: n= 2	40–52	6 (1–15)	ITT (n= 6), GST (n= 6), TRH (n= 8) 200 µg 250 µg Synacthen, Clomiphene stim test (n= 5), LHRH 100 µg	4	62.5% (5/8)	50% (4/8)	12.5% (1/8)	12.5% (1/8)	37.5% (3/8)	NR

ACTH adrenocorticotrope hormone; E_2, estrogens; F, female; FSH, follicle stimulating hormone; GH, growth hormone; GHRH, growth hormone releasing hormone; GST, glucagon stimulation test; Gy, Gray; HPA, hypothalamus pituitary axis; ITT, insulin tolerance test; LH, luteinizing hormone; LHRH, luteinizing hormone releasing hormone; N, number; NR, not reported; M, male; PRL, prolactin; Rtx, radiotherapy; T, testosterone; T_4, thyroxine; T_3, triiodothyronine ;TRH, thyreotropin releasing hormone, TSH, thyroid stimulating hormone;
a Evaluation galactorrhea, libido, menstrual function, texture of skin and hair, weight change, constipation, leg cramping, heat/cold intolerance. When abnormal quationaire: basal hormone levels, 2 patients did fill out questionnaire but did not proceed to testing.

Risk of bias assessment

One study was classified as high risk (received 1 point) (28), eight studies as intermediate risk (20;22;29–31;33–35), and nine studies as low risk for selection bias (21;23;26;27;32;36–39).

Radiotherapy

The radiation dose was reported in all, but one study (31) and ranged from 14 to 83 and 40 to 97 Gy in patients treated for nasopharyngeal carcinomas and intracerebral tumors, respectively. A total of nine studies (six involving patients treated for nasopharyngeal tumors and three for intracerebral tumors) also calculated the estimated dose delivered to the pituitary, ranging from 46 to 83 Gy (in patients treated for nasopharyngeal tumors) and 25 to 97 Gy (in patients with intracerebral tumors) (21;23;26;29;30;36–39).

Endocrine assessment

The overall prevalence of any degree of hypopituitarism differed considerably between the studies, ranging from 25% (22) to 100% (21;37) in studies involving patients treated for nasopharyngeal tumors, and from 37% (31) to 77% (39) in patients treated for intracerebral tumors (Figure 2, Table 1 and 2).

GH-IGF-I axis (n=724)

Fourteen studies evaluated the GH-IGF-I axis. However, in only 61% (440 of 724) of the patients the axis was evaluated using basal serum IGF-I and/or GH levels and/or a stimulation test [glucagon stimulation test, insulin tolerance test (ITT), arginine test, and combined GHRH plus arginine tes] (20–23;26;27;30–32;35–40). The prevalence of GH deficiency varied between 24 and 100%. The prevalence of 100% was assessed in one study of six patients that evaluated only two patients using ITT (35).

Hypothalamic-pituitary-adrenal (HPA) axis (n=751)

The HPA axis was evaluated in 14 studies. In only 61% (460/751) of the patients the axis was tested by basal serum cortisol levels and/or a stimulation test (CRH test, ITT, glucagon or ACTH test). Adrenal insufficiency was diagnosed in 0–50% of patients with nasopharyngeal tumors and in 3–62% of the patients with intracerebral tumors.

Hypothalamic-pituitary-thyroidal-axis (n=488)

Sixteen studies evaluated thyroid function using either basal serum hormone levels or a TRH-stimulation test. TSH deficiency was diagnosed in 26% of the patients (126/488). The prevalence rates ranged from 0 to 67% and 13 to 25% in patients with nasopharyngeal cancers and intracerebral tumors, respectively.

Hypothalamic-pituitary-gonadal axis (n=469)

The pituitary-gonadal axis was assessed in 14 studies. Hypogonadotropic hypogonadism was present in 30% (143/469): in 30–82% of cases treated for nasopharyngeal cancer and in 38–61% of cases treated for intracerebral tumors.

Hyperprolactenemia (n=502)

Prolactin levels were measured in 15 studies, documenting hyperprolactinemia in 144 of 502 patients (29%, 2–100% in patients treated for nasopharyngeal cancers, and 7–100% in patients treated for intracerebral tumors). One study did not use basal prolactin levels for definition of a prolactin secretion disturbance but defined abnormal prolactin secretion as a failure to rise more than three-fold in response to a TRH test (39). Therefore, this study was not included in the analysis on this axis.

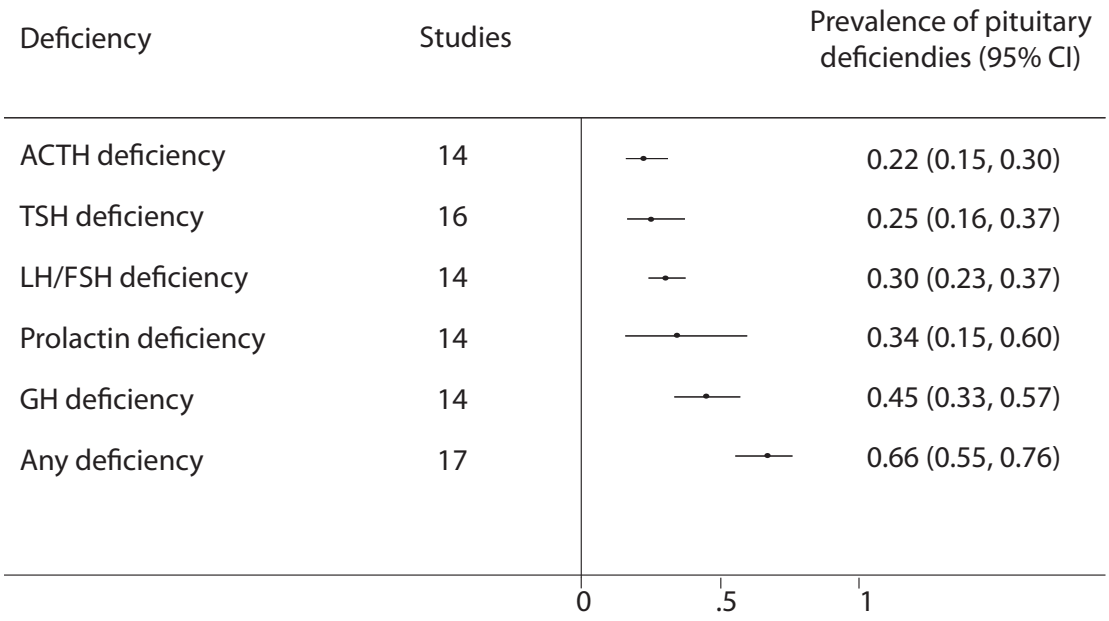

Figure 2A. Random effects meta-analysis of prevalence of pituitary insufficiency after cranial radiotherapy.

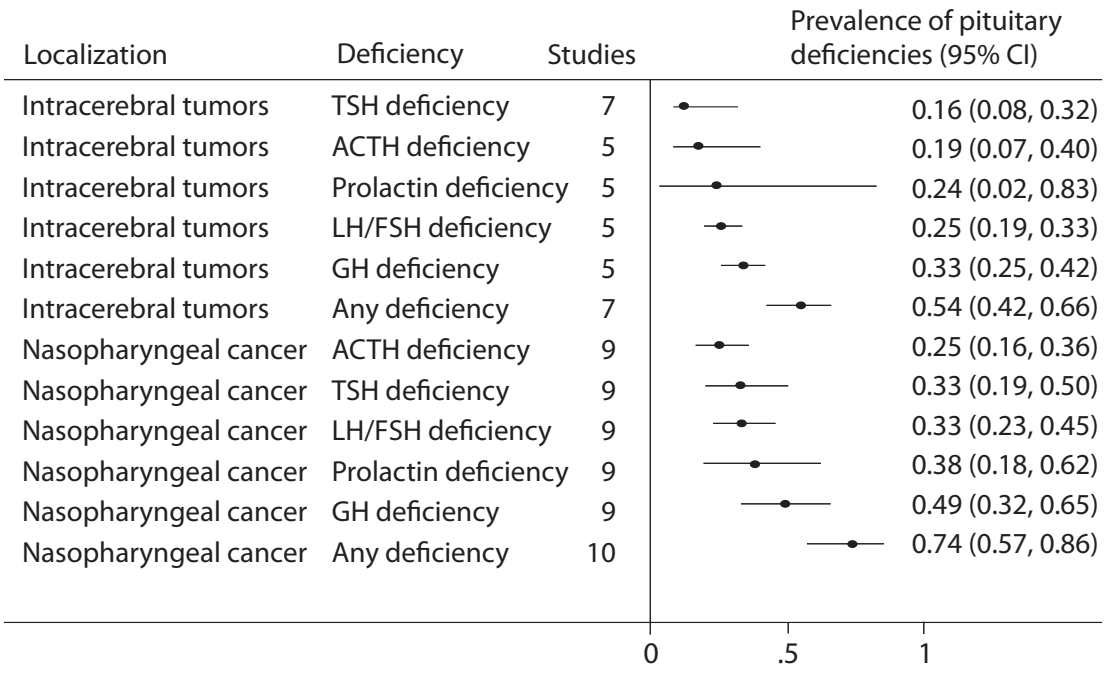

Figure 2B. Random effects meta-analysis of prevalence of pituitary insufficiency according to tumor site

Meta-analysis (Figure 2A and B)

The pooled prevalence of any degree of hypopituitarism was 0.66 [95% confidence interval (CI), 0.55–0.76). GH deficiency was the most prevalent pituitary deficiency, with a prevalence of 0.45 (95% CI, 0.33–0.57), followed by LH/FSH deficiency 0.3 (95% CI, 0.23–0.37) and TSH deficiency 0.25 (95% CI, 0.16–0.37), respectively. The prevalence of hyperprolactinemia was 0.34 (95% CI, 0.15–0.6) and ACTH deficiency had the lowest prevalence 0.22 (95% CI, 0.15–0.3).

In a random effects meta-regression, the effect of tumor localization (nasopharyngeal *vs* cerebral) on the prevalence of deficiencies was assessed. There was no statistically significant association between the probability of any pituitary deficiency ($P = 0.14$), GH deficiency ($P = 0.36$), ACTH deficiency ($P = 0.75$), TSH deficiency ($P = 0.11$) LH/FSH deficiency ($P = 0.21$) as well as hyperprolactinemia ($P = 0.44$) and the indication for radiotherapy (nasopharyngeal cancer *vs.* intracerebral tumors).

A sensitivity analysis with four studies explicitly mentioning the inclusion of consecutive unselected patients was performed (23;29;36). The pooled prevalence of any pituitary deficiency was 0.62 (95% CI 0.45–0.77), which is similar to the pooled prevalence of 0.66 when combining all the studies.

Pituitary insufficiency related to duration of follow-up after radiotherapy

Two studies reported on the occurrence in time of hypopituitarism (23;26). The prevalence of pituitary failure in patients treated for nasopharyngeal tumors was 6% after 1 yr, 35% after 2 yr, 56% after 3 yr and 62% after 4 and 5 yr (23). Samaan *et al.* (26) reported on the classical sequential order of failure of individual pituitary functions in time. GH deficiency occurred after a mean of 2.6 yr, followed by failure of the pituitary-gonadal axis and hyperprolactinemia after approximately 3.8 yr, ACTH insufficiency after 6 yr, and finally TSH insufficiency after a mean of 11 yr.

Discussion

This systematic review and meta-analysis demonstrated that pituitary insufficiency is a highly prevalent condition in adult patients after cranial radiotherapy for nasopharyngeal and intracerebral tumors. The prevalence of any form of hypopituitarism was 0.66 (95% CI, 0.55–0.76). There were considerable variations in the reported prevalence rates of hypopituitarism after cranial radiotherapy, ranging from hardly any effect on pituitary function to almost 100% of the patients being affected. These variations were associated with differences in the number of patients included in the study and the manner of endocrine evaluation.

The risk of development of hypopituitarism after cranial radiotherapy is a well recognized phenomenon in children. The likelihood to develop hypothalamic-pituitary insufficiency increases with increasing radiation exposure and with prolonged duration of follow-up up after radiotherapy (11;12). In the CCSS 43% of pediatric patients treated for cerebral tumors had one or more endocrinopathies (10). Our meta-analysis showed that hypopituitarism is present in approximately two thirds of all adult patients previously treated with cranial irradiation. The prevalence of hypopituitarism after cranial radiotherapy is affected by several factors including radiation dose and techniques. Furthermore, the time interval between radiotherapy and the assessment of pituitary functions is important because the development of pituitary failure is likely to increase during prolongation of follow-up after radiotherapy (11;12).

A random effects meta-regression revealed no significantly different effects of underlying disease on pituitary function between the two groups of adult patients reported in literature; *i.e.* those treated for nasopharyngeal cancer *vs.* intracerebral tumors. In addition, the overall difference in radiation dosage did not differ between groups: 40–83 Gy for the patients treated for nasopharyngeal carcinoma and 40–97 Gy for the patients with intracerebral tumors. The use of different radiotherapeutical techniques, however, will most likely affect the rate of

subsequent hypopituitarism because higher cumulative radiation doses are associated with increasing incidence rates of pituitary failure (11;12).

Patients treated for nasopharyngeal tumors are usually treated with a higher average dosage and additive high dose single tumor boost. Therefore, a separate analysis of the studies concerning nasopharyngeal tumors *vs.* the other studies was performed (Figure 2A). However, there were no significant differences in the prevalence of any pituitary insufficiency between both groups. There are various possible explanations for this lack of significant differences between the two patient groups despite differences in irradiation dose. In nine studies from which the estimated doses delivered to the pituitary could be extracted (six involving patients treated for nasopharyngeal tumors and three for intracerebral tumors), the dose ranges were wide in both patient groups and showed a considerable overlap. In patients treated for nasopharyngeal tumors, the dose ranged from 46–83 Gy, and in patients with intracerebral tumors the dose ranged from 25–97 Gy. Duration of follow-up since radiotherapy varied from 11–253 months in the patient group treated for nasopharyngeal tumors and from 12 – 156 months in the group treated for intracerebral tumors. Finally, the overall prevalence of pituitary insufficiency is already high in both groups with 0.54 (95% CI, 0.42–0.66) for intracerebral tumors *vs.* 0.74 (95% CI, 0.57–0.86) for nasopharyngeal tumors. This 0.2 difference in prevalence, however, did not result in significant differences between groups ($P = 0.14$).

According to our risk of bias stratification, nine studies were considered as being at low risk of bias. The majority of studies used cross-sectional study designs with large differences in the time of evaluation in relation to previous radiotherapy. The selection of patient groups differed largely between the studies. Patient selection criteria were not stated in some of the reports (20;28;31), whereas the description of the selection procedures in other studies suggests preselection of patients, like recruitment from a radiotherapy complication outpatient clinic or by including only symptomatic patients suspected for any degree of hypopituitarism (21;30;32;33). Two studies, (n=186), used a prospective design; the reasons for loss to follow-up were not mentioned in any of the studies, precluding definite answers after 5 yr of follow-up (23;26). We additionally performed a sensitivity analysis of studies that qualified as a potential low – intermediate risk of bias (23;29;36;39). This analysis revealed a pooled proportion of any pituitary deficiency of 0.62 (95% CI,

0.45–0.77), which is remarkably close to the overall found prevalence of 0.66 (95% CI, 0.55–0.76) calculated for all studies. This outcome illustrates that signs and symptoms of hypopituitarism after cranial irradiation apparently are not predictive of hypopituitarism in individual patients with their condition.

Differences in endocrine evaluation may also affect the reported prevalence. The majority of patients were not evaluated by proper stimulation tests. Therefore, it is likely that the estimates of hypopituitarism after cranial radiotherapy represent a rather conservative estimation of the true prevalence of hypopituitarism. In addition, studies that did perform stimulation tests used different tests and cut-off values, and only 10 of 18 studies assessed all pituitary axes (but even then, not all patients were tested for each axis). Moreover, the hypothalamic-pituitary-thyroidal axis and the hypothalamic-pituitary-gonadal axis can also be influenced by the use of alkylating chemotherapeutics and exposure of the thyroid gland and gonads to irradiation (19; 41–43). Primary hypothyroidism in patients treated for nasopharyngeal carcinoma occurs up to 20–30% within the first year after treatment (44). In the random effects regression model the prevalence of TSH deficiency was 0.33 (95% CI, 0.19–0.5), and 0.16 (95% CI, 0.08–0.32) for the patients treated for intracerebral tumors. These differences were not significant, with P=0.11. Hypogonadism after cranial radiotherapy was difficult to quantify because some studies reported testosterone or estrogen levels, whereas others used delayed or insufficient LH/FSH responses to GnRH as a criterion for hypogonadism. In addition, primary gonadal failure is highly prevalent in patients treated with chemotherapy, especially when treated with alkalyting agents which could overestimate the results (41). Patients treated for nasopharyngeal tumors were more likely to receive chemotherapy but, again, no significant differences between groups were found.

Prolactin might be another possible tool to estimate the likelihood of radiation induced damage of the hypothalamic area. Because hyperprolactinemia might be a consequence of decreased hypothalamic dopamine secretion, hyperprolactinemia is variable in severity and often subclinical; it diminishes and might even normalize in time due to slowly evolving radiationinduced damage of lactotrophs. If hyperprolactinemia is to be considered as an indicator of disturbed hypothalamic dopamine secretion, one could expect the prolactin level to be high in the first years

after radiation and normal after several years when lactrotroph function has declined. Unfortunately, none of the studies provided information on prolactin levels in relation to the time interval since radiotherapy.

Considering the high prevalence of hypopituitarism found, 0.66 (95% CI, 0.55–0.76), and that there was no significant difference between groups, assessment of pituitary function should be included in the long-term follow-up of all cranially irradiated patients. Current literature does not provide a timeline or a sequence of axis failure. Hypopituitarism can occur as soon as the first year after treatment, but can also occur 11 yr after treatment (23;26). Taken into consideration the improved survival of patients, duration of follow-up for at least 15 yr should be advisable. This follow-up period should include a basal morning hormone sample and dynamic testing of the HPA axis in every patient not on corticosteroids. Dynamic testing of the somatotrope axis should be defined per patient, since GH failure will not have therapeutical consequences, although it might be an indicator for radiation induced pituitary damage.

This systematic review underscores the need for structured, periodical, endocrine assessments of all patients who survive after cranial radiotherapy for all kinds of diagnosis. Therefore, an increasing number of patients will require a structured tailored periodical evaluation of pituitary functions after cranial radiotherapy.

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