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Radiotherapy-induced Hypothalamic-Pituitary axis dysfunction in adult Brain, head and neck and skull base tumor patients – A systematic review and Meta-Analysis

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ABSTRACT

Background and purpose: Radiotherapy for brain, head & neck (HN), and skull base (SB) tumors may deliver significant radiation dose to the hypothalamic-pituitary axis (HPA), leading to impaired functioning of this region and hence, to endocrine disorders. The purpose of this systematic review and *meta*-analysis is to investigate literature on HP dysfunction after radiation for non-pituitary brain, HN, or SB tumors at adult age, aiming to give insight in the prevalence of HP dysfunction related to radiation dose.

Materials and methods: Literature search of the PubMed database was performed for HP dysfunction after radiotherapy in adult patients. A risk of bias assessment was performed to rate the quality of the included papers. Besides clinical and treatment variables, reported insufficiencies for adrenocorticotrophic hormone, thyroid stimulating hormone, growth hormone, prolactin and follicle stimulating hormone and luteinizing hormone and for insufficiency of any axis were extracted. The prevalence for hormonal insufficiency per axis and for multiple axes was calculated using a random effects *meta*-regression with a random effect at the study level.

Results: The literature selection process resulted in a total of 22 original papers, suitable for full assessment (n = 1,462 patients). Literature showed a wide variation in HP dysfunction, along with wide dose ranges given to the hypothalamus and pituitary, with varying follow-up times. The calculated prevalence for any pituitary insufficiency was on average 0.61 (95 % CI 0.44–0.75). For growth hormone the mean prevalence was 0.40 (95 % CI 0.22–0.61), for prolactin 0.22 (95 % CI 0.17–0.28), for gonadotropin 0.20 (95 % CI 0.14–0.28), for adrenocorticotropic hormone 0.16 (95 % CI 0.08–0.30) and for thyroid stimulating hormone 0.16 (95 % CI 0.11–0.23). The prevalence for any insufficiency of 1 axis was 0.19 (95 % CI 0.11–0.30), of 2 axes 0.22 (95 % CI 0.12–0.38), of 3 axes 0.05 (95 % CI 0.03–0.09) and of panhypopituitarism 0.17 (95 % CI 0.08–0.32). Patients irradiated for nasopharyngeal carcinoma (NPC) seemed to be at highest risk for developing any endocrine insufficiency with a mean prevalence of 0.68 (95 % CI 0.45–0.85). A significant correlation between any endocrine insufficiency and follow-up time was observed (p = 0.015). A correlation between dose to the pituitary and occurrence of insufficiency on the hormonal axes could not be observed.

Conclusion: Endocrine insufficiency is reported in over half of the patients irradiated for brain, HN and SB malignancies. The hypothalamus is likely to be more vulnerable to radiation dose compared to the pituitary gland. More research is needed to establish dose thresholds for the hypothalamus and the pituitary to minimize the risk for pituitary insufficiency. Based on this knowledge, radiotherapy and follow-up of these patient groups should be standardized to establish a normal tissue complication probability (NTCP) model for the HPA.

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Introduction

Radiotherapy is a widely applied modality in the treatment of primary brain tumors, brain metastasis, head & neck (HN) and skull base (SB) malignancies. Depending on pathology, location and staging of the tumor, treatment of these malignancies occurs in most cases in a multimodal way by combining surgery, radiotherapy, chemotherapy and immunotherapy [1–3].

Radiotherapy has become more accurate over the years due to technical improvements for dose delivery to the target volume. However, treatment planning remains challenging when aiming for an optimal treatment effect while minimizing the dose delivery to the surrounding healthy structures. Defining organs at risk (OAR's) and their tolerance dose is of major importance to prevent these healthy structures from radiation damage and hence, causing detrimental effects in the short or long term [4,5]. Surgery, chemotherapy and immunotherapy may induce specific negative side effects on healthy brain tissue, including insufficient functioning of the hypothalamus and/or pituitary gland. In addition, irradiation may cause HP dysfunction, even when given to tumors distant from the HP region. HP dysfunction may, cause negative effects on the quality of life of cancer survivors [6,7]. The HP-axes can be defined as a cascade of interactions between the hypothalamus, the pituitary gland and hormone producing organs as a response to a stimulus to maintain physiological homeostasis. The importance of surveillance and early management of dysfunction of one or more HP axes is widely recognized in the oncologic treatment in children, due to the risk of lifelong undesired effects and the possibilities for adequate treatment of pituitary insufficiency [8–11]. Late effects in adults after dose delivery to the HPA in the treatment of non-pituitary brain and HN tumors and guidelines for surveillance of cancer treatment of adult patients is less well investigated [12].

This systematic review and *meta*-analysis aims to give an overview on HP insufficiency after radiation exposure and its relationship to radiation dose to the HPA in adults after radiotherapy at adult age for brain, HN and SB tumors.

Design

Search strategy and eligibility criteria

A literature search in the PubMed database was based on the search strategy as published by Appelman-Dijkstra *et al.* [13] in 2011 (appendix 1). Publications were eligible for inclusion if they met the following criteria: 1) papers in English, 2) papers published between January 2010 and June 2024, 3) patients at adult age at the time of radiotherapy, 4) radiation for primary brain tumors or cerebral metastasis, HN and SB malignancies, 5) radiation dose information available, 6) information on follow-up available, 7) information on endocrine function of at least one HPA after exposure to cranial irradiation. Exclusion criteria were defined as 1) patients with pituitary adenomas, 2) patients with craniopharyngiomas, 3) cohorts of 5 or less participants, 4) literature reviews, 5) animal studies, 6) radiotherapy planning studies, 7) non-radiotherapy related publications.

Data review and analysis and risk of bias assessment

The purpose of the systematic review was to retrieve and analyze data on endocrine insufficiency related to radiation dose to the HPA. Information on additional treatment modalities such as surgery and chemotherapy was collected but the effects from these modalities on HP-functioning were not taken into account for the results of this analysis. The author (J.P.) selected publications for inclusion by review of titles and abstracts. Selected papers were retrieved for full assessment on basis of the in- and exclusion criteria by two reviewers (J.P. and D.H.). To rate the quality of included papers, the two reviewers independently performed a risk of bias assessment, using the Newcastle-Ottawa-Scale (NOS) for cohort studies. For this assessment, endocrine outcome was taken into consideration. The used NOS allocation system is displayed in Table 1. The selection criterion for non-exposed cohorts was left out of the assessment since no publications with non-exposed cohorts, e.g. patient who did not receive radiotherapy, were included. A maximum of 8 points was allocated if a study met all quality criteria.

For dose information to the pituitary and the hypothalamus, the Biologically Equivalent Dose (BED) was calculated and reported in Table 2a. The α/β ratios for the pituitary and the hypothalamus were 2 and 3 respectively [14]. In case dose to the HPA was reported, an α/β of 3 was chosen.

Statistical analysis

A *meta*-analysis was performed. Percentages of patients with endocrine insufficiency were calculated for each study and for each axis separately by taking the number of patients with an insufficiency and dividing it by the total number of patients tested. Proportions were then logit transformed to effect sizes. A random effects *meta*-analysis (with a random effect at the study level) was carried out to estimate the pooled proportion of patients with a deficiency for a specific axis. A random effects model was chosen by default because of the expected clinical heterogeneity between the studies. Additionally, a *meta*-regression analysis was performed for insufficiency on any axis with tumor site as a covariate (SB vs. intracerebral vs. NPC and others). All analyses were performed using The metafor Package (version 4.4–0) for R. For the *meta*-regression, a maximum likelihood estimator was used [15]. By means of the *meta*-analysis, reporting of the prevalence for any insufficiency, insufficiency per axis and insufficiency for multiple axes was possible. In this context, prevalence can be defined as the number of existing cases (patients with an insufficiency) at a specific time point (end of follow-up) within a specific population (patients tested) [16].

Correlations between HP insufficiency and dose to the HP region and between HP insufficiency and follow-up time were investigated by a Pearson correlation test.

Table 1
Allocation of quality criteria related to NOS scale.

NOS criterion	Assessed quality criterion	points
Selection		
Representativeness of the exposed cohort	Age 17 or higher described	1
Selection of the non-exposed cohort	No non-exposed cohorts (no radiotherapy) were used for this review	skipped
Ascertainment of exposure	Dose to pituitary, hypothalamus or HP-axis described	1
Demonstration that outcome of interest was not present at start of the study	Absence of endocrine insufficiency at the start of the study described	1
Comparability		
Comparability of cohorts on the basis of the design or analysis:	Endocrine insufficiency of at least 3 different axes described	1
	Insufficiency in more than one axis described	1
Outcome		
Assessment of outcome	Methodology of endocrine evaluation described	1
Was follow-up long enough for outcomes to occur?	Median or mean follow-up period for at least 24 months described	1
Adequacy of follow-up of cohorts	Complete follow up of at least 75 % of subjects per axis described	1

Table 2a

Patient characteristics, risk of bias assessment, nature and location of the primary tumor, radiation dose to tumor and/or HP AXIS, follow-up period, method of endocrine evaluation and additional treatment modalities. Publications with * were excluded from the *meta*-analysis. *Abbreviations:* NSCLC: Non-small cell lung carcinoma; SCLC: small cell lung carcinoma; NPC: nasopharyngeal carcinoma; BM: brain metastasis; Gy: Gray; TD: total dose; PCI: prophylactic cranial irradiation; WBRT: whole brain radiotherapy; SRS: stereotactic radiosurgery; RT: radiotherapy; SRT: stereotactic radiotherapy; FSRT: fractionated stereotactic radiotherapy; IMRS: intensity-modulated radiosurgery; gEUD: generalized equivalent uniform dose; RBE: relative biological effectiveness; IDL: isodose line; IGF-1: insulin-like growth factor; LH: luteinizing hormone; FSH: follicle stimulating hormone; SHBG: sex hormone binding globulin; PRL: prolactin; TSH: thyroid stimulating hormone; fT4: free T4; ACTH: adrenocorticotrophic hormone; GH: growth hormone; ITT: insulin tolerance test; GST: glucose suppression test; GHRH: growth hormone releasing hormone; CV: cardio-vascular; (c)ChT: (concurrent) chemotherapy; TMZ: temozolomide; D_{pit} : dose to pituitary gland; D_{hypo} : dose to hypothalamus; D_{hpa} : dose to hypothalamic-pituitary axis; NA: data not available.

First author, year of publication, [Ref.]	No. of pts, age (range), gender	Risk of bias	Tumor characteristics	Irradiation	Single fraction dose	BED HP structures	Follow-up period	Endocrine evaluation	Other treatment modalities
Gebauer, 2020 [55]	26, Median 58 (36–81), 16F/10 M	6	BM from NSCLC (n = 6), breast cancer (n = 3), SCLC (n = 2), urothelial cancer (n = 2) or PCI in SCLC (n = 12). Total pts 25.	WBRT for BM: TD 36 or 35–37.5 Gy or 40 GY (n = 14); PCI TD 30 Gy (n = 12). Equal on HP-axis due to homogenic dose distribution	TD 36 or 40 Gy: 2 Gy; TD 35–37.5 Gy: 2.5 Gy	TD 36 Gy: 60 Gy; TD 40 Gy: 66.67 Gy; TD 35–37.2 Gy: 64.17–68.75 Gy	Median 20.5 months (6–151 months).	Early-morning measurement of IGF1, LH, FSH, Testosterone, SHBG (M), 17 beta-estradiol, PRL, TSH, fT4, cortisol, ACTH	NA
Kyriakakis, 2019 [20]*	58, Mean 41 (30–52), 26F/32 M	7	Astrocytoma (n = 32), Oligodendroglioma (n = 12), Glioblastoma (n = 8), Ependymoma (n = 5), Uncategorized glioma (n = 1)	Dose to tumor 53.9 Gy +/- 5.6 Gy; Mean D_{hpa} 36.7 Gy +/- 15.9 Gy	2 Gy	Mean D_{hpa} 61.17 Gy	Mean 98.4 months (36–161)	ITT and GST (ACTH, GH). Basal serum levels LH/FSH, TSH, fT4, PRL, testosterone, estradiol	Surgery + RT (n = 20); Chemo + RT (n = 6); Surgery + chemo + RT (n = 25)
Kyriakakis, 2016 [24]	107, Mean 40 (27–53), 52F/55 M	7	Glioma (n = 60), Meningioma (n = 22), Medulloblastoma (n = 9), Pinealoma (n = 8), Other primary (n = 7), No histology (n = 1)	Photons: Mean dose to tumor 54 Gy (n = 101); 30–50 Gy (n = 16), > 50 Gy (n = 83), unknown (n = 2); Protons: 74 Gy (n = 1), 77 Gy (n = 1), unknown dose (n = 2); Photons + protons (n = 1) 71 Gy, SRS (n = 1)	NA	NA	Median 96 months (63–132)	ITT and GST (ACTH, GH). Basal serum levels LH, FSH, TSH. PRL, IGF-1, fT4, testosterone, estradiol	Surgery + RT (n = 54); Chemo + RT (n = 5); Surgery + RT + chemo (n = 34),
Ratnasingam, 2015 [26]	50, Mean 57 (44–69), 19F/31 M	8	NPC stage I-IV	Mean dose 66 Gy +/- 3.2 Gy facio-cervical; Mean dose 62 Gy +/- 2.9 Gy anterior neck; Minimum D_{pit} 40 Gy.	2 Gy	Minimum D_{pit} 80 Gy	Median 96 months (36–252 months)	Early-morning (fasting) baseline measurement of cortisol, fT4, TSH, PRL, LH, FSH, estradiol, testosterone, renal function. ITT on second visit	Chemo + RT (n = 36); RT alone (n = 14);
Appelman-Dijkstra, 2014 [27]	80, Median 47 (18–89),	6	Brain (n = 40, 18F/22 M), NPC (n = 15, 4F/11 M), cerebral metastasis (n = 2), Meningioma (n = 14), other (n = 9)	Cerebral mean dose 55.8 Gy +/- 4.4 Gy (46–62), NPC mean dose 63 Gy +/- 9.8 Gy (40–70), other mean dose 53 Gy +/- 7 Gy (40–69). Mean D_{pit} 56.3 Gy (40–70)	NA	NA	Median 72 months (6–420)	Early-morning (fasting) ITT measurement of IGF-1, GH, TSH, fT4, ACTH, cortisol, LH, FSH, estradiol, testosterone, SHBG, PRL, renal and liver function, CV parameters	NA
Huang, 2013 [19]	98, Median 47 (17–70), 28F/70 M	6	NPC	Mean D_{pit} 51.2 Gy (40–70 Gy)	NA	NA	Median 17 months (6–51)	Early morning measurements	Chemo + RT (n = 92)
Hauptman, 2012 [56]	15, Median 56 (29–74), 7F/8 M	3	Chordomas & chondrosarcomas	SRT 53–84 Gy (n = 10), SRS (n = 5). 1 patient SRT	SRT 2 Gy, 1.9 Gy, 2.3 Gy. SRS single	NA	54 months	NA	Surgery n = 15; (100 %)

(*continued on next page*)

Table 2a (*continued*)

First author, year of publication, [Ref.]	No. of pts, age (range), gender	Risk of bias	Tumor characteristics	Irradiation	Single fraction dose	BED HP structures	Follow-up period	Endocrine evaluation	Other treatment modalities
				67.6 Gy at 95 % IDL	fractions of 15, 18, 20, 19, 16 Gy				
Madaschi, 2011 [22]	26, Median 39 (33–47), 12F/14 M	6	Gliomas, meningiomas, neuroectodermal tumors. 26 RT, 6 controls	RT dose to target volume: 59.4 Gy (50.1–60) Median D_{hpa}: 41.8 Gy (30.7–49.8 Gy)	2 Gy	Median D_{hpa} 69.67 Gy	HP-axis dysfunction at median 32 months (12–111)	GHRH + arginine test: IGF-1, ACTH and cortisol, PRL, TSH, fT4, testosterone, estradiol	Surgery + RT (n = 15) Surgery + chemo + RT (n = 11)
Löfdahl, 2012 [57]	15, Median 56 (32–66), 4F/11 M	4	Oropharyngeal cancer (n = 13), epipharyngeal cancer (n = 2)	Oropharyngeal: mean D_{hypo} 1.9 Gy (1.5–2.2 Gy), mean D_{pit} 2.4 Gy (1.8–3.3 Gy). Epipharyngeal: D_{hypo} 6.0–9.3 Gy, D_{pit} 33.5–46.1 Gy.	1.7 Gy twice a day	Oropharyngeal; mean D_{hypo} 2.98 Gy, mean D_{pit} 4.44 Gy. Epipharyngeal; D_{hypo} 9.40–14.57 Gy, D_{pit} 61.98–85.29 Gy.	72 months (48–120)	Early morning IGF-1, PRL, testosterone, FSH/LH, fT4, TSH, cortisol. ITT for GH	Chemo + RT (n = 10)
De Marzi, 2015 [17]	103 adults	5	Chordoma and chondrosarcoma	Mean D_{pit} with tox 63.5 +/- 6.8 Gy-RBE (34.0–72.8). Mean gEUD pituitary with tox 65 +/- 5 Gy.	1.8—–2.0 Gy	Mean D_{pit} 120.65–127 Gy	Minimum 26 months	NA	Surgery, post-operative RT; 100 %
Ipekci, 2015 [58]	30, Mean 42 (33–51), 10F/20 M	6	NPC	Mean D_{pit} 46.2 Gy, mean D_{hypo} 10.3 Gy	2 Gy	Mean D_{pit} 92.40 Gy, mean D_{hypo} 17.17 Gy	Single evaluation at 24.4 months (9.8–133) between RT and testing. 13 pts had second evaluation 12.9 +/- 2.4 months after first evaluation	ITT after 8 h fasting, early-morning: cortisol, GH, ACTH, gonadotropin, testosterone, estradiol, FSH, LH, fT4, TSH, IGF-1, PRL	Chemo + RT (n = 28)
Shih, 2015 [23]*	20, Median 37 (22–56), 7F/13 M	7	Grade II glioma	Proton therapy up to 54 Gy (RBE) to tumor or surgical bed. 6 pts > 30 Gy to pituitary, 14 pts < 30 Gy to pituitary	1.8 Gy (RBE)	TD 30 Gy = BED 57 Gy to pituitary	Median 60 months.	Serum levels of prolactin, IGF-1, TSH, fT4, cortisol, cortisol after cosyntropin stimulation, testosterone, LH, FSH, estradiol	TMZ: 2/20. Surgery: Gross total res 4/20, subtotal 12/20, biopsy 4/20
Tabrizi, 2019 [21]	20, Median 37 (22–56), 7F/13 M	5	Grade II glioma	Proton therapy up to 54 Gy (RBE) to tumor or surgical bed. Dose range above and under 20 Gy to pituitary or hypothalamus reported	1.8 Gy (RBE)	NA	Median 60 months. Deficiency after median 10.9 months (4.8–37.8)	Serum levels of prolactin, IGF-1, TSH, fT4, cortisol, cortisol after cosyntropin stimulation, testosterone, LH, FSH, estradiol	TMZ: 2/20. Surgery: Gross total res 4/20, subtotal 12/20, biopsy 4/20
Partoune, 2021 [29]	48, Median 49 (37–61), 45F/3 M	8	Skull base meningioma	Median D_{pit}: 48.9 Gy (6.0–55.1), median D_{hypo}: 15.8 Gy (2.0–51.1)	1.8 Gy	Median D_{pit}: 92.91 Gy, median D_{hypo}: 25.28 Gy	median 90 months (17–217)	Early-morning after fasting: TSH, fT4, cortisol, ACTH, IGF-1, LH, FSH, PRL, estradiol, testosterone, GH (ITT)	NA
Vakilian, 2021 [18]	36, Median 58, 16F/20 M	7	Skull base, different tumor types: NPC, chordomas, primary brain	Median dose 54 Gy (50.4–70 Gy) to target volume. Dose threshold of 50 Gy (30 Gy mean dose) to	NA	NA	Median 32 months (18–85)	IGF-1, PRL, fT4, TSH, Early-morning cortisol, ACTH, FSH/LH, testosterone,	19 pts with hormone deficiencies: 79 % surgery, 21 % chemo. 17 pts without

(*continued on next page*)

Table 2a (*continued*)

First author, year of publication, [Ref.]	No. of pts, age (range), gender	Risk of bias	Tumor characteristics	Irradiation	Single fraction dose	BED HP structures	Follow-up period	Endocrine evaluation	Other treatment modalities
				pituitary for development of endocrinopathy.				estradiol/ progesterone	deficiencies (controls): 47 % surgery, 47 % chemo
Jensen, 2010 [59]	6, Median 61 (48–70), 5F/1 M	3	Cavernous sinus meningioma	IMRS 14.7–15.7 Gy	IMRS single fraction dose 14.7–15.7 Gy	NA	Median 42 months (13–78)	Serum measurements of TSH, T4, T3, cortisol, IGF-1, GH, ACTH	Craniotomy n = 4
McDowell, 2018 [31]	107, 86 for endocrine screening. Median 57 (32–82), 38F/69 M.	6	NPC	70 Gy to target volume	2 Gy	NA	> 48 months, 4 years after RT	Early-morning, after fasting. PRL, IGF-1, LH, FSH, fT4, TSH, ACTH, cortisol, testosterone	cChT (n = 100/ 107), 93 %
Raymond, 2021 [28]	52, Mean 56 (42–70), 42F/10 M	7	Skull base meningioma	Mean dose to tumor 54.1 +/- 1.6. Mean D_{hpa} 47 +/- 9.4 Gy.	1.8—2.0 Gy	Mean D_{hpa} 75.20–78.33 Gy.	Median 84 months (60–120)	Early-morning cortisol, ACTH, LH, FSH, estradiol, testosterone, IGF-1, GH, TSH, fT3, fT4, PRL	18 (34.6 %) post-operative RT
Minniti, 2011 [33]	52, Median 56 (34–74), 35F/17 M	5	Skull base meningioma	FSRT 50 Gy in 30 fractions. Pituitary fossa included in PTV = 50 Gy.	1.7 Gy	Pituitary fossa included in PTV = 92.50 Gy.	Median 36 months	Basal hormonal assessment and dynamic testing	18 post-operative FSRT, 7 pts with pre-existing hypopituitarism
Handisurya, 2019 [25]	436, Median 50 (19–83), 198F/238 M	3	Gliomas	54–60 Gy to target volume	2 Gy	NA	> 37 months	Serum concentrations of TSH, T3, T4, fT3, fT4, FSH, LH, testosterone, estradiol and prolactin	100 % surgery. 100 % cChT, TMZ + adj TMZ
Sharma, 2020 [32]	27, Median 67 (47–83), 10F/17 M	7	Sinonasal cancer	<= 60 Gy (n = 10), 66 Gy (n = 12), >= 68 Gy (n = 5). Mean D_{pit} 29.9 (15.0–68.1) Gy.	2 Gy	Mean D_{pit} 59.80 Gy.	Median 76.8 months (19.2–133.2)	Serum levels of LH, FSH, testosterone, estradiol, tT3, T4, PRL, IGF-1, plasma levels TSH and cortisol. 12 pts with corticotropin stimulation test	surgery (n = 20) 74 % concomitant Cisplatin (n = 6), 22 %
Contrera, 2023 [30]	50, Mean 54 (31–81), 19F/31 M	7	NPC (20), sinonasal cancer (30)	50 pts included, 76 % IMRT, 24 % IMPT. From 41 pts dosimetric data available. Median target dose 64 Gy (45–70 Gy). Normal pituitary function: mean D_{pit} 40.9 Gy, mean D_{hypo} 11.3 Gy. Abnormal pituitary function: mean D_{pit} 52.4 Gy, mean D_{hypo} 20.3 Gy	2.06 Gy	Normal pituitary function: mean D_{pit} 83.03 Gy, mean D_{hypo} 19.06 Gy. Abnormal pituitary function: mean D_{pit} 106.37 Gy, mean D_{hypo} 34.24 Gy	Median 20 months (3–145)	IGF-1, ACTH, total cortisol, fT4, T3, TSH, FSH, LH, total testosterone, estradiol	70 % concurrent cisplatin or carboplatin (n = 35)

Results

Systematic literature search

A literature search was performed on June 11, 2024. The selection and inclusion process, displayed in Fig. 1, provided a total of 22 publications, 12 prospective and 10 retrospective, for full assessment. Patient characteristics, results of the risk of bias assessment, tumor characteristics, radiation dose to the target volume and HPA, including single fraction dose, the BED, the endocrine follow-up period, methods of endocrine evaluation and other treatment modalities are displayed in Table 2a. Pituitary insufficiencies per axis and insufficiencies in multiple

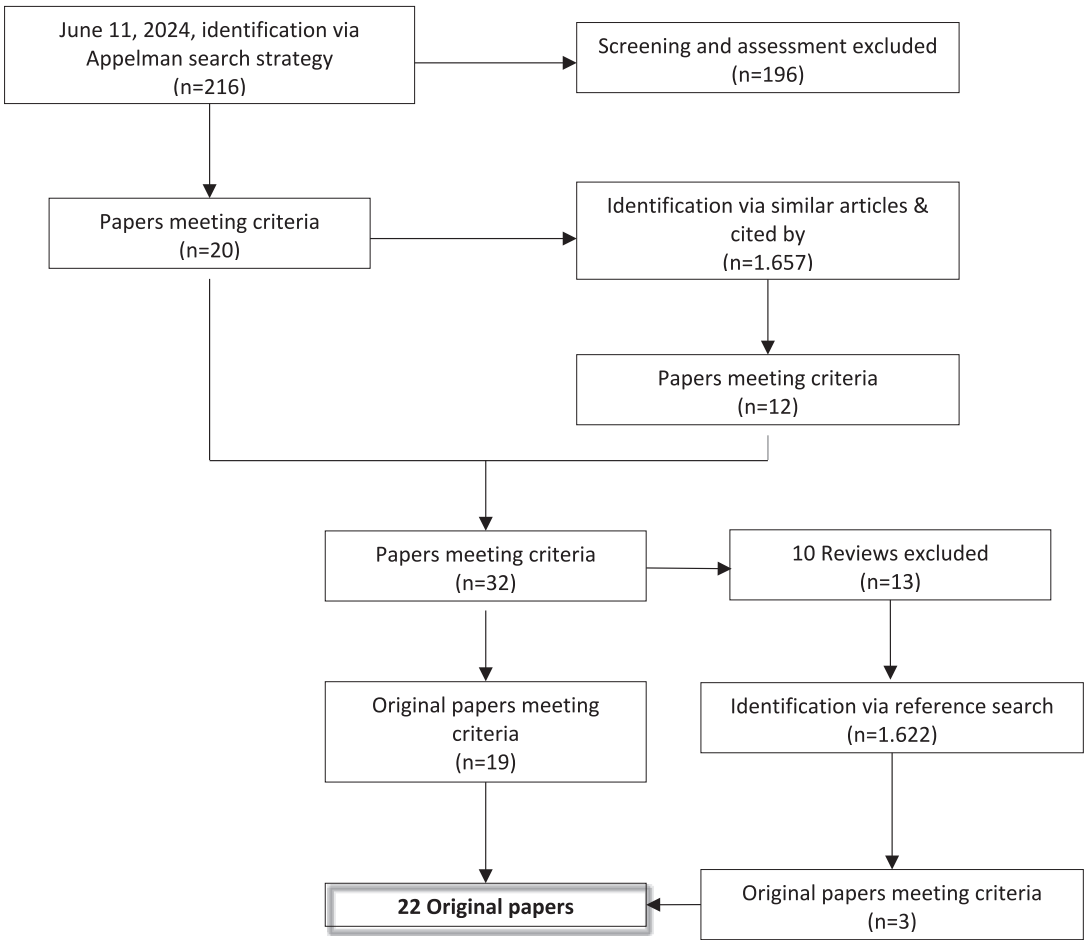

Fig. 1. Process of selection and inclusion of publications for systematic review.

axes are displayed in Table 2b.

Characteristics

The 22 selected papers included a total of 1,462 patients. In 20 papers, a gender distribution was described, consisting of 596 female (46.6 %) and 683 male (53.4 %) patients. The age of the population was described in 21 papers as mean or median. De Marzi *et al* [17] described 103 adults, without reporting a median or mean age however, the authors reported separately on endocrine data for children and adults. Vakilian *et al* [18] described a median age without reporting a range. Tumor characteristics were described in all included papers, consisting of primary brain tumors and brain metastasis, chordomas, chondrosarcomas and other tumors situated in the base of skull, nasopharyngeal carcinomas, sinonasal carcinomas and other HN cancers.

Radiation dose

Radiation treatment was delivered with photons or protons as a fractionated scheme, stereotactic radiotherapy (SRT) or radiosurgery (SRS) in higher fraction doses.

Included papers reported a mean or median dose range of 7.4 Gy to 63.5 Gy to the pituitary (D_{pit}) (n = 600; 41 %), a mean or median dose range of 2.6 Gy to 20.3 Gy to the hypothalamus (D_{hypo}) (n = 134; 9 %) and a dose range of 36.7 Gy to 47 Gy to the HPA in general (D_{hpa}) (n = 136; 9 %). Highest mean dose (D_{mean}) to the pituitary was reported in the treatment of chordoma or chondrosarcoma with a mean dose of 63.5 Gy and for the hypothalamus the highest mean dose was reported in the treatment of NPC or sinonasal carcinoma mean D_{hypo} of 20.3 Gy. The prevalence for endocrine insufficiency, related to dose to the HPA is displayed in Fig. 2a. A Pearson correlation test did not show a correlation between dose to the HPA and HPA insufficiency.

Follow-up

All studies reported on either mean or median follow-up of patient populations, varying from a minimum of 17 months [19] to a mean maximum of 98.4 [20] months. Two papers reported a threshold period of 10.9 months [21] and 32 months [22], respectively, for developing any endocrine insufficiency after radiation exposure to the HP region. The prevalence for insufficiency, related to follow-up time is displayed in Fig. 2b. A significant correlation between insufficiency on any axis and follow-up time was observed.

Additional treatment modalities

Multimodal treatment was reported in 19 papers. The papers by Kyriakakis *et al* [20] and Shih *et al* [23] were excluded from the calculations because the same cohorts of patients were also used by Kyriakakis *et* al [24] and Tabrizi *et al* [21], respectively. The remaining 17 publications in which multimodal treatment was reported consisted of 1,230 patients, comprising 377 HN cancer patients (31 %), 595 brain tumor patient (48 %), 222 SB tumor patient (18 %) and a mixed cohort of 36 patients (3 %). In the group of HN patients, 327 patients (87 %) received additional treatment, of which 307 patients (94 %) received chemoradiotherapy and 20 patients (6 %) had surgery plus radiotherapy. In the brain tumor group, 579 patients (97 %) received additional treatment, 5 patients (0.9 %) received chemoradiotherapy, 91

Table 2b

Pituitary insufficiency per axis and insufficiencies of multiple axes. *Abbreviations:* B: brain, H&N: head and neck; SB: base of skull; NPC: nasopharyngeal carcinoma; Gy: Gray; RT: radiotherapy; gEUD: generalized equivalent uniform dose; LH: luteinizing hormone; FSH: follicle stimulating hormone; TSH: thyroid stimulating hormone; ACTH: adrenocorticotrophic hormone; GH: growth hormone; D_{max} : maximal dose; D_{pit} : dose to pituitary gland; D_{hypo} : dose to hypothalamus; NA: data not available.

First author, year of publication, [Ref.]	Localization	Pituitary insufficiency per axis						Number of axes involved			
		Any	ACTH	TSH	GH	Hyperprolactinemia	FSH/LH	1 axis	2 axis	3 axis	≥ 4 axis
Gebauer, 2020 [55]	B	50 % (13/26)	4.8 % (1/21)	5.0 % (1/20)	8 % (2/25)	26.9 % (7/26)	37.5 % (9/24)	35 %	8 %	8 %	NA
Kyriakakis, 2019 [20]	B	84.5 % (49/58)	19.0 % (11/58)	6.9 % (4/58)	82.8 % (48/58)	10.3 % (6/58)	20.7 % (12/58)	47 %	NA	NA	38 %
Kyriakakis, 2016 [24]	B	88.8 % (95/107)	23.4 % (25/107)	11.2 % (12/107)	86.9 % (93/107)	15.0 %	34.6 % (37/107)	41 %	33 %	10 %	5 %
Ratnasingam, 2015 [26]	NPC	82 % (41/50)	40 % (20/50)	4 % (2/50)	78 % (39/50)	30 % (15/50)	22 % (11/50)	30 %	28 %	18 %	6 %
Appelman-Dijkstra, 2014 [27]	Mixed	62 %, 47 % after 5 years, 60 % after 10 years, 89 % after 15 years	31 % (25/80)	14 % (11/80)	33 % (27/80)	21 % (17/80)	25 % (20/80)	NA	NA	NA	NA
Huang, 2013 [19]	NPC	54.1 % (53/98)	1.0 % (1/98)	33.7 % (33/98)	NA	11.2 % (11/98)	20.4 % (20/98) and 0 % (0/98)	NA	NA	NA	NA
Hauptman, 2011 [56]	SB	6.7 % (n = 1)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Madaschi, 2011 [22]	B	38 % (10/26)	19 % (5/26)	12 % (3/26)	27 % (7/26)	0 % (0/26)	4 % (1/26)	23 % (6/26)	8 % (2/26)	8 % (2/26)	NA
Löfdahl, 2012 [57]	H&N	NA	NA	normal	normal	NA	NA	NA	NA	NA	NA
De Marzi, 2015 [17]	SB	gEUD > 65 Gy. 44 % (45/103)	NA	gEUD 60 +/- 8 (52–71) Gy. 11 % (5/45)	NA	gEUD 63 +/- 9 (34–72) Gy. 29 % (13/45)	NA	NA	NA	NA	gEUD 66 +/- 4 (59–75) Gy. 38 % (17/45)
Ipekci, 2015 [58]	NPC	93.3 % (28/30)	73.3 % (22/30)	26.7 % (8/30)	76.7 % (23/30)	43.3 % (13/30)	6.7 % (2/30)	20 % (6/30)	73.3 % (22/30)	NA	NA
Shih, 2015 [23]	B	NA	20 % (4/20)	17 % (3/18)	0 % (0/16)	0 % (0/7)	15 % (2/13)	NA	NA	NA	NA
Tabrizi, 2019 [21]	B	42 % (5/12) at D_{max} > 20 Gy, 13 % (1/8) at D_{max} < 20 Gy. 30 % (6/20)	20 % (4/20)	17 % (3/18)	NA	NA	15 % (2/13)	NA	NA	NA	NA
Partoune, 2021 [29]	SB	D_{pit} < 45 Gy: 5 %, D_{pit} > 45 Gy: 61 %, D_{hypo} < 20 Gy: 28 %, D_{hypo} > 20 Gy 53 %. 38 % (18/46)	D_{pit} < 45 Gy: 0 %, D_{pit} > 45 Gy: 25 %, D_{hypo} < 20 Gy: 7 %, D_{hypo} > 20 Gy: 26 %. 15 % (7/48)	D_{pit} < 45 Gy: 7 %, D_{pit} > 45 Gy: 46 %, D_{hypo} < 20 Gy: 17 %, D_{hypo} > 20 Gy: 53 %. 32 % (12/38)	D_{pit} < 45 Gy: 5 %, D_{pit} > 45 Gy: 56 %, D_{hypo} < 20 Gy: 23 %, D_{hypo} > 20 Gy: 53 %. 35 % (16/46)	11 % (5/39)	D_{pit} < 45 Gy: 0 %, D_{pit} > 45 Gy: 46 %, D_{hypo} < 20 Gy: 16 %, D_{hypo} > 20 Gy: 50 %28 % (11/39)	9 % (4/46)	13 % (6/46)	4 % (2/46)	13 % (6/46)
Vakilian, 2021 [18]	SB	Mean D_{pit} < 30 Gy: 0 %; 40 Gy: 11 %; 50 Gy: 21 %; 60 + Gy: 68 %. 53 %	NA	NA	NA	NA	NA	NA	NA	NA	NA
Jensen, 2010 [59]	SB	0 %	NA	NA	NA	NA	NA	NA	NA	NA	NA

(continued on next page)

Table 2b (*continued*)

First author, year of publication, [Ref.]	Localization	Pituitary insufficiency per axis						Number of axes involved			
		Any	ACTH	TSH	GH	Hyperprolactinemia	FSH/LH	1 axis	2 axis	3 axis	≥ 4 axis
McDowell, 2018 [31]	NPC	NA	Low in 3 % (3/86)	NA	Low in 55 % (47/86) and elevated in 3 % (3/86).	Elevated in 15 % (13/86)	FSH elevated in 7 % (6/86). LH elevated in 5 % (4/86)	NA	NA	1 % (1/86)	NA
Raymond, 2021 [28]	SB	3 years: 19.2 % (10/52), 5 years 31.5 % (16/39), 10 years 60.2 % (22/26)	3 years: 13.5 % (7/52), 5 years 15.4 % (8/37), 10 years 15.4 % (8/17)	3 years: 5.8 % (3/52), 5 years 14.0 % (7/35), 10 years 28.0 % (10/18)	3 years: 5.8 % (3/52), 5 years 9.8 % (5/35), 10 years 13.4 % (6/16)	3 years: 1.9 % (1/52), 5 years 10.1 % (5/35), 10 years 18.5 % (7/17)	3 years: 9.6 % (5/52), 5 years 17.8 % (9/37), 10 years 36.9 % (13/20)	NA	21 % at 10 years (11/52)	8 % at 10 years (4/52)	13 % at 10 years (7/52)
Minniti, 2011 [33]	SB	19 % (10/52)	NA	NA	NA	NA	NA	NA	21 % (11/52)	NA	NA
Handisurya, 2019 [25]	B	NA	NA	10.9 % (22/202)	NA	30 % (25/84)	FSH: 17 % (14/83), LH: 11 % (9/83)	NA	NA	NA	NA
Sharma, 2020 [32]	H&N	22 % (6/27)	4 % (1/27)	11 % (3/27)	15 % (4/27)	4 % (1/27)	15 % (4/27)	7 % (2/27) at mean dose of 23.5 Gy	11 % (3/27) at mean dose of 36.0 Gy	NA	4 % (1/27) at dose of 68.1 Gy
Contrera, 2023 [30]	NPC, SN	46 % (23/50)	2 % (1/50)	8 % (4/50)	0 % (0/50)	30 % (15/50)	6 % (3/50)	34 % (17/50)	22 % (11/50)	4 % (2/50)	NA

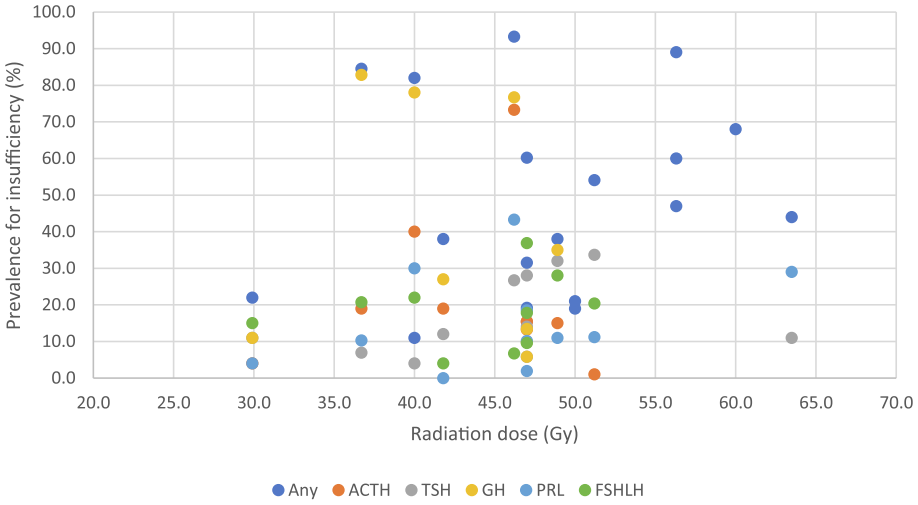

Fig. 2a. Reported prevalences (%-age) for insufficiency on any axis and per axis related to dose to HP axis as reported in the included publications.

patients (16 %) had surgery plus radiotherapy and 483 (83 %) patients were treated with surgery plus radiotherapy plus chemotherapy. Of this group, 436 patient were included from one paper by Handisurya *et al* [25]. In the SB tumor group 69 % received surgery plus radiotherapy.

In a univariate analysis, Ratnasingam *et al.* [26] reported an association between chemotherapy and development of HPA dysfunction in the treatment of NPC patients. Vakilian *et al* [18] described a group of 36 patients, treated for different types of SB tumors, in which 53 % showed pituitary deficiencies after treatment. In this group, 79 % had undergone surgery and 21 % had been given chemotherapy. 47 % did not show any pituitary deficiencies and in this group 47 % had undergone surgery and 47 % had been given chemotherapy.

Endocrine evaluation

In 20 papers, laboratory methods for endocrine evaluation were reported.Two studies report an endocrine evaluation without reporting the methods used. For this reason, endocrine evaluation was indicated as 'data not available (NA)'. Two papers reported on endocrine insufficiency at several timepoints during follow-up [27,28].

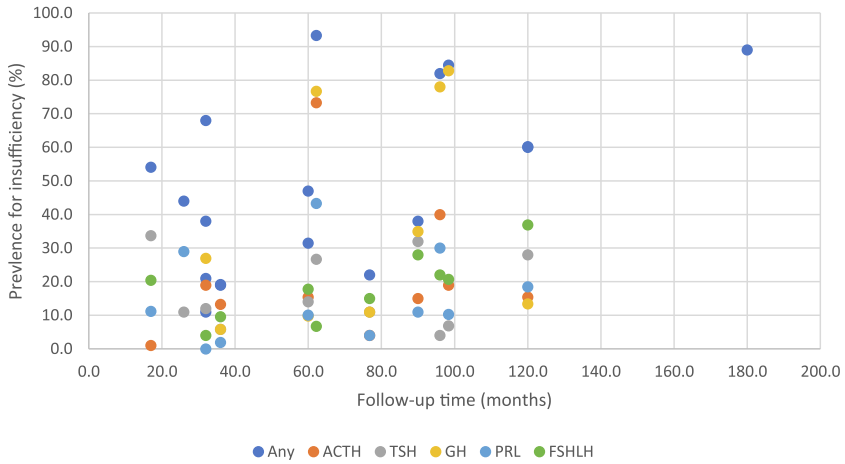

Fig. 2b. Reported prevalence (%-age) of insufficiency on any axis and per axis related to follow-up time as reported in the included publications.

Deficiency of any HP axis

Overall, a wide variety in prevalence for any HP deficiency was reported, ranging from 11.0 % to 93.3 % at varying doses to the target volume, pituitary, hypothalamus or HP region in general and at follow-up periods from 17 to 180 months.

Five papers reported on dose thresholds related to follow-up for insufficiency of any axis. De Marzi *et al* reported a 44 % prevalence at a mean D_{pit} of 63.5 Gy to the pituitary at a follow-up of minimum 26 months [17]. Tabrizi *et al* reported a prevalence of 42 % at a D_{max} over 20 Gy to the pituitary or hypothalamus and of 13 % at a D_{max} under 20 Gy at a median follow-up of 60 months with a later onset of insufficiency when the D_{max} is $\leq$ 20 Gy [21]. Partoune *et al* observed a prevalence of 5 % at a dose to the pituitary $\leq$ 45 Gy and of 61 % $>$ 45 Gy at a median follow-up of 90 months. Regarding dose to the hypothalamus, they reported a prevalence of 28 % at a $D_{mean} \leq$ 20 Gy and of 53 % at a $D_{mean} >$ 20 Gy [29]. Vakilian *et al* reported on an increasing prevalence of 0 % at a pituitary $D_{mean} \leq$ 30 Gy, of around 11 % at 40 Gy, around 21 % at 50 Gy and around 68 % at a $D_{mean} >$ 60 Gy at a follow-up of 32 months [18]. Contrera *et al* reported abnormal pituitary hormone levels at a mean dose of 52.4 Gy to the pituitary and a mean dose of 20.3 Gy to the hypothalamus, compared to a mean dose of 40.9 Gy to the pituitary and of 11.3 Gy to the hypothalamus in patient with normal pituitary hormone levels at a median follow-up of 20 months [30].

Adrenocorticotropic hormone

The prevalence for insufficiency of the hypothalamic–pituitary–adrenal axis ranged from 1.0 % – 73.3 % at a mean dose range of 29.9 Gy to 56.3 Gy and a follow-up ranging from 17 to 120 months. Kyriakakis *et al* reported a dose threshold of 32 Gy for development of adrenal axis insufficiency in 19 % of the cohort [20]. Partoune *et al* reported no insufficiency at a dose to the pituitary under 45 Gy and a prevalence of 25 % at a dose above 45 Gy. Furthermore, they reported a prevalence of 7 % at a dose of under 20 Gy to the hypothalamus and a prevalence of 26 % above 20 Gy [29]. Raymond *et al* reported a prevalence of 13.5 % after 3 years, 15.4 % after 5 years and 15.4 % after 10 years [28].

Thyroid stimulating hormone

The prevalence for insufficiency of the hypothalamic-pituitary-thyroidal axis ranges from 4.0 % to 33.7 % at a mean dose range to the HPA of 29.9 to 63.5 Gy and a follow-up ranging from 17 to 120 months. Kyriakakis *et al* reported a dose threshold of 40.8 Gy to develop thyroidal axis insufficiency in 6.9 % of the cohort [20]. Partoune *et al* [29] reported a prevalence of 7 % insufficiency at a pituitary dose under 45 Gy and a prevalence of 46 % above 45 Gy. Furthermore, a prevalence of 17 % was reported at a hypothalamic dose of under 20 Gy and of 53 % above 20 Gy. Raymond *et al* reported a HP-thyroidal axis deficiency of 5.8 % after 3 years, 14.0 % after 5 years and 28.0 % after 10 years [28]. In patient groups, irradiated for a head and neck tumor, a direct radiation effect on the thyroid gland may be expected in addition to the HP region, however, all publications on H&N carcinomas corrected for thyroid insufficiency.

Growth hormone

The prevalence of GH deficiency (GHD) in the studies included for this review ranged from 5.8 % to 82.8 % at a mean dose range to the HPA of 29.9 to 56.3 Gy and a follow-up ranging from 32 to 120 months. Kyriakakis *et al* reported on a dose threshold of 10 Gy to develop insufficiency of the somatotropic axis [20]. Partoune *et al* found 5 % insufficiency at a pituitary dose under 45 Gy, and of 56 % above 45 Gy. Furthermore, a GHD rate of 23 % was reported after radiation to the hypothalamus with doses less than 20 Gy and of 53 % above 20 Gy [29]. McDowell *et al* reported, besides an insufficiency rate of 55 %, elevated levels of GH in 3 % of the patients [31]. Raymond *et al*. reported GHD of 5.8 % after 3 years, 9.8 % after 5 years and 13.4 % after 10 years [28]. Contrera *et al* reported no GH insufficiency at 20 months follow-up and a median target dose of 64 Gy in sinonasal and nasopharyngeal cancer patients [30].

Hyperprolactinemia

Insufficiency of the hypothalamic–pituitary–prolactin axis leads to a decrease of the inhibitory effect of dopamine to the pituitary, leading to hyperprolactinemia. The reported prevalence for hyperprolactinemia ranged from 0.0 % to 43.3 % after a mean dose range to the HPA of 29.9 to 63.5 Gy and a follow-up ranging from 17 to 120 months. Raymond *et al* [28] reported hyperprolactinemia in 1.9 % of patients after 3 years, in 10.1 % after 5 years and in 18.5 % after 10 years.

Luteinizing hormone and follicle stimulating hormone

The prevalence for insufficiency of the hypothalamic–pituitary–gonadal axis ranged from 4.0 % to 36.9 % after a mean dose range to the HPA from 29.9 to 56.3 Gy and a follow-up ranging from 17 to 120 months. Kyriakakis *et al* reported a dose threshold of 30 Gy to develop insufficiency of the gonadal axis [20]. Partoune *et al*. found no gonadal insufficiency at a pituitary dose under 45 Gy, while a dose above 45 Gy resulted in an insufficiency rate of 46 %. A hypothalamic dose under 20 Gy lead to a gonadal axis insufficiency rate of 16 % and above 20 GY, insufficiency was 50 % [29]. In three studies, FSH and LH insufficiencies were separately reported. Huang *et al*. reports 20.4 % insufficiency of FSH and 0 % of LH [19], McDowell *et al* report elevated levels of FSH in 7 % of the patients and elevated levels of LH in 5 % [31] and Handisurya *et al*. report 17 % and 11 % insufficiency for FSH and LH

respectively [25]. Raymond *et al*. report a gonadal axis deficiency of 9.6 % after 3 years, 17.8 % after 5 years and 36.9 % after 10 years [28].

Multiple axes

In 13 studies, endocrine insufficiency of multiple axes was reported. Sharma *et al* reported a 7 % deficiency on 1 axis after a mean D_{pit} of 23.5 Gy, 11 % on 2 axes after a mean dose of 36.0 Gy and 4 % on 4 or more axes after a mean dose of 68.1 Gy, [32]. Raymond *et al* report in a time dependent way, showing 21 % insufficiency on 2 axes, 8 % on 3 axes and 13 % on 4 or more axes at a follow-up of 10 years [28].

Meta-analysis

Two publications were excluded from the *meta*-analysis. The publication by Tabrizi *et al*. [21] was an update from a publication by Shih *et al*. [23], for which reason the publication by Shih *et al*. [23] was excluded.The update shows a complete data collection on all assessments through the full 60-months follow-up period on all patients. The endocrine assessment provided the same results in the same cohort of patients in both papers. Another publication by Kyriakakis *et al*. [20] showed an analysis performed on a subgroup of a former study by the same author [24], for which it was excluded. In the study on the subgroup [20], long-term outcomes of chemoradiotherapy on the pituitary function were analysed and dose thresholds were provided for recognizing patients for whom endocrine surveillance was required.

In one publication, overlap of patients with insufficiency on 2 axes was suspected. In this publication, hypopituitarism was reported in 10 patients in whom hormone replacement with gonadal steroids was required in 7 patients, growth hormone replacement in 2 patients and thyroxine and hydrocortisone replacement in 4 patients. In this case, the reported numbers were regarded as individual patients in this review [33].

A significant correlation between insufficiency on any axis and follow-up time was observed (Pearson R = 0.57, p = 0.015, Fig. 2c). A Pearson correlation test did not show a correlation between dose to the HP region and any insufficiency (Pearson R = 0.16, p = 0.535), nor for the individual axes.

Results of the *meta*-analysis on the prevalence for insufficiency per axis is reported in Fig. 3a. Prevalence for any insufficiency per tumor localization is displayed in Fig. 3b.

By means of random effects *meta*-regression, a prevalence of 0.61 (95 % CI 0.44–0.75) for insufficiency on any axis was calculated. The highest mean prevalence for insufficiency on any axis was found in the treatment of NPC and other HN tumors (0.68; 95 % CI 0.45–0.85), followed by treatment of intracerebral tumors (0.60; 95 % CI 0.28–0.85) and SB tumors (0.50; 95 % CI 0.23–0.76). For the individual axes, insufficiency for growth hormone showed a mean prevalence of 0.40 (95 % CI 0.22–0.61). For hyperprolactinemia, a mean prevalence of 0.22 (95 % CI 0.17–0.28) was found, for gonadotropin deficiency of 0.20 (95 % CI 0.14–0.28), for adrenocorticotropic hormone deficiency of 0.16 (95 % CI 0.08–0.30) and for thyroid stimulating hormone deficiency 0.16 (95 % CI 0.11–0.23). Insufficiency of 1 HP axis showed mean prevalence of 0.19 (95 % CI 0.11–0.30), of 2 axes of 0.22 (95 % CI 0.12–0.38), of 3 axes 0.05 (95 % CI 0.03–0.09) and of 4 or more 0.17 (95 % CI 0.08–0.32), respectively (Fig. 3a).

Discussion

The purpose of this systematic review and *meta*-analysis was to investigate the reported prevalence on HPA dysfunction in adult patients after irradiation for non-pituitary, non-hypothalamic brain, HN, or SB tumors at adult age. Although a wide variation for the prevalence of HPA dysfunction was observed, depending on tumor characteristics, radiation dose and duration of follow-up, our *meta*-analysis, including publications between January 2010 and June 2024 showed similar results compared to the *meta*-analysis by Appelman-Dijkstra *et al* [13] from 2011, reporting publications between 1975 and 2009. The previous *meta*-analysis with older literature reported a prevalence of 0.66 (95 % CI, 0.55–0.76) for any form of hypopituitarism in the included cohorts, with a prevalence of 0.45 (95 % CI 0.33–0.57) for GHD, of 0.34 (95 % CI 0,15–0.60) for hyperprolactinemia, of 0.30 (95 % CI 0.23–0.37) for LH/FSH-D, of 0.25 (95 % CI 0.16–0.37) for TSHD and of 0.22 (95 % CI 0.15–0.30) for ACTH-D. Also, Ntali and Karavitaki [34] reported similar results with a prevalence for GHD of 30–100 %, around 30 % for FSH/LH, 20–30 % for ACTH and around 10 % for TSH for adult patients with non-pituitary brain tumors. Regarding NPC, Appelman-Dijkstra *et al* [13] reported a prevalence for any insufficiency of 0.74 (95 % CI 0.57–0.86) and for intracerebral tumors of 0.54 (95 % CI 0.42–0.66), which is also comparable to our findings.

To be aware of the radiation effects on the hypothalamic-pituitary function in cancer survivors is important as both quality of life (QoL) and cognitive functioning may be hampered in patients with pituitary insufficiency as a consequence of thyroid, cortisol, gonadal or GH deficiency. This is of special importance in adults surviving brain tumors due to the fact that they may already have deprived QoL due to for example previous brain surgery, the fear of cancer recurrence, acquired brain

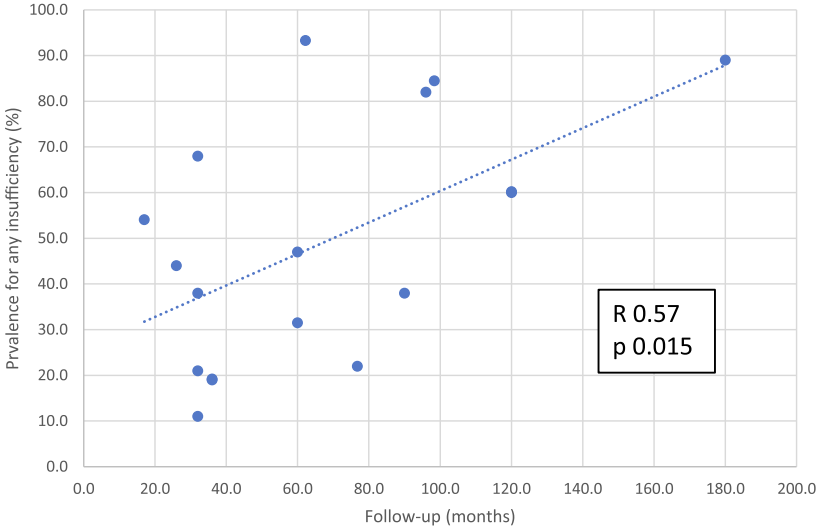

Fig. 2c. Reported prevalence (%-age) of insufficiency on any axis related to follow-up time as reported in the included publications. A significant correlation observed. R = 0.57, p-value = 0,015.

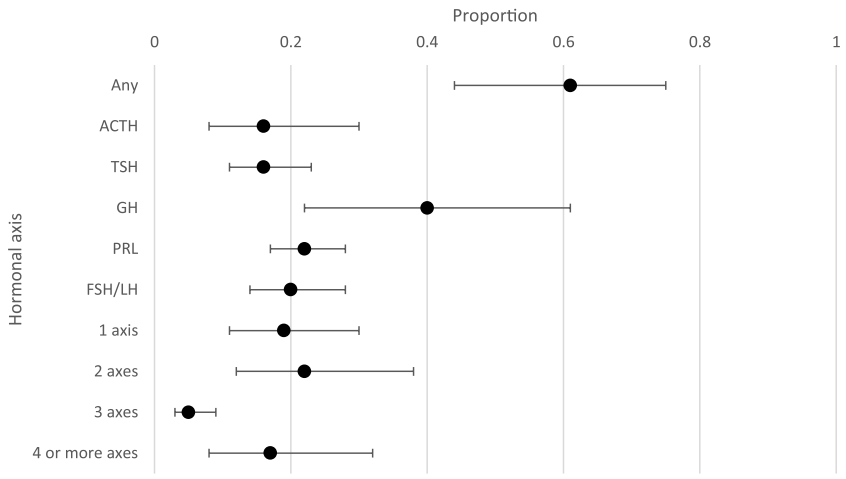

Fig. 3a. Mean proportion prevalences and 95% confidence interval for insufficiency on any axis, per axis and for multiple axes, derived from the *meta*-analysis.

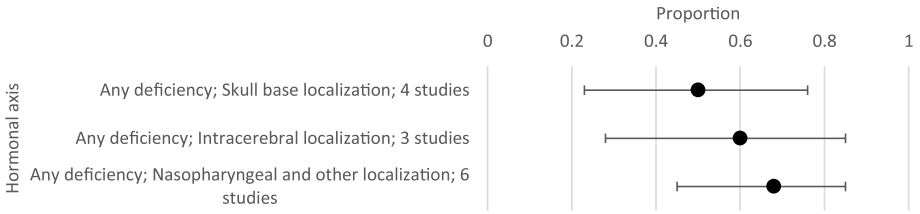

Fig. 3b. Mean proportion prevalences and 95% confidence interval for insufficiency on any axis per tumor localization.

damage, sleep problems, neurological problems or cognitive decline. An increased prevalence for anxiety and depression or changes in cognitive functioning after radiation exposure might be present in patients with an insufficient adrenocorticotrophic axis, due to decreased cortisol levels, which (next to the risk for adrenal crisis) emphasized the importance of surveillance and adequate management [35,36,37,38]. Disruption in the serotonin and norepinephrine circuity, in which the hypothalamus has a role, may also lead to these symptoms [39]. Working memory may be hampered in brain tumor survivors. In one study, involving 44 pediatric brain tumor survivors, an association between a higher mean dose to the pituitary gland and lower performance on working memory was found [40].

Besides insufficient pituitary function and deficiencies of pituitary hormones due to irradiation and its effects on QoL, radiation may also directly affect the hypothalamus and decrease QoL by hypothalamic dysfunction. Patients with hypothalamic dysfunction may be at risk for the development of obesity, behavioral problems and sleeping disorders [41–43] with radiation-induced neuroinflammation as a possible cause, more specifically in somnolence syndrome [44]. Post-irradiation somnolence syndrome itself may lead to cognitive dysfunction [45]. Nevertheless, in the current literature review the observed data on QoL and cognition in relationship to HPA was too limited for further analysis or conclusions.

Apart from radiotherapy treatment, other treatment modalities such as surgery and/or chemotherapy may also contribute to (late) pituitary insufficiencies. Hypopituitarism is a well-known adverse event of neurosurgery in patients with sellar and suprasellar tumors without additional radiotherapy [46,47]. There is still some uncertainty about the direct effect of chemotherapy on hypothalamic-pituitary functioning [7,48]. One study included in our review reported that concurrent chemoradiation was significantly associated with development of HPA dysfunction compared to the radiotherapy alone group [26], however, in a recent international consensus it was agreed that chemotherapy does not result in HP dysfunction [49]. The influence of chemotherapy on cognitive functioning however, is quite familiar. Treatment with chemoradiation or radiotherapy as a single treatment modality may lead to different effects on cognitive functioning. In a study in which two cohorts were compared, both showing cognitive decline, one group was treated with radiotherapy alone, but at high doses (46–62 Gy) to the temporal lobes and the other group received chemoradiation at lower doses (34 Gy) to the temporal lobes, but with addition of platinum-based chemotherapy. A possible explanation for these results is the disruption of the integrity of the blood–brain barrier by radiation, resulting in an increased brain exposure to chemotherapy [50]. Finally, the use of immune checkpoint inhibitors (ICI) gives rise to new concerns in causing secondary hypophysitis. Inflammation mechanisms differ between the types of ICI. Hypophysitis caused by CTLA-4 blockade often leads to panhypopituitarism and is associated with mild enlargement of the pituitary, while PD-1 blockade may lead to isolated ACTH deficiency without imaging abnormalities [51,7]. The current multimodal treatment approaches make it challenging to state whether endocrine insufficiency is caused by radiation dose, systemic treatment, surgery or, as may be expected, a combination of these treatment modalities.

In this review, several publications reported pituitary insufficiency at lower doses to the hypothalamus than compared to the pituitary gland. This finding is supported by other reviews [52,53,48,7], indicating that the hypothalamus may be more radiosensitive. The typical order in which the hormonal axes become insufficient underlines a mechanism in which a deficient hypothalamus leads to a decreased hypothalamic input to the pituitary gland and hence atrophy of the pituitary. Higher radiation doses may lead to a direct effect on the pituitary.

As a consequence, the expected higher vulnerability of the hypothalamus to radiation dose and the implications on endocrine homeostasis and quality of life in general, marks this structure as a potential organ at risk (OAR). This calls for a standardized delineation of the hypothalamus and pituitary gland in radiotherapy plans. For the development of an NTCP (normal tissue complication probability) curve for the hypothalamus and pituitary, more retrospective research on the relation between pituitary insufficiency and other quality of life issues such as anxiety and depression, sleeping disorders and cognitive

impairment and dose delivery to these structures is needed. Once NTCP models have been developed, radiation treatment plans can be further optimized to avoid complications, and in addition a standard systematic and longer endocrine and quality of life follow-up of patients with a dose delivery above a certain threshold to these structures can be recommended, in accordance with the EPTN guidelines [54].

This systematic review and *meta*-analysis has some limitations which must be acknowledged.

First, the cohorts included in the *meta*-analysis were rather heterogeneous, making the calculated insufficiency difficult to generalize to a specific patient population. A multivariate correction was not applied because of a lack of data on insufficiency for relevant confounders.

Second, the patient groups in this review consisted of prospective and retrospective cohorts. The retrospective cohorts consisted of patients referred for endocrine evaluation, making a selection bias probable. In the prospective cohorts, patients were invited to participate. This way of recruiting participants may lead to a selection bias in a way that patients with endocrine complaints may react in larger numbers to the invitation to participate.

Third, in all cohorts, the reported HP insufficiencies may have been the result of multimodal treatment of brain, HN and SB tumors, with neurosurgery, systemic therapy and radiotherapy often given in combination. Also systemic treatment may have affected the peripheral endocrine organs leading to combined pituitary-peripheral endocrine insufficiency. Alkylating agents for instance may have long-term effects on the gonadal function. The effects of surgery and systemic treatment on endocrine insufficiency were not calculated in the selected papers, making a multivariate *meta*-analysis less feasible.

Fourth, a risk of bias assessment was performed to rate the quality of the papers. The results of this assessment were discussed in relation to the *meta*-analysis, and one of the criteria was a completion of the follow-up of patients in cohorts of at least 75 %. However, information regarding patient loss to follow-up, incomplete follow-up due to deceased patients or recurrence of disease is lacking, making an accurate estimation of insufficiency prevalence difficult.

Conclusions

Hypothalamic-pituitary dysfunction is frequently encountered in patients, irradiated at adult age for brain tumors, HN cancers and SB tumors. This demands for further research on dose delivery to these important structures. Maximum tolerable dose data for the pituitary gland are in development, however, more research on dose tolerance to the hypothalamus asks for attention. Long term effects of hypothalamic dysfunction, such as endocrine insufficiency, sleep disorders, behavioural disorders, temperature dysregulation, anxiety and depression have to be investigated in larger patient cohorts.

This research may eventually result in an NTCP model for the hypothalamus and the establishment of guidelines for follow-up of these undesired conditions in survivors.

CRediT authorship contribution statement

J.M.J. Paulissen: Conceptualization, Methodology, Investigation, Writing – original draft. **C.M.L. Zegers:** Conceptualization, Methodology, Writing – review & editing. **R.M. Houben:** Formal analysis. **D. Hofstede:** Investigation. **M. Kars:** Writing – review & editing. **H.M. van Santen:** Writing – review & editing. **F.J.P. Hoebers:** Writing – review & editing. **D.K.M. De Ruysscher:** Writing – review & editing. **D.B.P. Eekers:** Methodology, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix 1

Search Strategy by Appelman-Dijkstra *et al*, J Clin Endocrinol Metab, August 2011, 96(8):2330–2340.

("radiotherapy"[subheading] OR "radiotherapy"[tw] OR "Radiotherapy"[mesh:noexp] OR "Cranial Irradiation"[mesh:noexp] OR "Radiosurgery"[mesh] OR "Radiotherapy, Computer-Assisted"[mesh] OR "Radiotherapy, Conformal"[Mesh] OR "Radiotherapy Dosage"[mesh] OR "Dose Fractionation"[mesh] OR "Radiotherapy, High-Energy"[mesh] OR "Neutron Capture Therapy"[mesh] OR "Radioisotope Teletherapy"[mesh] OR "X-Ray Therapy" OR "radiation therapy"[tw] OR "total body irradiation"[tw] OR "whole body irradiation"[tw] OR "whole-body irradiation"[MeSH Terms] OR "radiation injuries"[mesh] OR radiation[tw] OR irradiation[tw]) AND ("pituitary gland"[mesh] OR "pituitary glands"[tw] OR "pituitary gland"[tw] OR "pituitary function" OR hypophysis OR Corticotrophs OR Gonadotrophs OR Lactotrophs OR Somatotrophs OR Thyrotrophs OR Melanotrophs OR "Pituitary Function Tests"[mesh] OR Hypopituitarism OR pituitary axis) AND (("Brain Neoplasms"[mesh] NOT "Pituitary Neoplasms"[mesh]) OR "brain tumor" OR "brain tumors" OR "brain tumour" OR "brain tumours" OR "intracranial tumor" OR "intracranial tumors" OR "intracranial tumour" OR "intracranial tumours" OR "cranial tumor" OR "cranial tumors" OR "cranial tumour" OR "cranial tumours" OR "cerebral tumor" OR "cerebral tumors" OR "cerebral tumour" OR "cerebral tumours" OR "Nasopharyngeal Neoplasms"[mesh] OR "Nasopharynx Neoplasms" OR "Nasopharynx Neoplasm" OR "Cancer of Nasopharynx" OR "Nasopharynx Cancers" OR "Cancer of the Nasopharynx" OR "Nasopharynx Cancer" OR "Nasopharyngeal Cancer" OR "Nasopharyngeal Cancers" OR "Head and Neck Neoplasms"[mesh:noexp] OR (head[ti] AND neck[ti] AND (tumor[ti] OR tumour[ti] OR tumors[ti] OR tumours[ti] OR cancer[ti] OR carcinoma[ti] OR carcinomas[ti]))).

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