Endotext

HYPOPITUITARISM FOLLOWING CRANIAL RADIOTHERAPY

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ABSTRACT

Radiation treatment is used for patients with secreting and non-secreting pituitary adenomas, with residual pituitary adenomas, or recurrent pituitary adenomas with the aim to achieve long term disease control. Radiotherapy is an integral component of the management of other tumors in the sellar region (craniopharyngiomas) and for certain types of cancers and lymphomas. Pituitary hormone deficiencies are the commonest late complication of radiotherapy, which usually occurs after several years. The development of hormone deficiencies with time varies in the published literature. Predictors for the development of hypopituitarism are the dose of radiation and the age at time of treatment. Different pituitary axes appear to have different radio-sensitivity with the somatotrophic axis being the most sensitive. Long-term endocrine evaluations are recommended in patients after cranial radiotherapy to identify new pituitary hormone deficiencies and introduce appropriate hormone replacement therapy. Clinical evaluation, baseline pituitary hormone assessment, and dynamic testing for growth hormone and adrenocorticotropic hormone (ACTH) deficiency should begin one year after cranial radiotherapy. Compared with conventional radiotherapy, advanced radiation technologies (stereotactic radiosurgery, cyber knife, fractionated stereotactic radiotherapy, proton beam therapy) are presumed to have the ability to deliver radiation to the tumor with remarkable precision minimizing its effects on healthy tissues. Results from larger series with longer length of follow-up are needed to help clinicians identify who will benefit most from advanced radiation techniques.

INTRODUCTION

In the past few decades, the survival of patients with brain tumors, including malignant tumors has improved greatly. However, these patients tend to develop acute and late complications of tumor treatment, which includes cranial irradiation.

The rationale for radiotherapy is to achieve excellent long-term tumor control after partial surgical excision and published 10-year tumor control rates are reported to be high. The following diseases are treated with radiotherapy: pituitary adenomas or other sellar tumors not derived from pituitary tissue (craniopharyngioma, meningioma, germinoma), brain cancers, head and neck tumors, and acute lymphoblastic leukemia (ALL) (Table 1).

Table 1. Diseases Treated with Cranial Irradiation
PITUITARY
Acromegaly, Cushing disease, prolactinoma, nonfunctioning pituitary adenoma
OTHER SELLAR TUMORS
Craniopharyngioma, meningioma, germinoma
NONPITUITARY BRAIN TUMORS
Meningioma, metastases, neuroblastoma, lymphoma
HEAD AND NECK TUMORS
Nasopharyngeal carcinoma, rhabdomyosarcoma, retinoblastoma, skull-based tumors
HEMATOLOGICAL MALIGNANCIES
Acute lymphoblastic leukemia, lymphoma
OTHER DISEASES REQUIRING HEMATOPOIETIC STEM-CELL TRANSPLANTATION (after conditioning with total body irradiation)

Following radiotherapy, the side effects of radiotherapy may be acute toxicity (within weeks of completion of therapy) and late toxicity which occur years after treatment. The risk of toxicity depends on the total radiation dose. Doses are divided into fractions and the duration of cranial radiotherapy varies from one or a few days in short courses to several weeks of daily radiations in long courses. Higher doses (up to 60Gy) are used for pituitary tumors, non-pituitary brain tumors, head and neck tumors (nasopharyngeal cancer, rhabdomyosarcoma) and skull-base tumors, while lower doses are used in patients with ALL and total body irradiation as preconditioning before bone or stem cell transplantation (1-14).

Radiotherapy has greatly evolved over the past few decades. Conventional radiotherapy has been used for the longest period of time. Conventional radiotherapy is administered by a linear accelerator, with a total dose of 40-45Gy, in at least 20 sessions. A single beam of high-energy radiation is focused onto a small treatment area, but the radiation also includes healthy surrounding tissue. In photon-based radiotherapy, photons interact with the electrons and deposit energy, causing DNA damage. Maximum dose deposition occurs shortly after entering the body, decreasing then until the exit the body. Standard photon-beam radiotherapy (conventional fractionated photon-based) is administered by a linear accelerator and deliver 1.8-2Gy fractions of radiation dose 5 days a week for 4-6 weeks. 3D conformal radiation therapy, including whole brain and total body radiotherapy have been widely used for years but with little possibility of organ at-risk sparing. It involves the use of CT scans and manual optimization of the shaped dose to the tumor.

Technical advances in radiotherapy refer to high precision treatment (stereotactic) and they include radiosurgery (gamma knife), robotic arm mounted linear accelerator (cyber knife), and proton beam therapy (Table 2) (15).

Stereotactic radiosurgery (SRS) delivers a single fraction of high dose radiation focused on the tumor. SRS uses photons (gamma knife, LINAC, cyber knife) or heavy particles (protons). SRS delivers multiple beams stereotactically with high-dose gradients allowing good organ at-risk sparing. Stereotactic radiosurgery uses precise immobilization techniques, CT/MRI and multiple intersecting beams. With this

approach it is possible to deliver a single large radiation dose to a tumor volume, with reduced dose to surrounding healthy tissue.

Fractionated stereotactic radiotherapy (FRST) uses a linear accelerator (LINAC) to deliver photon radiotherapy. Tumor targeting and radiation planning are better with the use of computer assisted program. The patient is immobilized for precise delivery of radiation. The treatment is delivered by intensity-modulated radiotherapy or by volumetric-modulated arc radiotherapy. Intensity-modulated radiotherapy (IMRT) as an advanced method of delivering conventional radiotherapy, has been used since the 2000s. IMRT relies on several beams, normo-fractioned (with 1-2 Gy fractions), with focus on tumor volume and clear delineation of surrounding healthy tissues. IMRT uses a CT scan and a computer algorithm for automatic-planning of radiotherapy. This radiation technique allows dose escalation to the tumor tissue with sparring normal tissues. The photon radiotherapy has further improved over the next decades and new techniques were introduced: an image-guided radiotherapy (IGRT), volumetric-modulated arc therapy (VMAT) and helical tomo-therapy (16). In VMAT treatment is delivered using multiple arcs or beams shaped with multi-leaf collimators to the tumor's geometry.

Proton beam therapy uses the delivery of proton particles for the radiation treatment. Protons travel through tissue in a straight line, with more rapid fall-off of radiation with distance from the tumor and the absence of an exit dose (Bragg peak effect). Proton therapy is further indicated in order to spare healthy tissues from radiation due to lack of diffusion of the radiation.

Initial data suggest that the radiation-associated endocrine dysfunctions may be reduced with these new radiation techniques. However, further clinical studies with more patients, longer follow-up, control group, randomized prospective studies are needed to better define the consequences of these new radiation methods.

Table 2. Radiation Techniques

Type	Characteristics	Number of sessions
CONVENTIONAL	The fractionation allows normal tissue to recover, while tumorous tissue is destroyed + extra tumoral side effects	several
STEREOTACTIC	Higher accuracy, fewer side effects	
	Gamma knife radiosurgery	Single
	Fractionated stereotactic radiotherapy	several
	Cyber Knife	Single or 3-5 fractions (hypofractionated SRS)
PROTON BEAM	Lack of diffusion of the radiation + lack of extra tumoral side effects	

SRS: stereotactic radiosurgery

ACUTE AND CHRONIC COMPLICATIONS OF CRANIAL RADIOTHERAPY

Acute toxic effects of radiation include skin erythema, hair loss, tiredness, nausea, headache, and hearing problems. These short-term complications resolve spontaneously within days to weeks after radiotherapy. Long-term complications of pituitary irradiation include hypothalamic-pituitary dysfunction (hypopituitarism, hyperprolactinemia, central precocious puberty), optic neuropathy, cranial neuropathies (II, III, IV, V and VI cranial nerve injury), brain radio-necrosis (neurocognitive dysfunction, focal neurologic signs, seizures), carotid artery stenosis, cerebrovascular accidents, and second brain tumors (most commonly meningioma and glioma) (Table 3) (17-26). The risk of hypopituitarism varies, depending on the radiation technique, the radiation dose, and increases with the duration of follow-up. After conventional radiotherapy in patients with a pituitary adenoma, the incidence of hypopituitarism occurs in 30-60% of patients 5-10 years after irradiation. The risk for other radiation-induced chronic complications is usually low (< 5% for new visual deficits, cranial neuropathies, or brain radio-necrosis, and < 1% for secondary brain tumors) (27).

Table 3. Complications of Cranial Radiotherapy

ACUTE	CHRONIC
Skin erythema	**Hypothalamic-pituitary dysfunction** GH deficiency FSH/LH deficiency TSH deficiency ACTH deficiency Hyperprolactinemia Central precocious puberty
Hair loss	**Neuropathy** Optic Cranial (II, III, IV, V, VI)
Headache	**Brain radionecrosis** Neurocognitive dysfunction Focal neurological signs Seizures
Hearing impairment	**Carotid artery stenosis**
Nausea	**Cerebrovascular insult (stroke)**
Tiredness	**Second brain tumor**

INCIDENCE OF RADIATION-INDUCED NEUROENDOCRINE DYSFUNCTION

A number of studies reported very different incidences of radiation-induced hypopituitarism, central precocious puberty, or hyperprolactinemia, depending on indications for radiotherapy, radiation technique, radiation dose, and duration of follow-up.

Pituitary Adenomas and Craniopharyngiomas

The incidence rate of new onset hypopituitarism after conventional radiotherapy in patients with recurrent or residual functioning or nonfunctioning pituitary adenoma reaches 30-100% after follow-up of 10 years (28-31). According to the data from one of the largest cohorts of 4110 patients with adult-onset growth hormone (GH) deficiency (Pfizer International Metabolic Database, KIMS), 36% of patients with isolated GH deficiency and 37% of patients with multiple pituitary hormone deficiencies had a history of cranial radiotherapy (32).

New data indicate that modern radiation techniques, such as stereotactic radiosurgery or fractionated radiotherapy, can achieve long-term control with lower incidence of radiation-induced hypopituitarism (10-40% of patients at 5 years) compared with conventional radiation techniques (33, 34). A systematic review and meta-analysis of 24 studies with 1381 patients with pituitary adenomas treated with gamma knife radiosurgery (median marginal dose 22.6 Gy, maximum dose 50 Gy, and isodose line 50%) reported that 11.4% experienced endocrinopathies at a median of 45 months after radiotherapy, with pooled 5-year rates of 8% (35). Panhypopituitarism was reported in 19.6% of cases, secondary hypothyroidism in 42.4% and hypogonadotropic hypogonadism in 33.5% of cases.

A large multicenter international study followed 1023 patients with a median follow-up 51 months after gamma knife radiosurgery for pituitary adenoma and 24.2% of patients developed new anterior pituitary hormone deficiency (36). The median time to hypopituitarism was 39 months. Sixty percent of patients had single and 39.5% patients had multiple hormone deficiencies. ACTH deficiency developed in 21.6% patients, TSH deficiency in 35.6%, gonadotropin deficiency in 24.3%, GH deficiency in 15.6% and AVP deficiency in 2.9% patients. The 5-year rate of hypopituitarism was 22.4%, and 10-year rate of hypopituitarism was 31.3% Prognostic factors for hypopituitarism were: a lower isodose line, whole sella targeting and treatment of a functional pituitary adenoma (36). The authors concluded that the majority of hypopituitarism occurred within the first 1-5 years after radiotherapy, but delayed hypopituitarism can occur even beyond 10 years.

In patients with Cushing´s disease treated with conventional radiotherapy, hypopituitarism occurred in 50% of patients, with at least 5 years of follow-up (37). In a review of 1318 patients with Cushing´s disease treated with SRS, with a mean follow-up of 5 years, new anterior pituitary hormone deficiency developed in 20-30% of patients, usually within 2 years from radiotherapy (38). The use of intensity-modulated radiotherapy for Cushing´ disease reported 22.9% of hypopituitarism after a median follow-up time of 36.8 months (39).

The prevalence of at least one anterior-pituitary deficit after surgery and radiotherapy for a craniopharyngioma varies between 60% and 100% (40). A nationwide retrospective study included 145 patients with childhood-onset craniopharyngioma (mean age at diagnosis 8.4 years), with cranial radiotherapy in 39% of cases after surgery. All patients but one presented with at least one hormone pituitary deficiency. TSH deficiency was most frequent (98.3%), followed by ACTH (96.8%), arginine vasopressin (91.1%), and growth hormone deficiency (77.4%) (40).

Recently published study followed 101 children and adolescents with craniopharyngioma after treatment with photon-based conformal and intensity-modulated radiation therapy for 10 years (41). The 10-year cumulative incidence of growth hormone deficiency (GHD) was 68.42% for black patients and 94.23% for white patients. Cumulative incidence of TSH deficiency was 70.94% at 10 years for non-shunted patients, 91.67% at 6 years for shunted patients, 100% at 4 years for those with diabetes insipidus and 71.36% at 10 years for those without diabetes insipidus. The 10-year cumulative incidence of ACTH deficiency was 70.00% for those with diabetes insipidus and 48.39% for those without diabetes insipidus. The 10-year cumulative incidence LH/FSH deficiency was 43.33% age < 7 years, 61.29% aged 7-10 years, and 78.95% age ≥10 years. Predictive factors for the occurrence of hypopituitarism were hydrocephalus, host (race) and vasopressin deficiency (41).

Skull Base Meningioma

Patients with skull base meningioma underwent radiotherapy either as first-line treatment of following initial surgery (partial or total). Little information is available regarding the prevalence of hypopituitarism in patients irradiated for skull base meningioma. A study of 48 patients with a skull base meningioma, treated with radiotherapy, reported that complete hypopituitarism was present in 13% of patients, while at least one pituitary hormone deficit was present in 38% of patients after a median follow-up period of 7.5 years (42). The growth hormone and TSH deficiencies were the most prevalent deficiencies (35% and 32%, respectively), followed by FSH/LH deficiency (28%) and ACTH deficiency (13%). Several risk factors for radiation-induced hypopituitarism were identified: localization of meningioma, radio-sensitivity of meningioma (regression after radiotherapy), treatment duration and radiation dose (42). Another study with 52 adult patients receiving photon-beam therapy for skull base meningiomas reported up to 60.1% of patients who had 2 or more pituitary deficiencies 10 years after radiotherapy (43). The gonadotroph deficiency (37%) was the most prevalent abnormality, followed by thyrotroph (28%), corticotroph (18%) and somatotroph (15%) deficiencies. Hypopituitarism could appear very early, within the first year after radiotherapy, with increasing incidence of hypopituitarism later, during the follow-up. Large meningioma (more than 4cm) or a radiation dose of more than 50Gy were predictive factors for hypopituitarism (43).

Brain Tumors Distant from the Hypothalamus and Pituitary

Studies with shorter follow-up showed that 41% of patients irradiated for brain tumors distant from the hypothalamus and pituitary region developed hypopituitarism, 16% with isolated pituitary hormone deficiency and 25% with multiple pituitary hormone deficiencies (44). The largest study with long follow-up (median 8 years) showed a higher prevalence of pituitary dysfunction (88.8%) after cranial radiotherapy for adult-onset non-pituitary brain tumors (45). GH deficiency was the most frequent neuroendocrine abnormality (86.9% of patients), followed by gonadotrophin deficiency (34.6%), ACTH deficiency (23.4%) and TSH deficiency (11.2%). Hyperprolactinemia was reported in 15% of patients. Single pituitary axis dysfunction was reported in 41.1% of patients, while multiple pituitary hormone deficits were present in 47.7% of patients (45).

Conventional fractionated radiotherapy in adults with gliomas found a high prevalence of hypopituitarism in these patients (84.5%) after a follow-up of 8.2 ± 5.2 years (46). The mean radiation dose to the glioma was 53.9 Gy and to the hypothalamo-pituitary axis was 35.9 Gy. The most prevalent deficiency was growth hormone deficiency (82.8%), followed by central hypogonadism (20.7%), central hypocortisolism (19%) and central hypothyroidism (6.9%). Multiple pituitary hormone deficits were observed in almost 40% of

patients. Hyperprolactinemia was present in 10.3% of patients, all females, and was transient in the majority of patients. The hypothalamo-pituitary radiation dose thresholds for the growth hormone deficiency, hypogonadism, hypocortisolism and hypothyroidism were 10, 30, 32 and 40.8Gy, respectively. Neuroendocrine dysfunction following cranial radiotherapy correlated with the radiotherapy dose delivered to the hypothalamo-pituitary axis and duration of follow-up (46).

A meta-analysis of 18 studies with a total of 813 patients showed that approximately two thirds of all adults previously treated with cranial radiotherapy for an intracranial tumor or nasopharyngeal cancer developed some degree of hypopituitarism (47). Growth hormone deficiency was the most prevalent (45%), followed by gonadotropin deficiency (30%), TSH deficiency (25%) and ACTH deficiency (22%).

Recently published analysis of 45 studies from 2000 to 2022 of adult patients undergoing radiotherapy for pituitary adenoma, brain tumors, head and neck tumors showed that endocrine deficiencies occurred in about 40% of patients within a median follow-up of 5.6 years, without a clear difference between radiotherapy modalities (48). In this review, somatotropic axis was the most radiosensitive, while the thyrotropic axis was the least radiosensitive.

Systematic search of the literature showed that hypopituitarism can occur within the first year after radiotherapy (range 3 months-25.6 years) in 20-93% of adult cancer patients treated with cranial radiotherapy (49). It is important to notice early onset of hypopituitarism (within the first year after cranial radiotherapy) and to start replacement therapy (glucocorticoids, thyroxin) in patients with brain metastases or other malignancies treated with cranial radiotherapy (nasopharyngeal cancer, non-pituitary brain tumor, head and neck cancer), and in patients with small cell lung cancer treated with prophylactic cranial irradiation. Modern radiotherapeutic technique with a sparing approach of the hypothalamo-pituitary axis might be a promising option for these patients (50).

Childhood-Onset Brain Tumors

Cranial radiotherapy in childhood often affects growth causing growth retardation and affects sexual development causing early or delayed puberty (9, 51-55). ACTH deficiency may develop many years after the cranial irradiation, especially in childhood cancer survivors who had tumors located and/or had surgery near the hypothalamo-pituitary axis and who received radiotherapy dose of over 30Gy to the hypothalamo-pituitary region (56). Children treated with radiotherapy for brain tumors had decreased pituitary height and endocrine deficiencies at 2, 5, and 10 years post-diagnosis (57). In the largest cohort of childhood-onset brain tumors (Childhood Cancer Survivor Study, CCSS), 43% of 1607 children who survived their disease for 5 or more years developed one or more anterior pituitary hormone deficiencies (51). A retrospective clinical study reported the prevalence of hypopituitarism in a large cohort of 748 adult survivors in the USA treated with cranial radiotherapy in childhood (CCSS), among them 72% with a leukemia diagnosis (9). After a long duration of follow-up (mean 27.3 years, range 10-47 years), the prevalence of GH deficiency was 46.5%, gonadotropin deficiency 10.8%, TSH deficiency 7.5% and ACTH deficiency 4%. The same population of patients were investigated in 2019, when the authors compared the prevalence of neuroendocrine deficiency in irradiated and non-irradiated childhood cancer survivors (58). In the 1086 irradiated children 40.2% had GH deficiency, 11.1% had TSH deficiency, 10.6% had FSH/LH deficiency, and 3.2% had ACTH deficiency, after a median follow-up time of 24.1 years, higher than in non-irradiated children (only 6.2% had GH deficiency and less than 1% had other endocrinopathies) (58). Similar results were published in 2022, when the authors investigated the neuroendocrine dysfunction in 355 children and adolescents who were treated with

conformal radiation therapy for central nervous system tumors (low-grade glioma or ependymoma) at median age of 6.4 at radiotherapy and after the median follow-up of 10.1 years (59). The prevalence of GH deficiency was 37.2%, gonadotropin deficiency 17.7%, TSH deficiency 14.9%, ACTH deficiency 10.3% Hypothalamus mean dose ≥ 36 Gy was associated with higher odds of any deficiency (59). Recently published study on 41 adult survivors of childhood brain tumors treated with proton and photon irradiation showed that 63% of patients had GH deficiency after 14.8 years of follow-up (60).

A retrospective analysis of 102 children treated for brain, head and neck, and hematological malignancies with photon beam radiotherapy followed for 5.7 years showed that the majority (62.7%) developed pituitary insufficiency (61). Forty-one percent had one and 38% had two hormone deficiencies. Growth hormone deficiency was the most common (56.9%), followed with TSH deficiency (31.4%). Patients who developed pituitary insufficiency received higher maximum pituitary dose (median dose 44Gy). Doses of 40-49 Gy or more than 50 Gy led to a higher cumulative incidence rate of hypopituitarism compared with radiotherapy dose less of 20 Gy. However, even at lower dose of radiotherapy (less than 20 and 20-29 Gy), a five-year cumulative incidence of GH and TSH deficiency was about 30%.

It has been shown that large proportion (85.4%) of childhood nasopharyngeal carcinoma patients had reduced pituitary heights three months after radiotherapy (62). Some patients even had empty sella after radiotherapy. These changes of pituitary volume had long term side effects on the linear growth of these children (62). In addition, some childhood cancer survivors develop overweight or obesity (due to hypothalamic damage), dyslipidemia, metabolic syndrome and low bone mineral density (53).

Guidelines of the Endocrine Society addresses the diagnosis and treatment of hypothalamic-pituitary and growth disorders encountered in childhood cancer survivors (63).

THE PATHOPHYSIOLOGICAL MECHANISMS OF RADIATION-INDUCED NEUROENDOCRINE DYSFUNCTION

Cranial irradiation causes irreversible and progressive damage to the hypothalamic-pituitary region. There are several pathophysiological mechanisms of the radiation-induced hypopituitarism including direct hypothalamic neuronal and vascular injury, with secondary pituitary atrophy being the most common mechanism. Female acute lymphoblastic leukemia (ALL) survivors treated with cranial radiotherapy had smaller hypothalamic volume (measured on T1-weighed MRI images), compared to gender matched controls (64).

The integrity of the microstructure of the hypothalamus can be examined *in vivo* using the MRI technique diffusion tensor imaging (DTI), based on the direction and degree of the diffusion of water molecules. This MRI technique shows brain tissue microstructure alterations and provides information about brain white matter organization by assessing the restriction of randomly moving water molecules. Recently, this new technique of *in vivo* brain damage investigation was used in cranially irradiated patients (ALL and childhood craniopharyngioma survivors) (65). Important microstructure alterations in the hypothalamus were detected in ALL survivors, with worse alterations in overweight survivors compared to survivors with normal weight. These microstructure alterations suggest demyelination and axonal loss the hypothalamus and were not found in childhood onset craniopharyngioma survivors without hypothalamic involvement (65).

White matter lesions are pathological changes caused by obstruction of small cerebral vessels resulting in hypo-perfusion of the brain. These lesions can be visualized on T2-weighted MRI and correspond to

myelin loss and mild gliosis (66). In patients with childhood-onset craniopharyngioma after photon cranial radiotherapy (with 3-field technique) an increase in white matter lesions volume was found, as well as reduced hypothalamic volume (67). The exact time when white matter lesions started to develop seemed to be around 20 years after cranial radiotherapy. The authors reported that having received cranial radiotherapy in childhood-onset craniopharyngioma patients corresponded to the similar effect as being 18 years older. Patients with more white matter lesions had higher cardiovascular risk (67). Animal studies using radiation-induced brain injury with a total dose of 30Gy (15 Gy with 2 fractions) showed also deficits in axonal transport as a result of multiple factors, such as decline in motor proteins kinesin-1 and cytoplasmic dynein, neuronal apoptosis, synaptic damage and energy metabolism dysfunction (decline in expression of the energy metabolism-related proteins) (68).

The third mechanism of radiation-induced hypothalamic dysfunction is the alteration of the neurotransmitters in the hypothalamus and other brain regions which regulate hypothalamic function (69-71). Animal studies showed that whole brain irradiation (11Gy) decreased levels of inhibitory neurotransmitters (GABA, glycine, taurine, aspartate) and receptors (GABAa receptor) in the hypothalamus, causing a neurochemical imbalance and neuroendocrine disturbances (72).

Direct pituitary damage may also occur, as it is the case in patients after stereotactic radiosurgery for pituitary adenomas. Animal studies using transcriptomics reported also that irradiation significantly changed pituitary transcriptome (73). These authors found reduced cell proliferation and activation of apoptosis related-p53 signaling pathway in the pituitary gland after cranial irradiation. Also, irradiation increased the expression of pro-inflammatory genes, decreased the expression of anti-inflammatory genes and activated the TNF inflammatory signaling pathway in the pituitary gland, leading to persistent inflammation (73). These findings could be used to develop new strategies (for example, anti-inflammatory interventions) for reducing radiotherapy-induced side effects.

It is also proposed that immune system may be a potential mediator of neuroendocrine dysfunction after cranial radiotherapy. The presence of anti-hypothalamic and anti-pituitary antibodies were found in 47.8% of irradiated children with craniopharyngioma, germinoma or gliomas and none in the healthy controls (74).

The posterior pituitary gland is less sensitive to radiation injury.

NEUROENDOCRINE DYSFUNCTION AFTER CRANIAL IRRADIATION

The incidence and severity of radiation-induced neuroendocrine dysfunction depends on radiation dose, radiation schedule, and duration of follow-up.

Radiation Dose

The severity and frequency of pituitary hormone deficiencies, hyperprolactinemia, or central precocious puberty as a complication of cranial radiotherapy correlates with the total radiation dose (Table 4).

Table 4. Hypothalamic-Pituitary Dysfunction After Cranial Radiotherapy	
DYSFUNCTION	**HYPOTHALAMIC-PITUITARY DOSE OF IRRADIATION**
GH deficiency	≥ 18 Gy
Central precocious puberty	≥ 18 Gy
FSH/LH deficiency	≥ 30 Gy
TSH deficiency	≥ 30 Gy
ACTH deficiency	≥ 30 Gy
Hyperprolactinemia	≥ 50 Gy

The somatotroph axis is the most vulnerable and isolated growth hormone deficiency (GHD) may occur with a low radiation dose of 18 Gy (75, 76). If the radiation dose is less than 30 Gy, isolated GHD is present in 30% of patients (4, 28, 77). The incidence of GHD increases to 45-100% of patients if the radiation dose is 30-50Gy (47, 77-80).

If radiation dose is less than 18 Gy, central precocious puberty is a potential complication (with lower effective dose in girls compared with boys), while TSH and ACTH deficiencies are uncommon (13, 47, 81). A large retrospective study reported that the prevalence of central precocious puberty following the treatment of 80 patients with pediatric cancer and CNS tumors was 15.2% overall (29.2% for tumors in the hypothalamic-pituitary region and 6.6% for other CNS tumors) (82).

With an increase of radiation dose, GHD is followed by other pituitary hormone deficiencies: gonadotropin deficiency (30% of patients), TSH deficiency (6-25% of patients) and ACTH deficiency (22% of patients) (47, 83).

Radiotherapy Schedule

The severity of neuroendocrine dysfunction after cranial radiotherapy also depends on the radiotherapy schedule. If the total radiation dose is administered over a short period, it will induce more hypothalamic-pituitary damage than if the same dose is administered over a longer period.

Follow-Up Period

The incidence of radiation-induced hypopituitarism correlates also with the time elapsed since treatment (30, 31). Hormone deficits accumulate throughout the follow-up period, with the majority of hormone deficits developing during the first 5 years post-radiotherapy. In a large study of the effect of cranial radiotherapy in patients with non-pituitary brain tumors, the incidence of all pituitary deficiencies almost doubled between years 2 and 7 of follow-up (45).

GH deficiency occurred the earliest (mean of 2.6 years), followed by gonadotropin deficiency and hyperprolactinemia (after 3.8 years), ACTH deficiency (after 6 years) and TSH deficiency (after 11 years) (74). After a follow-up period of 10 years, multiple pituitary hormone deficiencies occurred in 30-60% of patients (77, 79).

NEW RADIATION TECHNIQUES AND HYPOTHALAMIC-PITUITARY DYSFUNCTION

New stereotactic radiation techniques (stereotactic radiosurgery with a Leksell gamma knife, a

stereotactic linear accelerator, a Cyber Knife, or proton beam therapy) have been developed with the aim to improve effectiveness, to irradiate less normal tissue, and to reduce toxic effects (17). The stereotactic radiation techniques involve photon energy from multiple ^{60}Cobalt radiation sources (gamma knife) or a modified linear accelerator (LINAC). It can be delivered as a single fraction stereotactic radiosurgery or as a fractionated stereotactic radiotherapy. Stereotactic radiosurgery is a single dose radiation technique at doses of 16-25 Gy used in patients with small and medium-sized pituitary adenoma at least 2-4mm from the optic chiasm, whereas fractionated stereotactic radiotherapy is used in patients with large (>2.5-3cm) pituitary adenoma, frequently involving the optic chiasm (84).

Gamma Knife Stereotactic Radiosurgery

Gamma knife stereotactic radiosurgery delivers in a single session a highly collimated dose of ionizing radiation (^{60}Cobalt) conformed to the shape of the target and sparing normal tissue, in contrast to conventional radiotherapy, which covers the tumor and the surrounding structures with a fractionated dose gradient of radio-toxicity between target cells and normal tissue. As already mentioned, gamma knife stereotactic radiosurgery is usually used in patients with relatively small tumors not in close proximity of the optic apparatus (at least 2-4mm away from the optic chiasm). The patient wears a rigid metal helmet fixed on the scull. The dose is usually prescribed at the 50% isodose, ensuring maximum dose at the isocenter and prescribed dose at tumor margins. The radiation is delivered in one session and the dose delivered to the tumor margin are higher for functioning pituitary adenomas (18-35 Gy), compared with nonfunctioning pituitary adenomas (10-20Gy) (84). The studies on long-term follow-up results of gamma knife stereotactic radiosurgery in patients with pituitary adenoma reported radiation-induced hypopituitarism in up to 50% of patients (25, 27, 85-92). Data published in last four years and meta-analysis of outcomes and toxicities following stereotactic radiosurgery for nonfunctioning pituitary adenomas showed lower incidence (15-28%) of radiotherapy-induced hypopituitarism (93-96). The retrospective study of long-term results (median of 64.5 months, range 14.5 – 236 months of follow-up) of gamma knife radiosurgery (median tumor margin dose 14 Gy, range 9-20 Gy) for postsurgical residual or recurrent nonfunctioning pituitary adenomas showed new hypopituitarism in 27.5% of patients, hypocortisolism being the most common deficiency (15 out of 80 patients) (93). The cumulative rates of developing new hypopituitarism at 1, 3, 5 and 10 years was 4%, 21%, 30% and 57%, respectively (93). Similar rates of new hypopituitarism (17.3% and 28%, respectively) after gamma-knife radiosurgery for functioning and nonfunctioning pituitary adenoma were also reported (95, 96). Pituitary deficits occurred after a median time of 22 months (96). Four percent of patients developed panhypopituitarism, while isolated hypocortisolism was observed in 16%, hypothyroidism in 14%, hypogonadism in 14% and growth hormone deficiency in 4% of patients (96). These authors tested biological effective dose (BED) as a possible predicting factor for tumor remission and radiation-induced hypopituitarism (96, 97). BED is defined as a dosimetric parameter that incorporates correction factors for both the slow and fast components of DNA repair which is activated by neoplasm during the radiotherapy (98). A shorter treatment time allows less opportunity for DNA repair and more efficient therapy. This dosimetric variable may be used for optimization of radiotherapy planning, rather than mean pituitary gland dose, for increased rate of remission and reduced rate of radiation-induced hypopituitarism. It was shown that BED above 45 $Gy_{2.47}$ was associated with a 14-fold increase in risk of hypopituitarism, while mean pituitary gland dose above 10 Gy was associated with a 12-fold increase in risk of hypopituitarism (97).

A study with long-term endocrine and radiographic follow-up of patients with acromegaly or Cushing's disease treated with gamma knife radiosurgery

showed more than a half of patients (58.3%) had new pituitary deficiencies after the median time of 61 months (range 12-160) (99). GH deficiency was the most common deficiency (28.3%) and the rate of hypopituitarism gradually increased with time of follow up (10% at 3 years, 21.7% after 5 years and 53.3% at 10 years of follow-up) (99). Recently published study of gamma knife radiosurgery for acromegaly showed lower incidence (29%) of post-radiotherapy hypopituitarism at a median 29.5 months (range 6-143 months) (97). This rate of radiotherapy-induced hypopituitarism in patients with acromegaly after stereotactic radiosurgery is lower compared with fractionated radiotherapy (100). Another study showed the that 19.6% of patients with acromegaly and Cushing´s disease developed radiation-induced hypopituitarism after a median follow-up time of 39 months (range 6-106 months) and the median margin dose of 30Gy (range 16-35 Gy) (101). In this study, the most common pituitary axis deficiency was hypothyroidism, in combination with other deficiencies - hypogonadism and growth hormone deficiency (in patients with Cushing´s disease), or hypocorticism (in patients with acromegaly) (101).

Gamma knife radiosurgery is also an option in patients with medically and surgically refractory prolactinomas, in whom hypopituitarism was reported in 30.3% of patients after median follow-up od 42 months (range 6-207.9) (90). Also, gamma knife radiosurgery may be the initial option for elderly patients with nonfunctioning pituitary adenoma (102). New-onset hypopituitarism was reported in 19.4% of these patients after the median time of 23.1 months.

Some predictors of hypopituitarism following gamma knife stereotactic radiosurgery have been identified and include margin dose to the tumor, supra-sellar extension, the radiation dose to the distal infundibulum (maximum safe dose of 17 Gy), cavernous sinus invasion of the tumor, male sex, smaller pituitary gland volume, tumor volume, mean gland dose, biological effective dose and the amount of healthy tissue within the high dose region (87, 89, 94-96, 99-104). Data referring to the development of hypopituitarism related to gamma knife radiosurgery shows that keeping the mean radiation dose to the pituitary under 15 Gy and the dose to the distal infundibulum under 17 Gy may prevent the development of radiation-induced hypopituitarism (103). Decompression of pituitary gland by surgical resection and dose reduction in pituitary gland may reduce the rate of new hypopituitarism after gamma knife radiosurgery for patients with pituitary adenoma (93).

Gamma knife radiosurgery might be a precipitating factor of new or worsened pituitary hemorrhage (95, 105). Pituitary apoplexy (clinical and subclinical) is not a rare phenomenon and could compromise the results of gamma knife radiosurgery. The mechanism of pituitary apoplexy after radiation may include vascular changes and chronic hypo-perfusion of the pituitary gland, associated with tumor infarction, necrosis and hemorrhage. In a study which investigated the incidence, risk factors and prognosis of pituitary hemorrhage in pituitary adenomas treated with gamma knife radiosurgery, 7.3% patients developed new or worsened pituitary hemorrhage after median time of 18.9 months following radiotherapy (range 3.1-70.7 months) (105). Some of these patients developed new hypopituitarism. Nonfunctioning pituitary adenoma was independent risk factor of new or worsened pituitary hemorrhage after gamma knife radiosurgery and some of patients received surgical resection for clinical pituitary apoplexy (105). On the other hand, tumor shrinkage might be accelerated by hemorrhage due to radiotherapy. Pituitary tumor volume (above $10cm^3$) was significantly associated with new apoplexy after gamma knife radiosurgery (95).

Fractionated Stereotactic Radiotherapy

Stereotactic radiosurgery is a convenient radio-therapeutic approach for patients with small either secreting or nonfunctioning pituitary tumors, but

caution should be used in patients with moderate or large-sized tumors (>3 cm) in close proximity to critical structures (optic chiasm and brainstem). For these patients, fractionated stereotactic radiotherapy (FSRT) may be a safer treatment option because of advantages of dose fractionation. This therapy is used at doses of 45-54Gy delivered in 25-30 daily fractions in patients with pituitary adenomas. In a study on the efficacy and safety of FRST in patients with large and invasive nonfunctioning pituitary tumors, the incidence of new anterior pituitary deficits was 40% at 5 years and 72% at 10 years, while no other radiation-induced complications occurred (106). Meta-analysis with more than 600 patients with pituitary adenomas showed that both stereotactic radiosurgery and fractionated stereotactic radiotherapy have comparable efficacy and safety (107). A recently published meta-analysis of 10 studies analyzed effects of fractionated stereotactic radiotherapy of 256 craniopharyngioma patients and found the new-onset hypopituitarism in 5% of cases (108).

In patients with tumors located near the optic structures, hypo-fractionated radiotherapy may be used, because of lower toxicity for the optic nerves compared with single-dose radiosurgery. Cyber knife uses a linear accelerator mounted on a mobile robotic arm and an image-guided robotic system and it delivers a radiation in 1 or few (2-5) sessions (hypo-fractionated SRS). The patient is immobilized with a thermoplastic masc. Recently published study analyzed 31 acromegaly patients treated with Cyber Knife stereotactic hypo-fractionated radiotherapy after 62 months of follow-up and reported endocrine remission in 86.7% of patients, with 22.4% cured disease rate at five years (109). Hypopituitarism was reported in 32.3% patients and no cases of radiation-induced optic neuropathy were reported.

Proton Radiotherapy

Pediatric diencephalic tumors, such as optic pathway/hypothalamic glioma, craniopharyngioma, germ cell tumors, Langerhans cell histiocytosis, and pituitary adenomas, have excellent survival outcomes and the focus in therapy has shifted toward methods which may reduce long-term morbidity and mortality (110, 111). One of the possibilities is the use of proton radiotherapy, as the preferred choice for children with diencephalic tumors, especially craniopharyngioma, low grade glioma and optic pathway glioma (110, 112).

Proton radiotherapy is the conformal technique used for certain types of cancer and lymphomas, with precise delivery of radiation to a tumor and decreased radiation dose to normal brain because of lower entrance dose and elimination of exit dose compared with photon beams. Less normal brain is irradiated at low or intermediate doses, and this could decrease the risk of late effects of radiation, such as endocrinopathy, second malignancy, or neurocognitive deficits (113). After the calculation of the expected costs and effectiveness regarding growth hormone deficiency for a specific mean radiation dose to the hypothalamus, it has been demonstrated that proton radiotherapy may be more cost effective (compared with photon radiotherapy) for children in which radiation dose to the hypothalamus can be spared, for tumors not originating in or not directly involving the hypothalamus (114). Initial studies suggest lower rates of endocrine complications in children treated with proton radiation for medulloblastoma and low-grade glioma, with increased sparing of normal tissues (115, 116). The comparison between photon radiotherapy and proton radiotherapy for medulloblastoma showed that newer proton radiotherapy may reduce the risk of some radiation-associated endocrine complications (hypothyroidism and gonadotropin deficiency), but not all complications (the incidence of GH and ACTH deficiency, or precocious puberty was not changed) (116, 117). In a study of 118 patients with medulloblastoma (the mean age at diagnosis was 7.6 years, followed for a median of 5.6 years after the radiotherapy) 66% of patients developed growth hormone deficiency, 31% developed hypothyroidism, and 18% developed adrenal insufficiency (117).

Primary hypothyroidism occurred less often after proton cranio-spinal radiotherapy (6%) compared to photon cranio-spinal radiotherapy (28%), while central hypothyroidism, growth hormone deficiency and adrenal insufficiency incidence rates were similar between the groups (117).

It seems that proton conformal radiotherapy has advantages over conventional photon therapy for children with gliomas. Depending on the tumor location, it can spare the hypothalamic-pituitary axis. There was only 1 patient with endocrinopathy in the 14 irradiated children in the low (radiation dose less than 12 Gy) or intermediate endocrine risk groups (radiation dose 12-40Gy) (115).

A study on the effects of proton radiotherapy in a large group of 189 pediatric and young adult patients treated for brain tumors showed that the rate of any pituitary hormone deficiency at four years was 48.8% (118). The incidence of hormone deficiencies was strongly associated with the dose of radiation and the age at time of treatment, with children being especially sensitive. The most frequent endocrine disorders according to the level of irradiation (< 20 Gy, 20-40 Gy, and 40 Gy) were as follows: GH deficiency (9%, 40%, and 79%), followed by TSH deficiency (4%, 25%, and 43%), ACTH deficiency (4%, 4%, and 18%), and gonadotropin deficiency (0%, 3%, and 14%) (118).

Children with brain tumors treated with combined conventional plus proton beam radiotherapy received a higher radiation dose and developed neuroendocrine dysfunction sooner (47% of patients after mean time of 0.33 year), compared with children treating with proton beam radiotherapy only (33% of patients after mean time of 1.17 years) (119).

In the future the late consequences of new radiation techniques should be more completely defined. Further studies are needed to investigate longer-term side effects of proton radiotherapy and confirm whether this technique of radiation and lower radiation doses with proton radiotherapy will change the risk for neuroendocrine dysfunction and secondary malignancy.

New Planning and Dose Delivery Techniques

Cranial radiotherapy has evolved with the development of new planning and dose delivery techniques of photons (intensity-modulated radiotherapy, volumetric-modulated arc radiotherapy) and proton beam radiotherapy (16, 120). These new planning and dose delivery techniques allow increasingly precise delivery of irradiation with reduction of the dose to surrounding neurovascular and brain structures, especially hypothalamic-pituitary axis and hippocampus (34, 120-122). Modern techniques of intensity-modulated proton therapy are able to produce acceptable cranio-spinal irradiation plans, avoid important intracranial structures (hypothalamus, pituitary and hippocampus receive 50% reduced dose of irradiation) and improve patient quality of life (122).

Patients with somatotroph adenoma that had not achieved complete remission after surgery and medical therapy, treated with fractionated intensity-modulated radiotherapy, developed hypopituitarism in 28.3% of cases, after the median follow-up time of 36 months (range, 6-105.5 months), similar to stereotactic radiosurgery (121). In this study, only age below 33 years was a significant predictor of radiation-induced hypopituitarism.

Modern radiotherapeutic technique such as volumetric-modulated arc therapy, with a sparing approach of both hippocampus and hypothalamus-pituitary axis might be a promising option for the patients undergoing whole-brain radiotherapy (50). The aim of this approach is to reduce dose application to these brain areas and to reduce common side effects (cognitive impairment and neuroendocrine dysfunction). A combined sparing approach involving both hippocampus and hypothalamo-pituitary axis

using volumetric modulated arc therapy allows simultaneous dose reduction (less than 50% of the prescribed dose to the target) to these functional brain areas without compromised target coverage (50). Even in patients with brain metastasis requiring whole brain radiotherapy (WBRT), protection of the hypothalamo-pituitary axis during WBRT may be unlikely to compromise the tumor recurrence rate, because the rarity of brain metastasis in the hypothalamo-pituitary area (123).

The selection of the radio-therapeutic method is based on the tumor size, distance from the optic structures and local invasion (124). SRS is reserved for tumors less than 3cm or small remnants in the cavernous sinus, located more than 3-5 mm away from the optic structures and the dose to the optic chiasm should not exceed 8 Gy. Fractionated radio-therapeutic methods are used for large pituitary tumors, or those which invade the optic nerves. Hypo-fractionated SRS (in 2-5 sessions) has been used for perioptic tumors.

New radiation technology including intensity-modulated proton therapy (IMPT), proton-based stereotactic radiosurgery, and FLASH-proton therapy (delivery of very high doses of radiation in fractions of a second), may provide in the future efficient control of the primary tumor with decrease of long-term complications (110). Prospective studies on endocrine and neurologic outcome are required to establish the long-term morbidity, neuroendocrine and cognitive sequelae.

Strategies for Precise Radioprotection

It is still a challenge how to protect the normal tissue from radiation-induced damage. There are studies on several agents which could protect the normal cells from radiation-induced damage with no affecting the radiation-induced killing of the tumor cells (memantine hydrochloride, amifosine, antioxidants). Recently published study on MitoQ, a mitochondria-targeted antioxidant, showed a good neuro-protective effect of this antioxidant in preclinical studies (125). MitoQ is absorbed to the inner mitochondrial membrane, affects mitochondrial respiration and induces selective protective autophagy among radiated normal cells (125). Tumor cells rely on aerobic glycolysis, mitochondria-independent energy supply pathway and are not protected due to the absence of autophagy.

SCREENING FOR NEUROENDOCRINE DYSFUNCTION FOLLOWING CRANIAL RADIOTHERAPY

Recently, recommendations for screening for hypopituitarism after cranial radiotherapy were suggested (13, 63, 112, 126, 127). According to this approach, clinical evaluation, baseline pituitary hormone assessment, and dynamic testing for GH and ACTH deficiency should begin one year after cranial radiotherapy (Table 5). Clinical examination of children (including linear growth and pubertal staging) should be done every 6 to 12 months until final height is attained, and then yearly thereafter (13, 63). In patients at risk for central precocious puberty, pubertal development should be monitored every 6 months until age 9 years in girls and 10 years in boys (13).

If results of the assessment are normal, reassessment should be done every 2-4 years until at least 10 years following radiation. GH testing should be done only in patients who are good candidates for GH replacement therapy (keeping in mind the safety in underlying malignancy). It is also recommended to perform an endocrine assessment at 1 year after radiotherapy in patients treated for non-pituitary intracranial neoplasms, since they also may develop hypothalamic-pituitary dysfunctions (128).

Table 5. Screening for Hypothalamic-Pituitary Dysfunction			
DYSFUNCTION	**Clinical data**	**Basal analysis**	**Dynamic test**
GH deficiency	Growth velocity (children)	IGF-I	ITT, glucagon, clonidine (children)
FSH/LH deficiency	Pubertal staging	FSH, LH, estradiol (female), testosterone (male)	GnRH
TSH deficiency	Clinical examination	TSH, FT4	TRH
ACTH deficiency	Clinical examination	Cortisol	ITT, Synacthen
Hyperprolactinemia		PRL	
Precocious puberty	Pubertal stage	FSH, LH, estradiol (female), testosterone (male)	

Somatotroph Axis

Two stimulation tests for estimating GH secretion are required in the case of isolated GHD, while in patients with multiple pituitary hormone deficiencies there is no need for formal testing to establish a diagnosis of GH deficiency. Interpretation of results for the GH stimulatory tests following cranial radiation may be complicated because of the different mechanisms governing GH release during the gold standard, the insulin tolerance test (ITT), and other tests (arginine+GHRH and GHRH+GHRP-6 test in the past). In some cases, the results of different GH stimulatory tests may be discordant (75, 129, 130). The hypothalamus is more sensitive to radiation-induced injury compared with pituitary. Provocative tests which directly stimulate the somatotrophs (GHRH) may give false negative results in the early years after radiotherapy (131). Failing to pass the hypoglycemia test (ITT) is more common after radiation than to other stimulatory tests but may not necessarily reflect GH deficiency (132-135). It has been suggested that lower radiation doses (<40 Gy) predominantly cause hypothalamic damage with GHRH deficiency and subsequent somatotroph atrophy. In cases with robust response to ITT it is suggested to repeat screening at four years, while in cases with borderline response to this test, it should be repeated at two years (126).

IGF-1 levels may be useful in screening for severe GH deficiency in children and adults (63). However, in childhood cancer survivors exposed to cranial radiotherapy, it is recommended against relying solely on serum IGF-I levels to make the diagnosis of GH deficiency (52, 60, 63, 136). Recently published study of 41 survivors of childhood brain tumors treated with proton and photon irradiation and followed for 14.8 years showed low diagnostic value of IGF-1 and high prevalence of undiagnosed GH deficiency (50%) (60). Meta analysis of 15 studies with 477 childhood cancer survivors showed the same diagnostic accuracy of various dynamic tests (ITT, GHRH, GHRH plus arginine, levodopa, clonidine) for GH deficiency in childhood cancer survivors as in other causes of GH deficiency (52).

In children with growth failure, risk factors and comorbidities, in which the GH stimulatory test may be uncomfortable, an evidence-based prediction model to diagnose GH deficiency was proposed (137). In the large cohort of 770 children the authors identified clinically relevant risk factors for GH deficiency (among them cranial radiotherapy ≥18 Gy), to build a clinical prediction model for GH deficiency, a

mathematical and machine-learning approach to avoid GH stimulatory testing in children with growth failure and comorbidities (137). The specificity of their prediction rule for GH deficiency without need for pharmacological stimulation tests in children with risk factors was 99.2%.

Hypothalamic-Pituitary-Gonadal Axis

Low radiation dose (< 18Gy) in pre-pubertal children may cause premature activation of hypothalamic-pituitary-gonadal axis leading to central precocious puberty, mostly in girls, due to loss of neurons with inhibitory γ-aminobutyric acid (30, 31, 81, 138, 139). Higher radiation doses may cause central hypogonadism with a cumulative incidence of 20-50% on long-term follow-up (4, 28, 44, 47, 77, 78, 83). Gonadotroph deficiency is defined as low or normal gonadotropin levels and low plasma testosterone in men and amenorrhea with low plasma estradiol in premenopausal women (<50 years old).

Hyperprolactinemia

Hyperprolactinemia may develop after cranial radiotherapy in 20-50% of patients and indicates hypothalamic damage and reduced inhibitory dopamine activity (4, 30, 31, 134). Elevated prolactin level is mostly seen in young females after high dose cranial irradiation (> 50Gy) (13, 44, 47, 77, 78, 140). Elevated prolactin levels may be asymptomatic, without clinical significance or may cause central hypogonadism (78). Elevated prolactin levels may decline and normalize during follow-up due to radiation-induced reduction of the pituitary lactotroph cells (28).

Hypothalamic-Pituitary-Adrenal Axis and Hypothalamic-Pituitary-Thyroid Axis

The hypothalamic-pituitary-adrenal axis and hypothalamic-pituitary-thyroid axis are more radioresistant than the GH and gonadotropin axes. Corticotroph deficiency is defined as low morning serum cortisol (normal range for morning serum cortisol, 7– 25 mg/dl; for evening serum cortisol, 2–14 mg/dl) and a normal or low serum ACTH level. Thyrotroph deficiency is based on a low free T4 with normal or decreased TSH. ACTH and TSH deficiency may occur after a large dose of cranial radiation (>50 Gy) used for nasopharyngeal cancer and skull base tumor, in 30-60% of patients after long-term follow-up (4, 28, 30, 31, 47, 77, 80). Central hypocorticism and hypothyroidism may be subclinical and diagnosed by stimulatory tests (ITT, glucagon, Synacthen test and TRH test).

OTHER CHRONIC COMPLICATIONS OF CRANIAL IRRADIATION

Cerebrovascular Insult (Stroke)

The large Dutch study which included 806 patients with nonfunctioning pituitary adenomas (456 treated with cranial radiotherapy) reported the increased incidence of cerebrovascular events in men treated with cranial radiotherapy (hazard ratio 2.99, 95% CI 1.31-6.79) (20).

Radiation-Induced Ocular Complications

Radiation-induced ocular complications include cataract, dry eye syndrome, corneal erosions, perforations and scarring, as well as radiation retinopathy, neuropathy and neo-vascular glaucoma (141). The use of fractionated robotic radiotherapy (Cyber Knife system) on benign para-sellar tumor located close to the optic pathway is safe and does not impair the structure and function of the anterior and posterior segments of the eye during the 24-month observation (142). Only the thinning of the retinal nerve fiber layer (RNFL) was described, but it did not impair visual function and it did not correlate with the dose delivered to the optic pathway. Single doses

lower than 8–10 Gy are considered safe in patients undergoing single and multi-fraction stereotactic radiotherapy (143). The dose per fraction received seems to be the most important factor and should not exceed 1.9 Gy.

Second CNS Tumor

The occurrence of a second intracranial neoplasm is a rare complication after radiotherapy, including the development of radiation-associated intracranial neoplasm and malignant transformation of a benign lesion (22, 23, 144, 145). Tumors such as meningioma, glioma or sarcoma are the most prevalent secondary neoplasms after cranial irradiation. The systematic review of 21 studies in children and adults who received cranial radiation for prophylactic or therapeutic purposes showed a 7-10-fold increase in subsequent CNS tumors in children, with a latency period ranging from 5.5 to 30 years (glioma developed 5-10 years and meningioma around 15 years after radiation) (22). Additional investigation is needed on the risk of radiation-induced secondary tumors in adults, because some studies showed no increased risk, while other studies reported a higher risk for secondary CNS tumors with a latency period from 5 to 34 years (22). A large study that included 8917 patients from the Pfizer International Metabolic Database (KIMS) reported an increased incidence for de novo brain tumors in patients treated for pituitary/sellar lesions (23). The risk of developing a malignant brain tumor increased by 2-4-fold and meningioma by 1.6-fold with every 10 years of younger age at radiotherapy, irrespectively of the type of radiotherapy (conventional vs stereotactic) (23).

Recently published retrospective, multicenter study of 3679 patients with long-term follow-up after radiotherapy (recipients of proton beam or stereotactic radiotherapy were excluded) for pituitary adenoma and craniopharyngioma reported the cumulative probability of second brain tumor of 0.9% after 10-years follow-up and 4% after 20-year follow-up (146). Medial latency period for secondary malignant tumor (glioblastoma, astrocytoma) was 8.3 years, and for secondary benign tumor (meningioma, acoustic neuroma, neurocytoma, low-grade glioma) was 17.7 years. The authors reported that older age at pituitary tumor detection was a predictor of developing a second brain tumor. Patients with second malignancy in the region of previous radiotherapy often present with aggressive clinical course and disease resistant to various treatment modalities several years after radiotherapy (145). Sarcoma of the sellar region is a rare malignant complication after radiotherapy of the pituitary tumor. In a systematic review of 94 sarcoma of the sellar region, one third was associated with radiotherapy and developed after median time of 10.5 years and mean radiation dose 47.5 ± 5.05 Gy (147). Ionizing radiation is a known risk factor for sarcomatous transformation of fibrous dysplasia of the bone in patients with McCune-Albright syndrome.

It is important to differentiate correctly radionecrotic lesion on contrast MRI from brain neoplasia (148). Brain radionecrosis is a neuronal death, vascular endothelial damage and demyelination lesions after high-dose radiotherapy and it can be differentiated from a tumor by molecular imaging techniques (18-FDG PET/CT, 11C-acetate PET/CT) (148).

There are some data that the risk for secondary malignancy is lower with stereotactic radiosurgery, in comparison with conventional radiotherapy (144). A large multicenter study of 4905 patients with gamma knife radiosurgery for arteriovenous malformation, trigeminal neuralgia, or benign intracranial tumors (including pituitary adenomas) reported the overall incidence of 6.8 per 100 000 patients-years, or a cumulative incidence of 0.00045% over 10 years, similar to the risk of developing a primary CNS tumor in the general population (144). Long-term follow-up for patients treated with new radiation techniques (stereotactic radiosurgery and proton beam therapy) are needed.

CONCLUSION

Hypothalamic-pituitary dysfunction is among the most common late effect of cranial radiotherapy. Radiation causes irreversible and progressive damage to the hypothalamic-pituitary region. The pathophysiology of the radiation-induced damage includes direct neuronal and vascular injury and fibrosis. The incidence and severity of hypopituitarism correlate with the total radiation dose delivered to the hypothalamic-pituitary region, the fraction size, the time between fractions, and the duration of follow-up. Periodical life-long endocrine assessment is recommended in all long-term survivors of childhood or adulthood tumors who were treated with cranial radiotherapy or with total body irradiation. With newer radiation techniques the dose and volume of normal tissue irradiated are reduced. Further analysis of new radiation techniques (stereotactic radiosurgery and proton beam therapy) and long-term hypothalamic-pituitary dysfunctions are needed.

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