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Pituitary Disorders

Efficacy and complications of pituitary irradiation

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ABSTRACT

Radiation therapy is widely used in the management of intracranial (including sellar and parasellar) and systemic disorders. Whilst in a number of cases the irradiation aims to prevent the growth or re-growth and to control the hormonal hypersecretion of a pituitary tumor, in a number of others, it adversely affects the hypothalamo-pituitary function simply because this area receives significant doses of radiation delivered for non-hypothalamo-pituitary disorders. Pituitary irradiation is usually offered post-operatively for tumors of the sellar and parasellar area and its efficacy varies widely mainly depending on the type of tumor, degree of hormonal hypersecretion and radiation technique and schedule used. The main long-term complications include hypopituitarism, optic neuropathy, cerebrovascular morbidity and second brain tumors. Radiation technique and schedule are important determinants of these adverse effects.

KEY POINTS

- Radiation therapy is widely used in the management of intracranial (including sellar and parasellar) and systemic disorders.
- Its place in the management algorithm of pituitary tumors depends on the type of tumor and is usually recommended post-operatively to prevent relapse or to control hormonal hypersecretion.
- Its efficacy varies widely mainly depending on the type of tumor, degree of hormonal hypersecretion and radiation technique and schedule used.
- With the advances in radiation planning and delivery, the long-term complications have improved, although hypopituitarism remains the protagonist in the list of adverse sequelae.

A. INTRODUCTION

Radiation therapy is widely used in the management of intracranial (including sellar and parasellar) and systemic disorders. These mainly include pituitary adenomas, other (para)sellar tumors (eg. craniopharyngiomas, meningiomas, germinomas, schwannomas, chordomas/chordosarcomas, haemangiopericytomas, gliomas, pituicytomas, pinealomas, medulloblastomas, brain metastases, vascular malformations), hematological malignancies (eg. acute lymphoblastic leukemia, lymphomas), face, neck and skull base tumors (eg. nasopharyngeal carcinomas) (1). Whilst in a number of cases the irradiation aims to prevent the growth or re-growth and to control the hormonal hypersecretion of a pituitary tumor, in a number of others, it adversely affects the hypothalamo-pituitary function simply because this area receives significant doses of radiation offered for non-hypothalamo-pituitary disorders.

This review will focus on the efficacy of various types of radiation techniques in the most common pituitary tumors and on the complications following irradiation which has included the hypothalamo-pituitary area.

B. EFFICACY OF PITUITARY IRRADIATION

The aim of radiation treatments to the sellar region is to prevent tumour (re)growth and to control the hormonal hypersection, while sparing the surrounding normal structures. Conventional fractionated radiotherapy delivers megavoltage doses of irradiation in fractions separated over time. The irradiation is given through multiple beams from a high energy radiation source focused on the tumor. Radiation treatments are most commonly delivered through photons (high energy X-rays) generated by a linear accelerator (LINAC). Cobalt 60 as a source of high energy gamma radiation has been mostly replaced with the exception of a

multiheaded cobalt unit (gamma knife). Charged particle beams in the form of photons and more recently helium and carbon ions have been also used as therapeutic radiation sources. Localised irradiation is achieved by offering treatment in 3-4 beams each shaped to conform to the shape of the tumor by using a multileaf collimator (MLC). MLC leaves can also modulate the intensity of radiation [intensity modulated radiotherapy (IMRT)] (1). In pituitary adenomas, the most commonly used protocol includes a total dose of 45-50 Gy offered in fractions of 1.6-1.8 Gy, 4-5 times per week during 5-6 weeks. Stereotactic techniques are related with further improvement in immobilization using relocatable or fixed frames, improved imaging and more precise treatment delivery. Stereotactic irradiation is offered as single fraction radiotherapy using either cobalt 60 gamma radiation emitting sources (gamma knife) or a LINAC or as stereotactic conformal radiotherapy delivered as fractionated treatment using a LINAC.

1. Acromegaly

The aims of the treatment of acromegaly are to inhibit GH hypersecretion, normalise IGF-I levels and reduce or control tumor growth, leading to symptom control and minimizing the associated clinical signs and co-morbidities (2). Biochemical control is generally defined as a normal IGF-I for age and gender and a GH less than 1.0 ng/ml on an oral glucose tolerance test. With sensitive assays, a GH of less than 0.4 ng/ml would be consistent with remission (2). Radiotherapy is generally reserved as third or second-line treatment in cases in which surgery and/or medical therapy have not achieved tumor growth control or normalization of hormone levels. It may also be used for those controlled on medical therapy aiming to stop it after the irradiation has led to hormonal control (2). Based on series with strict remission criteria, fractionated radiotherapy achieves remission rates in 50-60% of the patients within 10 years (Table 1). Predictive factors for remission are the initial GH and IGF-I levels (3,4). It has been shown that within the first 2 years after irradiation, the GH levels decrease by 50-

70% followed by a slow gradual reduction over the next 10-20 years (5). Data on the efficacy of fractionated proton beam irradiation in acromegaly are limited with no conclusive evidence on the superiority of this treatment. Stereotactic radiosurgery has been used in patients with small residual tumor, not close to the optic pathways and biochemical remission has been reported in 35-100%; the variable rates reflect the different observation periods and the different criteria used to assess control of the disease (6).

2. Cushing's disease

Radiotherapy is almost exclusively used as a second rather than as a primary choice therapy in corticotroph adenomas following non-curative surgery (in these cases medical treatment is usually offered until irradiation provides the desired results). The most widely accepted criterion to define remission after irradiation is normalization of the 24-hour urinary free cortisol but additional criteria [as normal basal ACTH and/or cortisol levels and suppression of cortisol on low-dose dexamethasone test) are variably used. The remission rates of hypercortisolism range from 42 to 83% without clear difference between the types of radiotherapy used (Table 2). Patients with Cushing's disease seem to have a shorter latency before achieving remission compared with those with acromegaly. Corticotroph tumor control is reported in 93-100% of the cases (7).

3. Prolactinomas

Radiotherapy is reserved for patients with prolactinoma not responding to dopamine agonists or surgery or in the rare cases of malignant adenoma (8). It aims to control tumor growth and to achieve normoprolactinemia. The hormonal response rates vary widely (0-100%) (8).

4. Non-Functioning pituitary adenomas (NFA)

Currently, radiotherapy is offered post-operatively to patients with NFA less frequently than previously, mainly due to the long-term risk of hypopituitarism and its indications are still not absolutely evident (9). However, it is generally accepted that radiotherapy is not required in patients with no residual tumor as the risk of relapse is very low (10). Based on a number of series, the 5-years regrowth rate following post-operative irradiation ranges between 0-28% (11,12,13). Randomised studies comparing surgery with or without radiotherapy are lacking; however, a report comparing the results of two institutions in the UK with different treatment strategies clearly showed the benefit of radiotherapy on tumor recurrence (14). Gamma knife radiosurgery offers tumor stabilization in 60-78% during mean/median follow-up periods 45-78 months with rates of tumor recurrence between 3-7% (15).

5. Craniopharyngiomas

Until 1937, when Carpenter *et al*. (16) first described the beneficial effects of radiotherapy following aspiration of cyst contents in 4 cases, craniopharyngiomas were considered radioresistant (17). The benefit of radiotherapy in preventing tumor recurrence has been demonstrated in a number of reports. Series with radiological confirmation of the radicality of resection show that the recurrence rates following gross total removal range between 0-62% at 10 years follow-up. These are significantly lower than those reported after partial or subtotal resection (25-100% at 10 years follow-up). In cases of limited surgery, adjuvant radiotherapy improves significantly the local control rates (recurrence rates 10-63% at 10 years follow-up) (18,17). Finally, radiotherapy alone provides 10 years recurrence rates ranging between 0-23% (17). These results were based on conventional fractionated external beam radiotherapy and tumour control rates with newer higher precision techniques, such as fractionated stereotactic conformal radiotherapy have remained optimal with 5 years progression free survival more than 90% (19). The beneficial effect of radiotherapy (preceded or not by second surgery) in recurrent lesions has been clearly shown (18). Stereotactic

radiosurgery achieves tumor control in a substantial number of patients with small volume lesions and reported 5 years progression free survival ranges between 61-68% (19). It may be particularly useful for well-defined residual disease following surgery or for the treatment of small solid recurrent tumors, particularly after failure of conventional radiotherapy.

C. COMPLICATIONS OF PITUITARY IRRADIATION

These are shown in Tables 3 and 4 with the most common being radiation-induced hypopituitarism.

D. FUTURE CONSIDERATIONS

Irradiation remains an important tool in our therapeutic armamentarium for intracranial (including sellar and parasellar) and systemic disorders. Studies comparing the efficacy and safety of different radiation techniques - particularly for sellar and parasellar lesions - are required aiming to provide reliable data on the place of each technique in the management algorithm. Furthermore, prospective studies of consecutive, non-selected patients relying on robust diagnostic criteria and on the biological effective dose to the hypothalamus-pituitary are needed aiming to clarify timing and frequency of damage to each axis and to provide the basis for safe and cost-effective surveillance protocols.

References

1) Fernadez A, Brada M, Zabulliene L, et al. Radiation-induced hypopituitarism. Endocr Relat Cancer 2009;16:733-72. *

2) Melmed S, Colao A, Barkan A, et al. Guidelines for acromegaly management: an update. J Clin Endocrinol Metab 2009;94:1509–17.

3) Barrande G, Pittino-Lungo M, Coste J, et al. Hormonal and metabolic effects of radiotherapy in acromegaly: long-term results in 128 patients followed in a single center. J Clin Endocrinol Metab 2000;85:3779-85.

4) Jenkins PJ, Bates P, Carson MN, et al. Conventional pituitary irradiation is effective in lowering serum growth hormone and insulin-like growth factor-I in patients with acromegaly. J Clin Endocrinol Metab 2006;91:1239-45.

5) Castinetti F, Morange I, Dufour H, et al. Radiotherapy and radiosurgery in acromegaly. Pituitary 2009;12:3-10. *

6) Minniti G, Scaringi C, Enrici M. Radiation techniques for acromegaly. Radiation Oncology 2011;6:167-74. *

7) Losa M, Picozzi P, Redaelli MG, et al. Pituitary radiotherapy for Cushing's disease. Neuroendocrinology 2010;92 Suppl 1:107-10. *

8) Sheplan Olsen LJ, Robles Irizarry L, Chao ST, et al. Radiotherapy for prolactin-secreting pituitary tumors. Pituitary 2012;15:135-45.**

9) Wass JAH, Reddy R, Karavitaki N. The post-operative monitoring of non-functioning pituitary adenomas. Nat Rev Endocrinol 2011;7:431-34. *

10) Reddy R, Cudlip S, Byrne RV, et al. Can we ever stop imaging in surgically treated and radiotherapy naïve patients with non-functioning pituitary adenoma? Eur J Endocrinol 2011;165:739-44.

11) Woollons AC, Hunn MK, Rajapakse YR, et al. Non-functioning pituitary adenomas: indications for postoperative radiotherapy. Clin Endocrinol (Oxf) 2000;53:713-17.

12) Park P, Chandler WF, Barkan A, et al. The role of radiation therapy after surgical resection of non-functional pituitary adenomas. Neurosurgery 2004;55:100-107.

13) Dekkers OM, Pereira AM, Roelfsema F, et al. Observation alone after transsphenoidal surgery for non-functioning pituitary macroadenoma. J Clin Endocrinol Metab 2006;91:1796-801.

14) Gittoes NJL, Bates AS, Tse W, et al. Radiotherapy for non-functioning pituitary tumours. Clin Endocrinol (Oxf) 1998;48:331-37.

15) Castinetti F, Régis J, Dufour H, et al. Role of stereotactic radiosurgery in the management of pituitary adenomas. Nat Rev Endocrinol 2010;6:214-23. *

16) Carpenter RC, Chamberlin GW, et al. The treatment of hypophyseal stalk tumours by evacuation and irradiation. Am J Roent 1937;38:162–67.

17) Karavitaki N, Cudlip S, Adams CB et al. Craniopharyngiomas. Endocr Rev 2006;27: 371-97. *

18) Karavitaki N, Brufani C, Warner JT, et al. Craniopharyngiomas in children and adults:systematic analysis of 121 cases with long-term follow-up. Clin Endocrinol (Oxf) 2005;62:397-409.

19) Karavitaki N. Management of craniopharyngiomas. J Endocrinol Invest 2014; 37:219-28. *

20) Thalassinos NC, Tsagarakis S, Ioannides G, et al. Megavoltage pituitary irradiation lowers but seldom leads to safe GH levels in acromegaly: a long-term follow-up study. Eur J Endocrinol 1998;138:160-3.

21) Epaminonda P, Porretti S, Cappiello V, et al. Efficacy of radiotherapy in normalising serum IGF-I, acid-labile subunit (ALS) and IGFBP-3 levels in acromegaly. Clin Endocrinol (Oxf) 2001;55:183-9.

22) Minniti G, Traish D, Ashley S, et al. Fractionated stereotactic conformal radiotherapy for secreting and nonsecreting pituitary adenomas. Clin Endocrinol (Oxf) 2006;64: 542-8.

23) Nagesser SK, van Seters AP, Kievit J, et al. Treatment of pituitary-dependent Cushing's syndrome: long-term results of unilateral adrenalectomy followed by external pituitary irradiation compared to transsphenoidal pituitary surgery. Clin Endocrinol (Oxf) 2000;52:427-35.

24) Höybye C, Grenbäck E, Rähn T, et al. Adrenocorticotropic hormone-producing pituitary tumors: 12- to 22-year follow-up after treatment with stereotactic radiosurgery. Neurosurgery 2001;49:284-91;discussion 291-2.

25) Castinetti F, Nagai M, Dufour H, et al. Gamma knife radiosurgery is a successful adjunctive treatment in Cushing's disease. Eur J Endocrinol 2007;156:91-8.

26) Jagannathan J, Sheehan JP, Pouratian N, et al. Gamma Knife surgery for Cushing's disease. J Neurosurg 2007; 106:980-7.

27) Minniti G, Osti M, Jaffrain-Rea ML, et al. Long-term follow-up results of postoperative radiation therapy for Cushing's disease. J Neurooncol 2007;84:79-84.

28) Petit JH, Biller BM, Yock TI, et al. Proton stereotactic radiotherapy for persistent adrenocorticotropin-producing adenomas. J Clin Endocrinol Metab 2008;93:393-9.

29) Constine LS, Woolf PD, Cann D, et al. Hypothalamic-pituitary dysfunction after radiation for brain tumors. N Engl J Med 1993;328:87-94.

30) Brada M, Rajan B, Traish D, et al. The long-term efficacy of conservative surgery and radiotherapy in the control of pituitary adenomas. Clin Endocrinol (Oxf) 1993; 38:571-8.

31) Tishler RB, Loeffler JS, Lunsford LD, et al. Tolerance of cranial nerves of the cavernous sinus to radiosurgery. Int J Radiat Oncol Biol Phys 1993;27:215-21.

32) Brada M, Ashley S, Ford D, et al. Cerebrovascular mortality in patients with pituitary adenoma. Clin Endocrinol (Oxf) 2002;57:713-7.

33) Darzy KH, Shalet SM. Hypopituitarism following radiotherapy. Pituitary 2009;12:40-50. *

34) Leenstra JL, Tanaka S, Kline RW, et al. Factors associated with endocrine deficits after stereotactic radiosurgery of pituitary adenomas. Neurosurgery 2010;67:27-32.

35) Sattler MG, van Beek AP, Wolffenbuttel BH, et al. The incidence of second tumours and mortality in pituitary adenoma patients treated with postoperative radiotherapy versus surgery alone. Radiother Oncol 2012;104:125-30.

36) Sicignano G, Losa M, del Vecchio A, et al. Dosimetric factors associated with pituitary function after Gamma Knife Surgery (GKS) of pituitary adenomas. Radiother Oncol 2012;104:119-24.

37) Sheehan JP, Starke RM, Mathieu D, et al. Gamma Knife radiosurgery for the management of nonfunctioning pituitary adenomas: a multicenter study. J Neurosurg 2013;119:446-56.

38) Leavitt JA, Stafford SL, Link MJ, et al. Long-term evaluation of radiation-induced optic neuropathy after single-fraction stereotactic radiosurgery. Int J Radiat Oncol Biol Phys 2013;87:524-7.

39) Capatina C, Christodoulides C, Fernandez A, Cudlip S, Grossman AB, Wass JA, Karavitaki N. Current treatment protocols can offer a normal or near-normal quality of life in the majority of patients with non-functioning pituitary adenomas. Clin Endocrinol (Oxf) 2013;78:86-93.

40) Ayuk J, Clayton RN, Holder G, et al. Growth hormone and pituitary radiotherapy, but not serum insulin-like growth factor-I concentrations, predict excess mortality in patients with acromegaly. J Clin Endocrinol Metab 2004;89:1623-17.

41) Mestron A, Webb SM, Astorga R, et al., 2004. Epidemiology, clinical characteristics, outcome, morbidity and mortality in acromegaly based on the Spanish Acromegaly registry (Registro Espanol de Acromegalia, REA). Eur J Endocrinol 2004; 151:439-46.

42) Agha A, Sherlock M, Brennan S, O'Connor SA, et al. Hypothalamic-pituitary dysfunction after irradiation of nonpituitary brain tumors in adults. J Clin Endocrinol Metab 2005;90:6355-60.

43) Appelman-Dijkstra NM, Kokshoorn NE, Dekkers OM, et al. Pituitary dysfunction in adult patients after cranial radiotherapy: systematic review and meta-analysis. J Clin Endocrinol Metab 2011;96:2330-40. *

Table 1. Series with outcome of fractionated radiotherapy in patients with acromegaly.

Reference	Type of Radiotherapy	No of patients	Follow-up	Remission criteria	Remission rate
(20)	Conventional	46	Mean 7.6 years	GH < 2.5 ng/ml	21%
(3)	Conventional	128	Mean 11.5 years	GH < 2.5 mcg/l	53% at 10 years
(21)	Conventional	67	Mean 10 years	GH < 2.5 mcg/l IGF-I normal	58% 55%
(4)	Conventional	656	Median 7 years	GH < 2.5 ng/ml IGF-I normal	60% at 10 years 63% at 10 years
(22)	Fractionated stereotactic	18	Median 39 months	GH < 2.5 ng/ml or GH < 1 ng/ml on oral glucose tolerance test and IGF-I normal	50% at 5 years

Table 2. Series with outcome of radiotherapy in patients with Cushing's disease.

Reference	Type of radiotherapy	No of patients	Follow-up	Remission criteria	Remission rate
(23)	Conventional	86	Mean 18 years	Clinical remission / normal excretion of urinary steroids / serum cortisol < 80nmol/l on low dose dexamethasone suppression test	64%
(24)	Gamma knife	18	Mean 17 years	Clinical remission / normal or low serum cortisol and plasma ACTH / normal or subnormal urinary free cortisol / normal response on dexamethasone suppression test	83%
(25)	Gamma knife	40	Mean 5 years	Normal urinary free cortisol / normal response on low dose dexamethasone suppression test	42%
(26)	Gamma knife	90	Mean 4 years	Normal urinary free cortisol	54%
(27)	Conventional	40	Mean 9 years	Normal urinary free cortisol /serum cortisol / normal response on overnight dexamethasone suppression test	78%
(28)	Proton stereotactic	33	Mean 5 years	Normal urinary free cortisol	52%

Table 3. Complications of pituitary irradiation (1, 29-41).

COMPLICATIONS	TYPE	COMMENTS
Short-term	Temporary skin changes (erythema) Hair loss Tiredness Nausea Headache Hearing problems	Resolve spontaneously within days to weeks after the completion of therapy.
Long-term	Radiation-induced hypopituitarism	Attributed to degenerative changes in glial cells leading to lack of trophic neural support, demyelination and hypothalamic damage, as well as to vascular derangements leading to endothelial cell death, obliteration of small vessels and tissue necrosis. Onset and severity affected by total radiation dose, dose fractionation (fraction size and time between fractions for tissue repair), length of follow-up (as late as 15-20 years after irradiation) and previous damage to the hypothalamo-pituitary system (eg. compression by tumor or surgery). There is differential radiosensitivity with GH and gonadotroph axes been affected first, followed by ACTH and TSH axes damage (also central precocious puberty may occur with doses 18-24 Gy). Frequencies for each axis and dose regimes are shown in Table 4. Predictors of pituitary dysfunction following gamma knife radiosurgery include mean dose to stalk/pituitary (cut-offs 15.7 and 7.3 Gy, respectively) - during median follow-up of 63 months, new hormone deficits reported in 29% of patients after 7.6-13.2 Gy, in 39% after 13.3-19.1 Gy and in 83% after > 19.1 Gy. Annual long-term surveillance of the pituitary function is required.
	Radiation-induced hyperprolactinemia	Attributed to hypothalamic damage and reduction of dopamine. Mainly following total dose > 30 Gy. 20-50% in adults – less common in children. Gradual decline may occur with time suggesting direct radiation-induced damage to lactotroph cells.
	Cranial neuropathy	Multiple cranial nerves, including II, III, IV, V, and VI, are at risk with reported rates 1.3-0.6% following various types of radiotherapy.

	Radiation-induced optic neuropathy	Typically presents with sudden, painless, unilateral visual loss, although bilateral involvement may rapidly follow. Visual acuity decreases to a variable degree and visual fields may show any pattern of optic nerve or chiasmal defects. No effective treatment. Attributed to microvascular obliteration in optic pathways. Onset ranges between 3 months to > 8 years after radiation exposure. Conventional radiotherapy may cause optic neuropathy resulting in visual deficit in 1–3% and radiosurgery in 2–5% of the patients. Susceptibility increases with increasing age, co-morbid diabetes, pre-existing compression to the optic nerves and chiasm, volume of the optic apparatus exposed to high-dose irradiation (for gamma knife) and prior external beam radiation therapy. Frequency is dose-dependent, increasing with total doses > 50-55 Gy (fractionated radiotherapy) or single doses > 10 Gy (stereotactic radiosurgery) or radiation fraction size > 2 Gy (fractionated radiotherapy) or total dose to the optic pathway > 8 Gy. For tumors close to the chiasm, even total doses of 45 Gy may cause optic neuropathy and the distance between tumor margin and optic apparatus should be at least 3 mm.
	Radiation-induced brain necrosis	May occur in the treated peri-tumoral area or distal from the original tumor but always within the radiation fields. The patients may present with raised intracranial pressure due to edema, cognitive dysfunction, seizures or focal neurological signs related to the position of the lesion. Related with microvascular obliteration, ischemic necrosis and demyelination of white matter. Onset ranges between a few months to > 40 years after the irradiation. The risk increases with increasing total dose and fraction size and it is almost unknown with total doses 45-50 Gy in fractions of < 2 Gy.
	Cerebrovascular accidents	Cerebrovascular mortality has been found increased in patients with pituitary adenoma treated by radiotherapy compared with the general population. Related to atherogenesis to the vascular lining from the radiotoxicity Risk factors include older age, previous aggressive intracranial surgery and total dose > 45 Gy. Particularly in patients with acromegaly, radiotherapy has been associated with increased mortality with cerebrovascular disease being the main cause of death.
	Second brain tumor	In a series of patients irradiated for pituitary adenoma probability 2% at 20 years, but another series comparing patients with pituitary adenoma and treated by surgery alone or postoperative radiotherapy did not confirm increased risk. Most commonly meningiomas, gliomas, chondrosarcomas. Risk factors including radiation thresholds not defined.

	Cognitive dysfunction	No consistent data and in studies using extensive psychometric testing the effect of irradiation could not be clearly distinguished from that of other interventions or of the tumor itself.
	Quality of life	Patients with non-functioning pituitary adenoma treated by rariotherapy show compromised scores in the areas of energy levels and perception of the overall health in health-related quality of life questionnaires.

Table 4. Hypopituitarism after cranial radiotherapy (1,33,42,43).

Condition treated with radiotherapy	**Radiation details**	**Pituitary hormone deficits**
Leukemia and lymphoma	Fractionated total body irradiation (7-16 Gy)	Isolated GH deficiency in children
Leukemia and lymphoma	Fractionated prophylactic cranial irradiation (18-24 Gy)	GH deficiency in children Small risk of other deficits in children/adults
Non-pituitary brain tumors	Conventional fractionated cranial irradiation (30-50 Gy)	GH deficiency 30-100% (higher in children) FSH/LH deficiency ~30% ACTH deficiency ~20-30% TSH deficiency ~10%
Nasopharyngeal carcinoma and skull-base tumours	Conventional fractionated cranial irradiation (50-70 Gy)	GH deficiency 55-100% FSH/LH deficiency ~35-82% ACTH deficiency ~18-25% TSH deficiency ~15-45%
Pituitary tumors	Conventional fractionated cranial irradiation (30-50 Gy)	GH deficiency ~100% FSH/LH deficiency ~65% ACTH deficiency ~40-50% TSH deficiency ~50%
Limitations of the studies these data rely on include selection bias of patients (eg. only the symptomatic ones may have been tested), various sample sizes, different diagnostic tests and criteria, various radiotherapy schedules (biological effective dose not usually estimated), variable follow-up, impact of previous cranial surgery or chemotherapy.		