REVIEW

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Radiation-induced hypopituitarism

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Abstract

The hypothalamic–pituitary unit is a particularly radiosensitive region in the central nervous system. As a consequence, hypopituitarism commonly develops after radiation treatments for sellar and parasellar neoplasms, extrasellar brain tumours, head and neck tumours, and following whole body irradiation for systemic malignancies. Increasing tumour-related survival rates provide an expanding population at risk of developing hypopituitarism. In this population, long-term monitoring tailored to the individual risk profile is required to avoid the sequelae of untreated pituitary hormonal deficiencies and resultant decrease in the quality of life. This review analyses the pathogenesis, prevalence and consequences of radiation-induced hypopituitarism (RIH) in diverse subgroups at risk. Also discussed is the impact of modern radiotherapy techniques in the prevalence of RIH, the spectrum of endocrine disorders and radiation-induced brain conditions that also occur in patients with RIH.

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Introduction

Radiation therapy (RT) is widely used in the management of intracranial and systemic disorders. While three-dimensional treatment planning and accurate radiation delivery enhance efficacy and safety of radiotherapy, the hypothalamic–pituitary unit often receives significant doses of radiation with the tendency to develop long-term radiation-induced hypopituitarism (RIH) and its sequelae.

Hypopituitarism is a common consequence of radiation treatments and is associated with increased morbidity and mortality (Tomlinson *et al*. 2001). RIH is a chronic onset disorder that can result in a variable and progressive impairment of pituitary function. The clinical consequences of RIH are present across the lifespan and need adequate lifelong monitoring and optimal replacement to avoid the well-known sequelae of pituitary failure. Furthermore, patients who have received radiotherapy involving the pituitary and hypothalamic areas are at risk of occasionally developing radiation optic neuropathy (Kline *et al*. 1985), second-brain tumours (Minnitti *et al*. 2005), vascular problems and other rare but serious radiation-related adverse effects that need specific monitoring. Survivors of non-pituitary neoplasms who develop RIH (mainly patients with extrasellar brain tumours, postnasal space cancer and some systemic malignancies) are also present with direct damage to the pituitary target organs, besides other systemic sequelae of treatment (Cohen 2005). As cancer survival rates steadily increase (Verdecchia *et al*. 2007), the forthcoming decades are expected to bring an upsurging number of survivors prone to developing endocrine sequelae of antitumoral treatments. These patients do not always undergo routine surveillance for endocrine complications when required. However, adequate management and treatment of RIH represents an important tool for optimising outcomes and improving the quality of life (QoL) in such patients.

This review analyses the pathogenesis, prevalence and clinical consequences of RIH. The impact of modern radiation techniques on its incidence, and strategies for optimising early diagnosis and treatment are also discussed.

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Common indications of radiotherapy resulting in RIH

RIH is a common consequence of RT for the conditions shown in Table 1. Tumours developing in the sellar and parasellar regions have a distinct clinical behaviour when compared with other brain tumours; nasopharyngeal carcinomas (NPC) and haematological malignancies are separately described.

The most common sellar neoplasms requiring radiation treatment are pituitary adenomas, which include non-functioning tumours, somatotroph, corticotroph adenomas and prolactinomas. Radiotherapy prevents tumour growth either when surgery is contraindicated or in the presence of a significant tumour remnant, usually in the cavernous sinuses. Radiotherapy is also used to treat refractory hormonal hypersecretion when medical and surgical approaches have not been successful (Plowman 2002, Petrovich *et al*. 2003*a*,*b*). The most common radiotherapy regimen for pituitary adenomas is fractionated radiotherapy using a total dose of 45 Gy administered in 25 fractions of 1.8 Gy. Although single-fraction radiotherapy (SFR), also known as radiosurgery, with doses averaging 15–30 Gy has also been used, its value is debated (Brada & Jankowska 2008). The combination of tumour compression of the pituitary parenchyma, surgical damage and the vicinity of the hypothalamic–pituitary unit to the radiation target makes RIH a common event, present in 50–100% of patients. Tables 2 and 3 show the incidence of RIH in diverse series of pituitary tumours depending on the radiation technique and the hypersecretion features.

RT for other sellar and parasellar tumours also results in RIH. Craniopharyngiomas are tumours with a remarkable incidence of hypopituitarism in different treatment stages (Karavitaki *et al*. 2005). The tumour invasiveness, the difficulty of total removal, and the contribution of radiotherapy (average total dose 50–60 Gy), make hypopituitarism virtually universal in these patients. RIH also presents the following RT

Table 1 Neoplasms associated with treatment-related endocrine sequelae

Type of neoplasm	Subtypes	Most common endocrine sequelae
Pituitary adenomas	Non-functioning adenomas Corticotroph adenomas Somatotroph adenomas Prolactinomas	Partial or complete pituitary failure (Littley *et al*. 1989)
Parasellar tumours	Craniopharyngiomas (Karavitaki *et al*. 2005) Meningiomas (Bassiouni *et al*. 2006) Germinomas Chordomas/chondrosarcomas Haemangiopericytomas Pituicytoma Gliomas	Partial or complete hypopituitarism (Karavitaki *et al*. 2005) Damage to thyroid gland from scattered radiation (dysfunction, oncogenesis) Tumour or surgical-related hypothalamic dysfunction (water balance, appetite, thermogenesis)
Non-parasellar brain tumours	Gliomas Meningiomas Pinealomas Medulloblastomas Brain metastases Schwannomas Vascular malformations	41% present some degree of RIH (Agha *et al*. 2006) 38.2% can present with hypopituitarism after non-pituitary intracranial surgery (Schneider *et al*. 2006) Scattered radiation to the thyroid bed can result in increased incidence of thyroid dysfunction and oncogenesis (Madanat *et al*. 2007)
Haematological malignancies	Acute lymphoblastic leukaemia, lymphomas	Total body irradiation (18–24 Gy): GHD, pubertal timing disruption Radiation and/or chemotherapy-induced primary gonadal damage Radiation and/or chemotherapy-induced thyroid dysfunction and oncogenesis (Sklar *et al*. 2000)
Postnasal space tumours	Nasopharyngeal carcinomas	Radiotherapy (total dose 50–60 Gy): some degree of RIH in 62% (Lam *et al*. 1991) Primary thyroid damage: thyroid dysfunction (Garcia-Serra *et al*. 2005) and oncogenesis (Mihailescu *et al*. 2002) Hyperparathyroidism: risk reported after radiotherapy for benign head and neck conditions only (Schneider *et al*. 1995)

Table 2 Incidence of radiation-induced hypopituitarism in pituitary tumours treated with different radiation techniques

Reference	Radiation technique[a]	Patients	Previous therapies	Follow-up[b]	Hypopituitarism
Conventional radiotherapy					
Littley *et al.* (1989)	CRT 37–42.5 Gy in 15–16 fractions	165 Patients 75 NFA 39 Acro 18 PRL 15 Cranio 4 CD 14 Other	142 Surgery 2 Ventriculoatrial shunt 1 Cyst aspiration 3 Biopsy	8 years	100% GHD 96% GT 84% ACTH 49% TSH
Brada *et al.* (1993)	CRT 45–50 Gy in 25–30 fractions	411 Patients 252 NFA 62 Acro 60 PRL 7 CD 1 TSHoma 1 Gonatrophinoma	82% Surgery	19 years	50% Hypopituitarism
Constine *et al.* (1993)	CRT 39.6–72 Gy to pituitary gland In 9 pts, also craniospinal RT 31 Gy	32 Patients 21 Gliomas 5 Medulloblastomas 2 Ependymomas 4 Other	8 Chemotherapy	7 years	GHD not evaluated 61% GT 35% ACTH 47% TSH 10% Primary hypothyroidism
Tsang *et al.* (1994)	CRT 45 Gy	128 Patients with NFA	100% Surgery	8.3 years	GHD not evaluated 13% GT 15% ACTH 23% TSH
Zierhut *et al.* (1995)	CRT 45.5 Gy in 25 fractions	138 Patients 70 NFA 50 Acro 11 PRL 7 CD	88% Surgery	6.5 years	19% GHD 27% GT 19.5% ACTH 12.5% TSH
Tsang *et al.* (1996)	CRT 50 Gy in 25 fractions	145 Patients 52 Acro 64 PRL 29 CD	128 Surgery	7.3 years	GHD not evaluated 10% GT 10% ACTH 22% TSH
Rush & Cooper (1997)	CRT 45 Gy in 25 fractions	70 Patients 40 NFA 6 Acro 24 PRL	34% Dopamine agonist 100% Surgery	8 years (median)	GHD not evaluated 9% GT 27.4% ACTH 40% TSH

Table 2 *continued*

Reference	Radiation technique[a]	Patients	Previous therapies	Follow-up[b]	Hypopituitarism
Langsenlehner *et al.* (2007)	CRT 50.4 Gy	87 Patients 61 NFA 11 Acro 12 PRL 2 CD 1 TSHoma	100% Surgery	10.5 years	98% GHD 96% GT 59% ACTH 64% TSH
Minniti *et al.* (2007*b*)	CRT 45–50 Gy in 25–28 fractions	40 Patients with CD	100% Surgery	9 years (median)	77% Hypopituitarism (56% after CRT)
Stereotactic fractionated radiotherapy					
Jalali *et al.* (2000)	SFRT 45–50 Gy in 25–30 fractions	22 Patients 13 NFA 5 Acro 4 PRL	100% Surgery 4 Medical therapy	0.7 years (median)	GHD not evaluated 25% GT 20% ACTH 19% TSH
Milker-Zabel *et al.* (2001)	20 pts SFRT (52.2 Gy) 5 pts LINAC (15 Gy)	25 Patients with Acro	96% Surgery	5 years	12% Hypopituitarism (all after FSRT)
Colin *et al.* (2005)	SFRT 50.4 Gy in 25–30 fractions	110 Patients 63 NFA 31 Acro 4 PRL 10 CD	81% Surgery	8 years	GHD not evaluated GT 13.9% ACTH 28.6% TSH 32.3%
Paek *et al.* (2005)	SFRT, median dose 50.0 Gy	68 Patients with NFA	96% Surgery	2.5 years	6% Hypopituitarism
Minniti *et al.* (2006)	SFRT 45 Gy in 25 fractions in 94% of patients	92 pts (44 F), median age 50 years 67 NFA 18 Acro 5 PRL 2 CD	100% Surgery	2.7 years	11% Partial hypopituitarism 11% Complete hypopituitarism
Kong *et al.* (2007)	LINAC SFRT 50.4 Gy in 25 fractions GKRS 25.1 Gy	125 Patients SFRT: 64 pts (42 NFA, 1 CD, 15 Acro, 6 PRL) GKRS: 61 pts (29 NFA, 7 CD, 15 Acro, 10 PRL)	93.6% Surgery	5 years	11.6% New pituitary deficiencies (90% presented in SFRT group)

Table 2 *continued*

Reference	Radiation technique[a]	Patients	Previous therapies	Follow-up[b]	Hypopituitarism
Gamma knife single-fraction radiotherapy					
Lim *et al.* (1998)	GKRS 25.4 Gy	65 Patients 22 NFA 20 Acro 4 CD 19 PRL	51% Surgery	2.12 years	1.5% New hypopituitarism
Martinez *et al.* (1998)	GKRS 22.3 Gy	30 Patients 14 NFA 7 Acro 5 PRL 3 CD	50% Surgery 10% CRT	2.5 years	3.3% New hypopituitarism
Morange-Ramos *et al.* (1998)	GKRS 28 Gy	25 Patients 6 CD 15 Acro 4 PRL	36% Surgery 4% CRT	1.7 years	16% New hypopituitarism
Izawa *et al.* (2000)	GKRS 22.5 Gy	79 Patients 23 NFA 29 Acro 15 PRL 12 CD	51% Surgery	2.3 years	0% Hypopituitarism
Höybye *et al.* (2001)	GKRS, maximum dose 60–240 Gy	18 Patients with CD	5% Bilateral adrenalectomy 10% Surgery 55% GKRS	16.8 years	100% GHD 33% GT 50% ACTH 56% TSH
Feigl *et al.* (2002)	GKRS 15 Gy	92 Patients 61 NFA 18 PRL 9 Acro 4 ACTH	100% Surgery	4.6 years	13% GHD 21.7% GT 8.7% ACTH 23.9% TSH
Attanasio *et al.* (2003)	GKRS 20 Gy	30 Patients with Acro	10% Somatostatin analogues 90% Surgery + somatostatin analogues 13% CRT	3.8 years	0% GHD 5.3% GT 7.6% ACTH 0% TSH
Degerblad *et al.* (2003)	GKRS 30–35 Gy	11 Patients with CD	18% Previous GKRS	6.8 years	81% GHD 45% GT 45% ACTH 54% TSH

Table 2 *continued*

Reference	Radiation technique[a]	Patients	Previous therapies	Follow-up[b]	Hypopituitarism
Pollock & Carpenter (2003)	GKRS 16 Gy	33 Patients All NFA	96% Surgery 33% Radiosurgery	5 years	28% GHD 25% GT 11% ACTH 8% TSH
Kong *et al.* (2007)	LINAC SFRT 50.4 Gy in 25 fractions GKRS 25.1 Gy	125 Patients SFRT: 64 pts (42 NFA, 9 CD, 15 Acro, 6 PRL) GKRS: 61 pts (29 NFA, 7 CD, 15 Acro, 10 PRL)	93.6% Surgery	5 years	11.6% New pituitary deficiencies (90% presented in SFRT group)
LINAC single-fraction radiotherapy					
Milker-Zabel *et al.* (2001)	20 pts SFRT (52.2 Gy) 5 pts LINAC (15 Gy)	25 Patients with Acro	96% Surgery	5 years	12% Hypopituitarism (all after FSRT)
Swords *et al.* (2003)	LINAC 20 Gy	142 Patients 37 NFA 64 Acro 17 CD 9 Nelson syndrome 13 PRL 2 TSHoma	100% CRT 90% Surgery	1.3 years	0% Hypopituitarism
Voges *et al.* (2006)	LINAC 20 Gy	142 Patients 37 NFA 64 Acro 17 CD 9 Nelson syndrome 13 PRL 2 TSHoma	96.5% Surgery 2.8% Iodine brachytherapy 6.3% CRT	4.6 years	12.3% Hypopituitarism

CRT, external beam conventional radiotherapy; GKRS, Gamma-knife radiosurgery; SFRT, stereotactic fractionated radiotherapy; LINAC, linear accelerator radiosurgery; GHD, GH deficient; GT, gonadotrophin deficient; ACTH, ACTH-deficient; TSH, TSH-deficient; NFA, non-functioning adenoma of the pituitary gland; Acro, acromegaly; PRL, prolactinoma; CD, Cushing's disease; Cranio, craniopharyngioma.

[a]Radiation delivery technique, margin total doses and number of fractions are specified.

[b]The length of follow-up describes the period of time when pituitary function testing was performed after radiation exposure. This is calculated as a mean unless specified otherwise.

Table 3 Incidence of radiation-induced hypopituitarism in different pituitary tumours classified according to secretory features

Reference	Radiation technique[a]	Patients	Previous therapies	Follow-up[b]	Hypopituitarism[c]	Therapeutic efficacy[d]
Cushing's disease						
Conventional radiotherapy						
Littley *et al.* (1990)	CRT 20 Gy in 8 fractions	24 Patients with CD	No previous therapy	7.7 years (median)	67% GHD 14% GT 12% ACTH 0% TSH	During follow-up: 46% BRR (45% relapse)
Estrada *et al.* (1997)	CRT 50 Gy in 25–30 fractions	30 Patients with CD	100% Surgery	3.5 years (median)	57% GHD 33% GT 17% TSH 3% ACTH	During follow-up: BRR 82%
Nagesser *et al.* (2000)	CRT 30 Gy in 15 fractions + unilateral adrenalectomy	86 Patients	Unilateral adrenalectomy	21.4 years	36% Hypopituitarism 58% GHD 23% GT 31% ACTH 9% TSH	During follow-up: BRR 64% (17% relapse)
Minniti *et al.* (2007*b*)	CRT 45–50 Gy in 25–28 fractions	40 Patients with CD	100% Surgery	9 years (median)	77% Hypopituitarism (56% after CRT)	10-year-PFS: 93% 10-year BRR 84%
Gamma-knife radiosurgery						
Höybye *et al.* (2001)	GKRS, maximum dose 60–240 Gy	18 Patients with CD	5% Bilateral adrenalectomy 10% Surgery 55% GKRS	16.8 years	100% GHD 33% GT 50% ACTH 56% TSH	During follow-up: BRR 83%
Degerblad *et al.* (2003)	GKRS 30–35 Gy	11 Patients with CD	18% Previous GKRS	6.8 years	81% GHD 45% GT 45% ACTH 54% TSH	Not assessed
Castinetti *et al.* (2007)	GKRS 29.5 Gy (median margin dose)	40 Patients	72.5% Surgery 5% CRT	4.5 years	15% Hypopituitarism	During follow-up: BRR 42.5%
Jagannathan *et al.* (2007)	GKRS 23 Gy	90 Patients with CD	99% Surgery 3% CRT 1% LINAC 1% GKRS	3.7 years	22% Hypopituitarism 7% GHD 10% TSH No data on GT or ACTH	During follow-up: BRR 54% (20% relapse) PFS 94%
LINAC radiosurgery						
Devin *et al.* (2004)	LINAC 14.7 Gy	35 Patients with CD	99% Surgery 3% CRT 23% Adrenalectomy during follow-up	3.7 years	40% Hypopituitarism 16% GHD 24% GT 11% ACTH 22% TSH	During follow-up: BRR 49% (19% relapse) PFS 91%

Table 3 *continued*

Reference	Radiation technique[a]	Patients	Previous therapies	Follow-up[b]	Hypopituitarism[c]	Therapeutic efficacy[d]
Nelson's syndrome						
Conventional radiotherapy						
Howlett *et al.* (1989)	CRT 45 Gy in 25 fractions	15 Patients with Nelson's syndrome 21 Patients with non-adrenalectomised CD	Not specified	9.6 years (median)	6.7% Hypopituitarism 0% GHD 6.7% GT 0% ACTH 6.7% TSH	During follow-up: PFS 93%
Gamma-knife radiosurgery						
Pollock & Young (2002)	GKRS 20 Gy	11 Patients	100% Bilateral adrenalectomy 100% Pituitary surgery 5% CRT	3.1 years	9% Hypopituitarism	During follow-up: PFS 78%
Mauermann *et al.* (2007)	GKRS 25 Gy	23 Patients	100% Bilateral adrenalectomy 22% CRT	1.75 years	40% Hypopituitarism 30% GHD 0% GT 0% ACTH	During follow-up: PFS 80%
Acromegaly						
Conventional radiotherapy						
Gutt *et al.* (2001)	CRT 50 Gy (median dose) in 25–30 fractions	41 Patients	80% Surgery	12.8 years (median)	44% Hypopituitarism, 6 years after radiotherapy 7-year cumulative risk of hypopituitarism: 63%	During follow-up: BRR 34%
Jenkins *et al.* (2006)	CRT 45 Gy (median dose)	696 Patients with Acro	71% Surgery	7 years (median)	10-year actuarial rates 58% GT (40% before CRT) 50% ACTH (35% before RT) 44% TSH (17% before radiotherapy) No data on GHD	10-year BRR: 60% normal GH day curve 63% Normal IGF-I
Minniti *et al.* (2005)	CRT 45 Gy in 25 fractions	47 Patients	100% Surgery	12 years (median)	82% Hypopituitarism (77% of which developed after radiotherapy) 75% GT 70% TSH 68% ACTH No data on GHD	15-year PFS 100% 15-year BRR 77% normal GH nadir after OGTT

Table 3 *continued*

Reference	Radiation technique[a]	Patients	Previous therapies	Follow-up[b]	Hypopituitarism[c]	Therapeutic efficacy[d]
Gamma-knife radiosurgery						
Attanasio *et al.* (2003)	GKRS 20 Gy	30 Patients with Acro	10% Somatostatin analogues 90% Surgery + somatostatin analogues 13% CRT	3.8 years	0% GHD 5.3% GT 7.6% ACTH 0% TSH	5-year PFS: 100% 5-year BRR: 37% normal GHDC (45% on medication)
Castinetti *et al.* (2005)	GKRS 25.8 Gy	82 Patients	77% Surgery	4.1 years	17% New-onset hypopituitarism	4-year PFS: 100% 4-year BRR: 17% normal OGTT nadir and IGF-I (23% on somatostatin analogues)
Jezková *et al.* (2006)	GKRS 32 Gy	96 Patients	74% Surgery 11.5% CRT	3.6 years	41% GT 14% ACTH 31.7% TSH No data on GHD	5-year PFS: 100% 5-year BRR: 45% normal OGTT nadir and IGF-I
LINAC radiosurgery and fractionated radiotherapy						
Milker-Zabel *et al.* (2001)	20 pts SFRT (52.2 Gy) 5 pts LINAC (15 Gy)	25 Patients	96% Surgery	5 years (median)	12% Hypopituitarism (all after FSRT)	5-year PFS: 100% 5-year BRR: 80% SFRT (31% on somatostatin analogues) 100% LINAC (40% on somatostatin analogues)
Non-functioning adenomas						
Conventional radiotherapy						
Brada *et al.* (1993)	CRT 45–50 Gy in 25–30 fractions	411 Pituitary adenomas (252 NFA, 131 secreting adenomas, 28 unknown status)	82% Surgery	10.8 years (median)	10-year hypopituitarism rate: 30% 19-year hypopituitarism rate: 50%	10-year PFS 97% 20-year PFS 92%
Tsang *et al.* (1994)	CRT 45 Gy in 25 fractions	128 Patients with NFA	100% Surgery	8.3 years	GHD not evaluated 13% GT 15% ACTH 23% TSH	10-year PFS 87%
Zierhut *et al.* (1995)	CRT 45.5 Gy in 25 fractions	138 Patients (70 NFA, 58 secreting adenomas)	88% Surgery	6.5 years	27% Hypopituitarism (in all pituitary adenoma subtypes)	5-year PFS 95%
Langsenlehner *et al.* (2007)	CRT 50.4 Gy (median dose) in 25–30 fractions	87 Patients (61 NFA, 26 secreting adenomas)	100% Surgery	10.5 years (median)	88% Hypopituitarism (in all the pituitary adenoma subtypes)	5-year PFS 98.7% 15-year PFS 93%

Table 3 *continued*

Reference	Radiation technique[a]	Patients	Previous therapies	Follow-up[b]	Hypopituitarism[c]	Therapeutic efficacy[d]
Gamma-knife radiosurgery						
Pollock & Carpenter (2003)	GKRS 16 Gy	33 Patients with NFA	96% Surgery 33% Radiosurgery	5 years	28% GHD 25% GT 11% ACTH 8% TSH	5-year PFS 97%
Losa *et al.* (2004)	GKRS 17 Gy	54 Patients with NFA	100% Surgery	3.4 years	24% Hypopituitarism 12.5% GT 8.6% ACTH 2.3% TSH	5-year PFS 88.2%
Iwai *et al.* (2005)	GKRS 14 Gy (median dose)	31 Patients with NFA	100% Surgery 3% CRT	5 years (median)	6.5% Hypopituitarism	5-year PFS 93%
LINAC stereotactic fractionated radiotherapy						
Colin *et al.* (2005)	SFRT, 50.4 Gy (median dose) in 30 fractions	110 Pituitary adenomas (63 NFA, 47 secreting adenomas)	81% Surgery	6.8 years (median)	4-year hypopituitarism rate: 28.5% 8-year hypopituitarism rate: 35% 14% GT, 32% ACTH, 29% TSH at the end of follow-up (median 6.8 years). No data on GHD	During follow-up: PFS 98.7% after a median of 6.8 years
Paek *et al.* (2005)	SFRT, median dose 50.0 Gy	68 Patients with NFA	96% Surgery	2.5 years	6% Hypopituitarism	5-year PFS 98%
Minniti *et al.* (2006)	SFRT 45 Gy in 25 fractions (95%) or 50 Gy in 30 fractions (5%)	92 Patients with pituitary adenomas 60 NFA 32 Secreting adenomas	100% Surgery	2.7 years	22% Hypopituitarism 9% GHD 7% GT 3% ACTH 6% TSH	1-year PFS 99% 5-year PFS 98%
Prolactinomas						
Conventional radiotherapy						
Grossman *et al.* (1984)	CRT 45 Gy in 25 fractions	36 Patients with prolactinoma	100% Dopamine agonists before and after radiotherapy	4.2 years	68% GHD 15% GT 0% ACTH 3% TSH	During follow-up: 30% normal prolactin 30% PFS during follow-up (skull X-ray, CT scan)
Tsagarakis *et al.* (1991)	CRT 45 Gy in 25 fractions	36 Patients with prolactinoma	100% Dopamine agonists before and after radiotherapy	8.5 years	94% GHD 23% GT 14% ACTH 14% TSH	During follow-up: 50% prolactin normalisation 97% Tumour PFS

Table 3 *continued*

Reference	Radiation technique[a]	Patients	Previous therapies	Follow-up[b]	Hypopituitarism[c]	Therapeutic efficacy[d]
Gamma-knife radiosurgery						
Pouratian *et al.* (2006)	GKRS 19 Gy	23 Patients followed for prolactin normalisation (1) 28 Patients followed for imaging parameters (2)	Group 1: 57% Dopamine Agonist at time of GKRS, 83% surgery, 17% CRT Group 2: 57% Dopamine agonist at time of GKRS, 85% surgery, 14% CRT	4.6 years (1) 4.8 years (2)	29% Hypopituitarism 7% GHD 7% ACTH 17.5% TSH	5-year BRR 26% 5-year PFS 89%
LINAC radiosurgery and fractionated radiotherapy						
Mitsumori *et al.* (1998)	18 Patients LINAC 15 Gy (4 Prolactinomas) 30 Patients SFRT 45 Gy in 25 fractions (11 prolactinomas)	48 Pituitary adenomas 15 PRL 7 CD 6 Acro 1 TSHoma 19 NFA	No data on dopamine agonists 100% Surgery 8% CRT	3 years	21.6% Hypopituitarism 22.9% in LINAC 20.1% in SFRT	During follow-up: BRR 47% PFS 91%
LINAC radiosurgery						
Yoon *et al.* (1998)	LINAC 21 Gy	24 Pituitary macroadenomas 11 PRL 2 Acro 1 CD 8 NFA 2 Mixed GH and PRL secreting tumours	96% Surgery	4 years	29% Hypopituitarism 8% Panhypopituitarism 4% GT 17% TSH No data on ACTH or GHD	During follow-up: BRR 84% PFS 96%

CRT, conventional radiotherapy; GKRS, Gamma-knife radiosurgery; SFRT, stereotactic fractionated radiotherapy; LINAC, linear accelerator radiosurgery; GHD, GH deficiency; GT, gonadotrophin deficiency; ACTH, ACTH-deficiency; TSH, TSH-deficiency.

[a]Radiotherapy technique, fractionation strategy, total margin dose and number of fractions are specified.

[b]Mean post-radiotherapy follow-up period is described unless otherwise specified.

[c]Rates of new-onset hypopituitarism during post-radiotherapy follow-up interval are described.

[d]Biochemical remission rates (BRR) and tumoral progression-free survival rates (PFS) are described in actuarial rates where available. If actuarial rates are not calculated in the study, the therapeutic efficacy end-points refer to those achieved at any moment of the study follow-up interval.

for meningiomas, gliomas, chordomas, pineal tumours and chondrosarcomas lying in parasellar location (Smith *et al*. 2006).

RIH can also result from radiation used for non-parasellar brain tumours and systemic malignancies. Endocrine sequelae in cancer survivors may be due to the direct effect of the malignancy and radiation treatment on hypothalamic, pituitary, thyroid and gonadal function and due to the effects of chemotherapy (Gleeson & Shalet 2004). Childhood cancer survivors have a decreased QoL, and their 30-years cumulative incidence of chronic health conditions is 73.4% with a 24% incidence of endocrine sequelae (Oeffinger *et al*. 2006), although other series report incidence figures as high as 41% (Stevens *et al*. 1998). The severity of RIH is related to the radiation doses given while whole body irradiation regimens to a dose of 18 Gy result merely in isolated GH deficiency (GHD; Clayton & Shalet 1991), higher dose schedules, such as those used for NPC (40–60 Gy falling on the hypothalamic–pituitary unit) result in 62% incidence of pituitary deficiencies, which involve the GH, gonadotroph, corticotroph and thyrotroph axes (Lam *et al*. 1991).

Pathophysiology of radiation-induced toxicity in the hypothalamic–pituitary unit

Radiation exerts effects on neoplastic and healthy tissues through ionisation of the cell DNA. Damage can occur directly, through the generation of dysfunctional conformational changes in cell DNA, or indirectly through the production of free radicals from water molecules, resulting in damage to the cell DNA (Belka *et al*. 2001). Radiation damage can induce immediate lethal effects or accumulate sublethal damage that limits the potential for cell replication, thus halting tumour growth (Shrieve 2006). Cell death after radiation, which occurs in the mitotic phase of the cell cycle (late G2-early S), may be the reason for a delayed onset of chronic complications of radiation in slowly replicating tissues, such as those present in the hypothalamic–pituitary unit (Dewey & Bedford 1998, Kunkler 2003).

Ionising radiation also induces degenerative changes in glial cells, leading to a lack of trophic neural support and demyelination, which in turn causes subacute and chronic neural damage in the hypothalamus and other central nervous system (CNS) structures. Radiation also causes vascular derangements (lifting of endothelia, vacuolation of the cytoplasm and nuclear swelling) that ultimately lead to endothelial cell death (Tofilon & Fike 2000, Belka *et al*. 2001). Vascular changes with alteration in vessel permeability may explain oedema in the acute phase of high-dose radiation treatments (Smith *et al*. 2006), which is rarely seen following RT for benign sellar and parasellar tumours. In the chronic phase, the vascular lining, exposed to the progressive loss of endothelia, responds by increasing endothelial proliferation, thickening the basement membrane and increasing the collagen synthesis. These changes lead to obliteration of the small vessels with necrosis of irradiated tissues and enhance atherogenesis in major brain arteries. The exposed vascular matrix in great vessels accelerates the formation of platelet aggregates and thrombi. Thrombotic vessel occlusion culminates the derangement in the vascular wall initially induced by radiation atherogenesis. The reported risk of cerebrovascular accidents in irradiated cohorts (Brada *et al*. 2002) has been attributed by some authors to the increased atherogenicity of the irradiated vascular lining.

Owing to the efficacy of radiotherapy in halting the growth and hormonal hypersecretion of sellar neoplasms, further surgery is rarely required and data on the histological changes occurring in the dysfunctional pituitary gland are scarce. The most commonly reported findings are fibrosis of the pituitary parenchyma, hyperplasia of folliculostelate cells, squamous metaplasia, oncocytic changes and increased cytokeratin immunoreactivity (Nishioka *et al*. 2002).

In radiation treatments for sellar and parasellar tumours, hypothalamic damage is considered to be present in the early pathophysiology of RIH, while pituitary atrophy has been classified as a late-onset contributing factor (Romer *et al*. 1991, Darzy *et al*. 2007). Studies on the effects of external radiotherapy on the lactotroph axis as well as the differential effects of pituitary brachytherapy compared with external radiation have provided evidence in favour of this pathophysiological hypothesis. Lactotroph cells, unlike any other pituitary-cell lines, receive predominantly inhibitory signals from the hypothalamus; this inhibitory control explains the increase in prolactin (PRL) levels that results from either radiation damage to the hypothalamus or hypothalamic–pituitary disconnection. By contrast, hyperprolactinaemia does not occur when direct damage to lactotroph cells occurs. Thus, measuring PRL levels in irradiated cohorts can provide clues as regards the pathophysiology of RIH. In two long-term follow-up studies, 96% of previously normoprolactinaemic patients with acromegaly (Ciccarelli *et al*. 1989) and up to 50% of patients after receiving external radiotherapy for extrasellar brain tumours developed hyperprolactinaemia (Constine *et al*. 1993). Radiation-induced

Table 4 Diagnosis of hypopituitarism

Pituitary function	Tests	Diagnostic value	Comments
GH deficiency (Biller *et al*. 2002, Hartman *et al*. 2002, Ghigo *et al*. 2007)[a]	IGF-I (Hartman *et al*. 2002)	41–69% Sensitivity, 95% specificity	A normal result does not exclude GHD, but a low value in patients with multiple pituitary deficiencies makes a stimulation test unnecessary
	Insulin tolerance test (ITT; Biller *et al*. 2002, Clayton *et al*. 2005, Maghnie *et al*. 2005*a*)	Sensitivity 89%, specificity 95% for a cut-off of 9 mU/l (Biller *et al*. 2002) in adult patients In the transition period, cut-offs of 15 mU/l (Clayton *et al*. 2005) and 18 mU/l (Maghnie *et al*. 2005*a*,*b*) have been advocated	Gold standard for the diagnosis of GHD Evaluates cortisol and GH reserve Only valid if nadir glucose value <2.2 mmol/l, close supervision required (Greenwood *et al*. 1966) Contraindicated in patients with stroke, epilepsy, coronary heart disease or heart failure Lack of body mass index-adjusted reference values Repeated hypoglycaemias can offset the stimulatory input of ITT in non GH deficient subjects (Davis *et al*. 2000, Davis & Tate 2001)
	Glucagon test (Leong *et al*. 2001, Gomez *et al*. 2002, Conceicao *et al*. 2003)	Sensitivity 97–100%, specificity 88–100% for a cut-off of 9 mU/l	Safe and accurate alternative to ITT Evaluates cortisol and GH reserve Contraindicated if fasting >48 h or clinical suspicion of phaeochromocytoma or insulinoma Lack of normative data for the transition period and obese patients
	GHRH + arginine (Aimaretti *et al*. 1998, Darzy *et al*. 2003, Ghigo *et al*. 2007)	95% Sensitivity and 85%, specificity for a cut-off of 13.8 mU/l (Biller *et al*. 2002) 100% Sensitivity and specificity for a cut-off of 27 mU/l (Aimaretti *et al*. 1998)	Safe and accurate Body mass index-related normative data are available Less sensitive than ITT in initial phases of radiation-induced GHD (Darzy *et al*. 2003) Optimal performance requires specific cut-offs (Aimaretti *et al*. 1998, Ghigo *et al*. 2007)
Gonadotroph deficiency (Verga 2002, Bhasin *et al*. 2006, Kazi *et al*. 2007)	Men: 0900 h total testosterone, FSH, LH Clinical assessment of symptoms of androgen deficiency	Low testosterone values in at least 2 consecutive measurements are required for diagnosis	Prior to biochemical measurements, intercurrent illnesses need to be excluded Drugs and conditions affecting sex-hormone-binding globulin values can interfere with total testosterone levels. Estimated free testosterone index is recommended in those instances Age-related total testosterone reference ranges currently lacking
	Premenopausal women: FSH, LH, oestradiol + menstrual history (Verga 2002)	Low oestradiol levels + low/normal FSH and LH levels in the follicular phase of the menstrual cycle Oligoamenorrhoea	Clinically, and/or biochemically oriented exclusion of other causes of menstrual disorders is required: functional hypothalamic hypogonadism, hyperprolactinaemia, primary ovarian failure (premature, menopausal), hyperandrogenism and drug interference

Table 4 *continued*

Pituitary function	Tests	Diagnostic value	Comments
	Postmenopausal women: FSH, oestradiol + menstrual history (Soules *et al.* 2001, Lumsden 2002)	During menopausal transition: oligoamenorrhoea, low oestradiol + low/normal FSH in follicular phase and exclusion of factors interfering in menstrual cycle	In normal menopausal transition, follicular phase FSH levels should increase before menstrual irregularity develops and keep elevated during postmenopause (Soules *et al.* 2001)
		After 12 months of menopausal amenorrhoea, failure of FSH to elevate above follicular-phase normal range for women of fertile age	Factors interfering in menstrual cycle: heavy aerobic exercise (>10 h/week), chronic menstrual irregularity and abnormal uterine or ovarian anatomy (Soules *et al.* 2001)
Adrenal insufficiency	0900 h Cortisol	89% Sensitive, 100% specific for a cut-off of 100 nmol/l after pituitary surgery (Courtney *et al.* 2000)	No studies have analyzed its accuracy after radiotherapy
			Cortisol pulsatility impairs its routine use to decide on long-term replacement therapy
	Standard short Synacthen test (SST; 250 μg)	57–100% Sensitive, 90–100% specific for a 30′ cut-off of 500 nmol/l (Shankar *et al.* 1997, Abdu *et al.* 1999, Rose *et al.* 1999*a*, Dorin *et al.* 2003, Schmiegelow *et al.* 2003*a*,*b*)	Normal SST predicts a safe clinical outcome in secondary adrenal insufficiency (Gleeson *et al.* 2003, Agha *et al.* 2006)
			Does not predict adrenal insufficiency shortly after corticotroph deprivation (Hjortrup *et al.* 1983)
			No test is completely reliable, clinical judgement remains essential to decide if reassessment is required (Maghnie *et al.* 2005*b*)
	Low-dose short Synacthen test (LDSST; 1 μg)	61–100% Sensitive, 90–96% specific for a cut-off of 500 nmol/l (Rasmuson *et al.* 1996, Gerritsen & Vermes 1997, Ambrosi *et al.* 1998, Mayenknecht *et al.* 1998, Abdu *et al.* 1999, Tordjman *et al.* 2000, Dorin *et al.* 2003)	Recent meta-analysis showed diagnostic superiority of LDSST over SST in secondary adrenal insufficiency (Kazlauskaite *et al.* 2008), which had not been shown in previous studies (Dorin *et al.* 2003)
		100% Sensitive, 68% specific for a cut-off of 550 nmol/l (Rose *et al.* 1999*a*)	Standardised dilution techniques of the adrenocorticotroph preparation are required for LDSST
		LDDST diagnostic area under the curve (AUC) 0.94, superior to SST (AUC 0.85; Kazlauskaite *et al.* 2008)	
	Insulin tolerance test (ITT; Lindholm 2001, Arlt & Allolio 2003)	Considered gold standard. Cut-off: 500 nmol/l (Lindholm 2001)	Gold standard for the evaluation of secondary adrenal insufficiency
		Some authors advocate higher cut-offs of 550 nmol/l (Stewart *et al.* 1998, Tuchelt *et al.* 2000) or 580 nmol/l (Mukherjee *et al.* 1997)	Contraindicated in patients with stroke, epilepsy, coronary heart disease or heart failure
			Test only valid if glucose nadir <2.2 mmol/l, close supervision required (Greenwood *et al.* 1966)
		Rare cases may be missed by the ITT (Tsatsoulis *et al.* 1988). Clinical judgement should decide on further testing	Prolonged fasting and malnutrition can impair cortisol response to hypoglycaemia (Adamson *et al.* 1989)
			Repeated hypoglycaemias can offset the stimulatory input of ITT in non ACTH-deficient subjects (Davis *et al.* 2000, Davis & Tate 2001)

Table 4 *continued*

Pituitary function	Tests	Diagnostic value	Comments
	Glucagon test	Cortisol peak >500 nmol/l is commonly accepted as cut-off (Rao & Spathis 1987) Other authors advocate 580 nmol/l (Orme *et al*. 1998)	Safe and accurate alternative to ITT (Leong *et al*. 2001) Evaluates cortisol and GH reserve Contraindicated if fasting >48 h or clinical suspicion of phaeochromocytoma or insulinoma
	Overnight metyrapone test (Meikle *et al*. 1969, Spiger *et al*. 1975, Feek *et al*. 1981, Fiad *et al*. 1994, Berneis *et al*. 2002)	Serum cortisol <138 nmol/l after last metyrapone dose confirms adequate blockade Serum 11-deoxycortisol 210–660 nmol/l or more shows normal ACTH reserve If insufficient 11-deoxycortisol response, ACTH <200 pg/ml (2–44 pmol/l) suggests secondary adrenal insufficiency	Evidence suggests safety as outpatient test Accurate test that allows integrative assessment of corticotroph axis: detects primary and secondary adrenal failure Metyrapone is not always readily available Side effects are uncommon but require attention: hypotension, nausea, vomiting, abdominal pain, sedation, allergic rash or (rare) decreased white cell count Tailored dosing required if increased metyrapone clearance (idiogenic or drug-induced) Specific attention to RIH wanted in currently available literature
TSH deficiency	Basal TSH and free T_4 (Roberts & Ladenson 2004)	Low free T_4 with normal/low TSH value in 2 consecutive measurements Markers of hidden central hypothyroidism not fully validated (Rose *et al*. 1999*b*, Darzy & Shalet 2005*a*,*b*) Free T_3 measurement is not useful due to preferential secretion of T_3 when thyrotroph or thyroid function is partially impaired (Ferretti *et al*. 1999, Alexopoulou *et al*. 2004)	Interfering drugs and illnesses should be assessed while interpreting thyroid hormone profile (Roberts & Ladenson 2004)

[a]Adequate interpretation of tests for the assessment of GH reserve requires the absence of intercurrent illnesses and optimal replacement of other pituitary deficiencies, if these are present.

hyperprolactinaemia would not be commonly expected if pituitary atrophy was the primary phenomenon in RIH. Furthermore, follow-up studies of patients with pituitary adenomas treated with brachytherapy (instillation of Yttrium-90 in the sella turcica, total dose 50–150 Gy) revealed a reduced risk of hypopituitarism when compared with a total dose of 37.5–45 Gy delivered through external radiation treatments (Sandler *et al*. 1987, Littley *et al*. 1989). Meanwhile, observational studies have failed to show an increase in PRL levels after sellar brachytherapy (Clark *et al*. 1983). The lower incidence of RIH after sellar brachytherapy despite higher total doses when compared with external radiotherapy, together with the preservation of normal immunoactive serum PRL levels in the former group suggests a lower threshold for radiation-induced damage in hypothalamic tissue (preferentially injured by external radiotherapy). Subsequently, an earlier role of hypothalamic secretory derangements in the pathophysiology of RIH has been inferred. Pituitary atrophy, either through direct radiation damage or lack of hypothalamic stimulatory input, would contribute to RIH at later stages.

Controversy surrounds the nature of the hypothalamic derangements leading to pituitary dysfunction. While some authors suggest a reduced release of hypothalamic releasing factors as the primary phenomenon, others argue in favour of an increased basal stimulatory tone from the hypothalamus, which results in reduced hormonal release in the pituitary gland (Darzy *et al*. 2007). The initial derangements in the pituitary function of irradiated cohorts are mild and subclinical, but can progress over time and become clinically apparent, requiring early recognition and therapy by regular yearly assessment.

Understanding the pathophysiology of RIH is important for the choice of diagnostic strategies used to assess the pituitary function. This requires the use of appropriate stimulation tests acting at the hypothalamic level. The GH-releasing hormone (GHRH) plus Arginine stimulation test has proven to be significantly less sensitive, as compared with the insulin tolerance test (ITT) in patients with radiation-induced GHD (Darzy *et al*. 2003). Futhermore, a flat TSH response to thyrotroph releasing hormone (TRH) stimulation has been traditionally postulated as a sensitive marker of hidden impairment of TRH secretory reserve (Trejbal *et al*. 1994, Rose *et al*. 1999*b*), although the value of these tests has recently been questioned (Darzy & Shalet 2005*a*,*b*). The absence of pituitary atrophy in the initial stages of RIH and derangements in the secretory rate of hypothalamic releasing factors could explain lower sensitivities of functional tests directly dependent on the integrity of the pituitary tissue. Table 4 displays the most commonly used pituitary function tests in the assessment of irradiated cohorts.

The mechanisms underlying the characteristically evolving pattern of RIH, in which GHD and gonadotrophin deficiency appear more commonly and usually earlier than corticotroph and thyrotroph insufficiency (Littley *et al*. 1989) is not known. The thyrotroph and corticotroph axes are known to be less sensitive to radiation damage and develop later; diabetes insipidus does not occur as a consequence of radiation treatments. Although 61% of patients present the usual temporal sequence of pituitary failure (GHD, gonadotrophins, ACTH and, last, TSH deficiency), RIH can present with any temporal sequence of hormonal deficiencies (Littley *et al*. 1989). Therefore, routine testing for all the pituitary axes is warranted. RIH, as other effects of radiation, is a concept of probability, and this probability increases with time. Although RIH tends to be present in the first 5 years after exposure, new deficiencies can appear even 20 years later, necessitating lifelong surveillance (Shalet *et al*. 1976, Littley *et al*. 1989).

RIH is more common in patients with previous insults to the pituitary gland (Duffner *et al*. 1985). Compressive damage by an adjoining tumour causes ischaemic derangements in the normal pituitary parenchyma and a degree of pituitary dysfunction, which is dependent on tumour size and location, duration of pituitary compression and tumoral invasiveness. Tumours located in the hypothalamic region tend to produce a higher degree of hypopituitarism, presumably by depriving the pituitary gland of trophic factors and blood supply from the hypophyseal portal system. Surgical insults to the pituitary gland are also risk factors for the ultimate development of RIH, with 7.2–20.6% of patients presenting new pituitary deficiencies after a transsphenoidal approach in experienced centres (Ciric *et al*. 1997, Ahmed *et al*. 1999). The excision of pituitary parenchyma and the compromise in blood supply following surgery in the sellar and parasellar regions could account for surgically-induced hypopituitarism. Remarkably, this phenomenon, as well as the surgery success rates, is highly dependent on surgical expertise (Bates *et al*. 2008). Postsurgical pituitary dysfunction occurs more commonly in patients undergoing craniotomy, as compared with transsphenoidal approach (Nomikos *et al*. 2004) and this is related to size and invasiveness of the tumour, which may also influence the development of postsurgical hypopituitarism.

RIH can also ensue after RT for non-pituitary brain tumours, such as gliomas, meningiomas, pinealomas

and medulloblastomas. A cross-sectional pituitary function evaluation of adult brain tumour survivors, performed at an average age of 6 years after radiation exposure, found that 41% of the patients had evidence of some degree of hypopituitarism. This included 16% with a single hormonal deficiency, 25% with multiple deficiencies and 7% with panhypopituitarism. The hormonal deficiencies presented in the same frequency order as previously shown with RIH from other causes (32% had GHD, 27% gonadotrophin failure, 21% ACTH deficiency and 9% central hypothyroidism), but were less common than following RT for parasellar tumours (Agha *et al*. 2005). The hormonal deficiencies correlated with the length of follow-up after radiation exposure and with the biologically effective dose (BED). The high-incidence of pituitary dysfunction in adult brain tumour survivors treated with radiotherapy is not dissimilar to RIH found in childhood brain tumour survivors. These findings further highlight the need for regular surveillance of pituitary function in patients with non-pituitary brain tumours treated with radiation fields including the hypothalamic–pituitary unit.

The hypothalamic–pituitary unit commonly falls within radiation fields in the treatment of NPC, due to the vicinity of the postnasal space to the sellar region. Radiotherapy for NPC brought about a 62% incidence of RIH after 5 years of follow-up following mean doses of 40 Gy to the hypothalamus and 62 Gy to the pituitary gland (Lam *et al*. 1991) with 63.5% GH deficiency, 30.7% gonadotroph deficiency, 26.7% ACTH and 14.9% TSH deficiency. The shielding of the pituitary gland may reduce the risk of developing hypopituitarism apparently without decreasing anti-tumoural efficacy (Sham *et al*. 1994), although further studies are needed to confirm this.

Radiotherapy techniques

The purpose of radiation treatments to the sellar region is to prevent tumour growth and normalise hormonal hypersecretion while sparing the surrounding normal structures. The last decades have seen advances in the techniques of irradiation. These include improved imaging and three-dimensional visualisation of tumour and normal tissue, better immobilisation and more localised means of radiation delivery. The term ‘stereotactic’, borrowed from neurosurgery, indicates the use of more precise patient immobilisation and the use of a coordinate system to better define the three-dimensional spatial orientation of radiation beams. We discuss the principal technical developments and their clinical impact on the management of pituitary adenoma.

Radiotherapy equipment

External beam radiotherapy, which is the principal means of delivering radiation to targets in the brain, is given through multiple beams from a high-energy radiation source focused on the tumour. Local delivery of radiation with brachytherapy (interstitial radiotherapy) is rare, if ever employed in this location.

Radiation treatments are most commonly delivered through photons (high energy X-rays), generated by a linear accelerator (LINAC). Cobalt 60 as the source of high-energy gamma radiation has largely been replaced with the exception of a multiheaded Cobalt Unit (gamma knife). Charged particle beams in the form of protons, and more recently Helium and Carbon ions have been tested as therapeutic radiation sources. The principal theoretical advantage of protons is marginally more localised radiation delivery. Helium and carbon ions also have higher linear energy transfer properties (Bolsi *et al*. 2003; Ronson *et al*. 2006) and theoretically produce a more potent biological effect.

In modern pituitary RT, the tumour is localised on unenhanced magnetic resonance imaging coregistered with planning computed tomography (CT). The treatment delivery is planned in three-dimensions (Littmann *et al*. 2006) with improved visualisation of dose distribution within the target and the organs at risk of radiation toxicity. Localised irradiation is achieved by giving treatment in 3–4 beams each shaped to conform to the shape of the tumour using a multileaf collimator (MLC). This is described as conformal radiotherapy and is part of the standard practice in departments specialised in the treatment of benign brain tumours.

MLC leaves, apart from altering the shape of the radiation beam, can also be used to modulate the intensity of radiation and this is described as intensity modulated radiotherapy (IMRT). Studies of dose distribution in tumour and normal tissue show no clear benefit for IMRT compared with fixed-field stereotactic conformal radiotherapy (SCRT) in the treatment of pituitary adenomas.

Stereotactic techniques

Stereotactic techniques are a refinement of conformal radiotherapy with further improvement in immobilisation using relocatable or fixed frames, improved imaging and more precise treatment delivery. Stereotactic irradiation can be given as SFR using either multiheaded cobalt unit (gamma knife) or a LINAC or as SCRT delivered as fractionated treatment using a LINAC. The theoretical benefit of stereotactic compared with conventional RT is further reduced in

the amount of normal tissue treated to high doses with the hope of reducing long-term treatment-related morbidity.

Neither conventional nor stereotactic RT's are currently able to avoid treating the hypothalamus and the pituitary itself receives equally high radiation doses. Based on spatial dose distribution alone, it is unlikely that modern RT will be associated with a significantly lower risk of RIH unless techniques are developed for selective hypothalamic avoidance.

Dose fractionation

Conventional external beam radiotherapy is given in small daily fractions (fractionated RT) over an extended period of time. Although fractionated RT developed largely empirically the rationale is based on differential recovery of radiation-induced damage due to altered repair mechanism in neoplastic as compared with healthy tissues that selectively favour recovery of normal tissue over tumour.

In most sellar neoplasms (Bauman *et al*. 2006), replication is a relatively slow process, which enables fractionation strategies to provide antitumour and antisecretory efficacy with preferential recovery of normal tissue without decreasing tumour control. Radiotherapy for pituitary adenomas is generally delivered in 25–30 fractions over five to six weeks, with a total dose of 45–50 Gy. Individual fraction doses above 1.8 Gy and total doses above 45 Gy are independent risk factors for RIH (Littley *et al*. 1989).

SFR can be delivered through either a LINAC or a 60-Cobalt unit (gamma knife). SFR, despite smaller total doses than fractionated RT, is associated with a higher risk of radiation damage to normal CNS such as the optic apparatus (Pouratian *et al*. 2006, Jagannathan *et al*. 2007) and can only be employed for lesions away from the optic chiasm and nerves. It is less effective in achieving tumour control than fractionated treatment with no faster decline in hormone levels (Brada *et al*. 2004, Jagannathan *et al*. 2007, Brada & Jankowska 2008). Although some studies report the reduced prevalence of RIH (Vladyka *et al*. 2003) there is currently no evidence of reduced risk of RIH following SFR compared with conventional or stereotactic fractionated RT (Pollock & Young 2002, Pollock *et al*. 2002, Degerblad *et al*. 2003, Petrovich *et al*. 2003*a*,*b*).

RIH as a dose-related complication

Hypopituitarism, similar to other radiation-related complications, is a dose-dependent event. RIH occurs more commonly following total doses >45 Gy or fraction doses >1.8 Gy (Littley *et al*. 1989). From these thresholds, the risk of pituitary deficiencies is proportional to the increase in the total and fraction dose. RIH is virtually universal in the high-end of the dose spectrum, with total doses as high as 60 Gy occasionally used for craniopharyngiomas and other aggressive parasellar neoplasms. Early SFR studies suggest a dose-threshold for GH and gonadotroph deficiency of 15 and 18 Gy for ACTH and TSH deficiencies (Vladyka *et al*. 2003).

For a given total dose, the effects of radiation on tissues can vary markedly depending on the fractionation schedule and tissue radiosensitivity. These variables are included in the concept of BED, which predicts antitumoural efficacy and side effects of radiation treatments more accurately than total doses. The BED has been shown to be a close predictor of GHD (Schmiegelow *et al*. 2000), but data on other pituitary axes are lacking.

Clinical consequences of RIH

In the presence of hypopituitarism, mortality is increased by almost twofold (Tomlinson *et al*. 2001). The clinical consequences of a given radiation schedule vary according to patient's age and sex. In childhood, RIH can impair somatic, sexual and psychological development by undermining GH and thyrotroph secretory reserve and disrupting pubertal timing processes. Furthermore, somatotrophs are reported to be more radiosensitive in children as compared with adults: 59% of childhood cancer survivors receiving 18 Gy of total body irradiation for haematological malignancies show a blunted response on GH stimulatory tests (Costin 1988) which is more than twice the frequency of adult GHD after the same dose (Brennan *et al*. 1998). This discrepancy has been explained by the need of greater GH secretory reserve in children (Shalet *et al*. 1976), rather than through variations in radiosensitivity of somatotroph cells through the lifespan (Clayton & Shalet 1991). A direct effect of age on the incidence of other pituitary hormonal deficits has not been demonstrated. Age-related changes in radiosensitivity have nevertheless been reported, when the gonads and the thyroid gland fall within the radiation fields (Sklar *et al*. 2000, Wallace *et al*. 2005).

GH deficiency

GH has consistently shown to be the most radiosensitive pituitary axis, with series reporting a prevalence of GHD between 50 and 100% after radiotherapy for sellar masses. Radiation-induced GHD is also progressive with time, developing more

frequently in the first 10 years after radiation delivery (Shalet *et al*. 1976, Toogood *et al*. 1995). GHD severity and speed of onset closely correlate with lower final height, decreased lean body mass (LBM) and higher fat mass in children with RIH. GHD in the adult conveys an increased risk of fracture, a deranged cardiovascular risk profile and, mainly, a decreased QoL. These abnormalities reverse partially or completely with adequate replacement (Molitch *et al*. 2006), and early diagnosis is therefore very important for optimising outcomes.

The diagnosis of GHD in irradiated patients is based on a low insulin-like growth factor-I (IGF-I) level in patients with multiple pituitary hormonal deficiencies or structural abnormalities in the pituitary region, which has 96% accuracy in predicting GHD (Hartman *et al*. 2002). However, 31–60% of patients with GHD have normal IGF-I values, thus requiring a stimulation test for the diagnosis of GHD (Biller *et al*. 2002, Hartman *et al*. 2002). The ITT is considered the gold standard for the diagnosis of GHD in irradiated cohorts (Molitch *et al*. 2006). Tests using glucagon or GHRH–arginine are less sensitive for the detection of hypothalamic damage, but can be used when epilepsy or cardiac disease contraindicates the ITT (Aimaretti *et al*. 1998, Gomez *et al*. 2002).

Notwithstanding the test of choice, obesity is increasingly being considered an important confounding factor in the assessment of GHD. Both patients with systemic malignancies and brain tumours are at increased risk of excess body weight through various mechanisms (Reilly *et al*. 2000, Harz *et al*. 2003, Oeffinger *et al*. 2006, Brouwer *et al*. 2007, Garmey *et al*. 2008). Radiation treatments, supraphysiological glucocorticoid therapy (Reilly *et al*. 2001), young age at exposure, decreased sleep duration, diminished physical activity and the effects of pituitary hormonal deficiencies represent some of the risk factors for obesity in this population. Particularly in brain tumour survivors, hypothalamic involvement (either induced by the tumour itself or surgical or radiation treatments) conveys a significantly increased risk of excess body weight (Müller *et al*. 2001, Lustig *et al*. 2003). Notwithstanding the underlying cause of increased adiposity, it is well known that GH secretion is attenuated by obesity (Williams *et al*. 1984, Iranmanesh *et al*. 1991). Recently, studies by Corneli & Makimura have established GH cut-offs in the GHRH–arginine stimulatory test adjusted according to body mass index (Corneli *et al*. 2005) and waist circumference (Makimura *et al*. 2008). By contrast, currently available evidence suggests that IGF-I reference values are not affected by increased adiposity (Nam *et al*. 1997, Maccario *et al*. 1999*a*,*b*). As regards the diagnostic value of ITT in obese patients, to our knowledge only a comparative study between 8 hypopituitary patients, 10 obese subjects and 10 normal individuals has been performed (Cordido *et al*. 2003); this survey found no overlap in somatotroph responsiveness between normal obese and hypopituitary individuals. In previous studies on the diagnostic value of ITT, GH dynamics were analyzed comparing subjects with a putative insult to the pituitary gland with healthy controls that were adjusted for body mass index; these studies defined stringent cut-offs for the diagnosis of GHD in order to minimise false positive results (Hoffman *et al*. 1994, Biller *et al*. 2002). As a result, although further research aimed to define if adiposity-related cut-offs are needed for the ITT as a diagnostic test for GHD, the stringency of current GH thresholds should minimise any possible diagnostic interference.

GHD in childhood

Children who receive doses >18 Gy for the treatment of haematological malignancies, sellar neoplasms and other brain tumours have an increased risk of developing the classical child sequelae of GHD (Shalet *et al*. 1976). Patients with untreated childhood-onset GHD (CO-GHD) attain average final heights 1 S.D. below ethnically, age and sex matched controls (Adan *et al*. 1996, Melin *et al*. 1998). In GH-deficient children, height outcomes are directly proportional to the severity of GHD, age of onset and whether adequately-dosed and timely GH replacements were undertaken (Darzy & Shalet 2006). In the Childhood Cancer Survivor Study (Brownstein *et al*. 2004), which followed 183 survivors of childhood tumours treated with cranial or craniospinal irradiation, the S.D. score of children who received GH therapy improved from -2.08 ± 0.08 to -1.48 ± 0.10 ($P<0.0001$). Children with lower final height received spinal radiotherapy and lower doses of GH replacement. GH treatment is generally well tolerated and the use of human recombinant GH is not considered to be associated with significant adverse effects. GH replacement does not increase the risk of tumour recurrence in pituitary adenomas, craniopharyngiomas (Karavitaki *et al*. 2006) and childhood cancer survivors (Sklar *et al*. 2002). These data altogether underline the need for timely and careful consideration of GHD assessment in cancer survivors in order to optimise height outcomes and health-related QoL.

Substantial research has also emphasised the role of factors not directly related to the somatotroph axis in determining height outcomes; among these, direct irradiation of the spine (through arrest of vertebral

growth), nutritional imbalances, deficiencies in other pituitary hormones, early puberty, chemotherapy and the transient effect of the tumour itself should be considered (Cohen 2005). Although GH therapy partially prevents height loss in irradiated children, both timely and weight-adjusted replacements and a comprehensive assessment of additional factors involved play a relevant role in decreasing disparities between height potential and outcome in cancer survivors.

GHD in the transition period

In subjects with childhood-onset RIH, GH replacement has been customarily used for the attainment of height potential, and subsequently stopped. By contrast, substantial research performed over the last decade has focused its attention on the additional benefits of continuous GH therapy after cessation of growth. In the transition age, defined as the period of time between final height acquisition and full adult maturation (usually 6–7 years after final height has been achieved), GH promotes the attainment of peak bone mass and stimulates LBM gain and fat mass reduction (Bonjour *et al*. 1991, Theintz *et al*. 1992, Matkovic *et al*. 1994, Mukherjee *et al*. 2003, Clayton *et al*. 2005, Veldhuis *et al*. 2005, Giustina *et al*. 2008). Conversely, GHD in the transition period results in derangements of these processes (Mukherjee *et al*. 2003, Baroncelli *et al*. 2004, Radovick & DiVall 2007). Therefore, reassessment of GH requirement is required at final height completion (Clayton *et al*. 2005).

The choice of biochemical reassessment method for GHD in the transition period is highly dependent on the pretest likelihood of persistently deranged secretory reserve. Patients with multiple pituitary hormonal deficiencies, with structural disease or radiotherapy-induced GHD are very likely to need GH continuation, and thus an IGF-I measurement after GH withdrawal suffices to confirm the need for continued GH replacement (Clayton *et al*. 2005).

The changes in body composition during the transition period are an important hallmark of subsequent cardiovascular risk. Patients with CO-GHD have 80% of the LBM and increased fat mass content, as assessed by height-normalised dual energy X-ray absorptiometry (DEXA), when compared with patients with adult-onset GHD (AO-GHD; Attanasio *et al*. 2002). Randomised trials confirmed that GH replacement in the transition period restores body composition to normal: LBM and LBM/height ratio increased and body fat mass decreased, and these changes were dependent on GH dose in three out of four clinical trials analyzed. LBM response was more marked in males, probably reflecting the recovery of sexual dimorphism in LBM gain on GH replacement (Vahl *et al*. 2000, Underwood *et al*. 2003, Attanasio *et al*. 2004, Mauras *et al*. 2005).

Adults with GHD are ~1 SD. below the age and sex matched reference ranges for bone mineral content, as assessed by DEXA absorptiometry (Holmes *et al*. 1994). However, when interpreting bone density tests in untreated GHD patients, the effects of age of GHD onset (Kaufman *et al*. 1992), other pituitary hormonal imbalances (Mancini *et al*. 2004, Vieira da Costa *et al*. 2004) and their treatment strategies (Prince *et al*. 1991, Kayath *et al*. 1993, Behre *et al*. 1997, Colao *et al*. 2000, Rossouw *et al*. 2002, Jódar *et al*. 2003, Naliato *et al*. 2005) should be considered. GHD predominantly affects cortical sites, such as the radius, as compared with the spine. Bone size is also significantly smaller, but trabecular density is relatively preserved (Murray *et al*. 2004, 2006). Discontinuation of GH replacement in transitional patients with severe GHD limits peak bone mass accrual and places transitional patients at long-term risk for fractures (Drake *et al*. 2003). A GH replacement trial in the transition period showed an increase in bone mineral density when GH replacement was continued after final height completion. This effect was dose-dependent, and particularly significant in severely GHD patients (Shalet *et al*. 2003).

Other more controversial benefits of GH replacement in this period involve an improvement in lipid profile and QoL. Severely GHD patients have increased total cholesterol, low-density lipoprotein (LDL) cholesterol and decreased high-density lipoprotein (HDL). The abnormalities in lipid status classically described for adult GHD apply for the transition period. One clinical trial showed a significant decrease in LDL and LDL:HDL ratio following GH replacement (Underwood *et al*. 2003), but these findings have not been confirmed by other authors (Attanasio *et al*. 2004). The multifactorial nature of cardiovascular derangements in the irradiated cohorts, including increased obesity, sedentarism and possible changes in diet, should be taken into account when analyzing changes in lipid markers in this population. The effect of GH on carbohydrate metabolism is dual, improving insulin sensitivity by inducing favourable changes in body composition, but bearing a direct antagonistic effect on insulin action. The outcome is dependent on baseline insulin resistance parameters (influenced by puberty) and GH dose.

The effects of GHD on QoL in the transition period are not as clear as in adults. Significant impairments of QoL in patients with CO-GHD in the transitional period have not been confirmed by all authors, and the

effect of GH therapy on this variable remains controversial in transitional patients (Vahl *et al*. 2000, Underwood *et al*. 2003, Attanasio *et al*. 2004, 2005, Mauras *et al*. 2005).

GHD in the adult

Adults who receive cranial or craniospinal radiotherapy have a high prevalence of GHD, present in 50–100% adult patients irradiated for sellar neoplasms and up to 32% of patients with extrasellar brain tumours receiving radiotherapy. In AO-GHD, decreased QoL, adverse changes in body composition, increased risk of fracture and worsening cardiovascular risk profile are the main sequelae (Molitch *et al*. 2006).

GHD patients have increased fat mass that preferentially accumulates in the visceral compartment (Hoffman *et al*. 1995, Snel *et al*. 1995), and this pattern of fat deposition has adverse consequences on long-term cardiovascular risk. GHD is also associated with decreased LBM (Binnerts *et al*. 1992, Hoffman *et al*. 1995) that is associated with impaired exercise capacity. These parameters are at least partially reversible on GH therapy (Jorgensen *et al*. 1989).

Severe GHD has been related to impaired vasodilatation responses to stress and exercise (Boger *et al*. 1996), which could explain why patients with severe GHD tend to be more hypertensive. Increased inflammatory markers (Sesmilo *et al*. 2001) have been found to correlate inversely with IGF-I levels in GHD patients, and it is estimated that 26–45% of adults with GHD harbour abnormalities in lipoprotein metabolism: increased total and LDL cholesterol levels and decreased HDL are the main reported abnormalities (Bengtsson *et al*. 1999). The effect of GHD on insulin resistance is, as in the transition period, dose-dependent (Al-Shoumer *et al*. 1998, Yuen *et al*. 2002). High doses increase insulin resistance parameters, while doses close to physiological ranges could even prevent age-related increases in insulin resistance (Svensson *et al*. 2002). Overall, routine monitoring of glucose abnormalities in replaced GHD patients remains a cautionary measure.

GH therapy has shown to decrease fat mass content (Bengtsson *et al*. 1993), increase flow-mediated vasodilatation responses to stress and/or exercise (Boger *et al*. 1996), decrease the values of inflammatory markers (Sesmilo *et al*. 2000), and improve the lipid profile derangements (Boot *et al*. 1997, Kearney *et al*. 2003). However, even adequate replacement has failed to demonstrate an effect on mortality (Molitch *et al*. 2006).

GHD is also associated with decreased left ventricular mass and impaired ejection fraction at rest and after physical exercise testing, as assessed by echocardiography (Colao *et al*. 2001). These abnormalities are particularly important in young GHD patients, in whom the benefit of GH therapy on cardiac parameters is of greater significance (Colao *et al*. 2004).

Fracture rates are increased two- to fivefold when compared with non-GHD control populations (Wuster *et al*. 2001, Vestergaard *et al*. 2002). These findings have been related to decreased bone mineral density values, ~1 S.D. below the mean (Rosen *et al*. 1993, Holmes *et al*. 1994). The presence of osteoporosis in GHD cohorts varies from 20% in AO-GHD to 35% in CO-GHD (Kaufman *et al*. 1992). This effect is more pre-eminent in cortical bone sites. GH replacement enhances peak bone mass accrual in young adults and decreases bone resorption in middle-aged adults. However, the biphasic nature of GH bone action, in which bone resorption is preferentially increased during the first year and bone formation is enhanced at later stages, makes necessary a delayed assessment of bone mineral density after starting GH replacement (Hansen *et al*. 1996). Currently randomised trials that directly assess the effect of GH on fracture risk are lacking.

Deranged QoL remains a milestone of GHD syndrome. Through disease-specific QoL questionnaires (Burman *et al*. 1995, Holmes *et al*. 1995), energy and vitality have consistently shown to be decreased in GHD patients. Adults with GHD experience functional limitations in the social and laboural spheres, increased fatigue and deranged vitality (Woodhouse *et al*. 2006). Decrease in LBM, particularly of muscle mass, diminished erythropoiesis (Christ *et al*. 1997) and worsened cardiac performance have been related to functional limitations in GHD populations (Colao *et al*. 2001). Notwithstanding the mechanisms of GH effect on physiological variables, adequate replacement restores diverse aspects of QoL derangements in GHD patients, and the degree of improvement is directly proportional to the level of pre-treatment impairment (McGauley 1989, Drake *et al*. 1998, Murray *et al*. 1999, Blum *et al*. 2003).

GH replacement has associated side effects that need monitoring. The most common are fluid retention and oedema that are present more frequently in older populations (Holmes & Shalet 1995) and reinforce the need for age-related therapy initiation regimens. Possible effects of GH on carbohydrate metabolism should be routinely assessed and GH therapy should only be introduced in patients with clinically and radiologically inactive neoplasms.

Anomalies in gonadotroph axis: early and delayed puberty, adult gonadotrophin deficiency

Gonadotroph deficiency is the second most common clinical consequence of radiotherapy on the hypothalamic–pituitary region. Pituitary-driven secretion of gonadal steroids (testosterone and oestradiol) is essential in the development of secondary sexual characteristics during puberty and the initiation and maintenance of sexual activity and fertility during adult life. Furthermore, gonadal steroids play a role in the achievement of an optimal peak bone mass. Other actions involve the regulation of body composition (muscle-fat proportion), lipid, carbohydrate and mineral metabolism, regulation of hypothalamic thermoneutral zone and dilatory responses of vascular smooth muscle. Gonadal steroids play unique roles in the different stages of life, and their effects clearly require a degree of sexual dimorphism. As a consequence, the clinical expression of radiation-induced gonadotrophin dysfunction is time and sex dependent.

Disorders of pubertal timing

The correct timing in the attainment of secondary sexual characteristics and somatic maturation is essential for a normal physical and psychological progress into adult life. Cohorts receiving cranial radiation treatments have an increased incidence of pubertal timing disorders that require specific surveillance and treatment (Brauner *et al*. 1984, Quigley *et al*. 1989, Brauner & Rappaport 1990, Ogilvy-Stuart *et al*. 1994, Rose 2008). A list of the risk factors for pubertal timing disruption in cancer survivors is provided in Table 5.

Radiation-induced disorders in pubertal timing can result in:

Precocious puberty: initiation of thelarche before the age of 8 or increase in testicle size before the age of 9. Pathophysiologically, it is hypothesised that precocious puberty is caused by late-onset disruption of cortical inhibitory influences in the initiation of puberty (Roth *et al*. 2001). Central precocious puberty in cancer survivors usually occurs as a result of the use of low-dose cranial irradiation (total dose averaging 18–24 Gy) as a prophylactic treatment for childhood-onset haematological neoplasms (Leiper *et al*. 1987) and brain tumours distant from the hypothalamic–pituitary area (Lannering *et al*. 1997). Female sex and young age at treatment onset are considered as risk factors for radiation-induced precocious puberty (Ogilvy-Stuart *et al*. 1994).

Rapid puberty: puberty starts within 2.5 S.D.S of the reference population range, but the transition from thelarche to menarche takes <18 months (Bath *et al*. 2002) or the increase by >10 ml in testicle size occurs in <12 months.

Inadequate pubertal development in the presence of slow linear growth (Toogood 2004, Darzy & Shalet 2005*a*): in the presence of any factor interfering in growth processes, even a normally-timed puberty can contribute to a suboptimal height outcome. In this context, pharmacological arrest of puberty might be indicated until the factors interfering in somatic growth are identified and addressed.

Delayed puberty: if low doses of radiation disinhibit the initiation of puberty, doses above 24–30 Gy irreversibly damage the central input that drives the initiation of puberty (Stubberfield *et al*. 1995, Müller 2002). Pubertal delay can actually characterise the initial stages of permanent gonadotroph deficiency in children irradiated for the treatment of brain neoplasms (Rappaport *et al*. 1982). The consequences of delayed or absent puberty involve a decrease in peak bone mass accrual (Finkelstein *et al*. 1987, 1992, Moreira-Andres *et al*. 1998, Hawker *et al*. 2002, Ho & Kung 2005) and the psychological sequelae resulting from delayed pubertal milestones (Graber *et al*. 1997). Thus, in irradiated children, the absence of breast development by 12 years of age in girls or the failure to increase the size of the testes by 14 years of age should prompt evaluation by a paediatric endocrinologist. If cancer therapy is being administered during the pubertal years, 'catch-up growth' and resumption of pubertal progress should resume in <1 year after completion of cancer therapy. At this stage, or previously if there are treatment or tumour-related risk factors for hormonal deficiencies, full endocrinological evaluation should be performed.

Arrested puberty: radiation-related damage to GnRH producing cells is slowly progressive. Thus, early, rapid or normally-timed puberty can be followed by the cessation of pubertal progression before treatment is inititiated. Unless nutritional imbalances or psychosocial factors interfere, radiation-related arrested puberty is frequently followed by permanent gonadotroph dysfunction. Some patients might initially experience precocious puberty (induced by radiotherapy or by direct tumoral compression) after which arrested pubertal development with permanent gonadotroph deficiency, usually caused by radiation treatments, might ensue; the fact that radiotherapy can provoke opposite effects in gonadotroph physiology at different stages in the same patient may be explained by the slow onset of radiation-induced damage, with

Table 5 Risk factors for cancer-related disruption of pubertal timing

Female sex
Radiation fields involving the hypothalamic region. Doses >18 Gy can cause early puberty in girls and GHD. Doses >24 Gy can cause early puberty in boys
Age at radiaton exposure <6 years
Scattered radiation to the thyroid bed (primary hypothyroidism) can delay puberty
Doses to the gonads >20 Gy: high risk of primary hypogonadism with pubertal failure. Greater risk in males with prepubertal radiation exposure
Neoplasms in the hypothalamic region: tumour compression, surgical injury and radiation toxicity cause delayed or absent puberty
b-HCG secreting tumours: germ cell tumours secreting b-HCG can induce pubarchia and phallic enlargement in male children, but do not induce early puberty in girls
Chemotherapy regimens with known gonadal toxicity: chlorambucil, melphalan, busulfan, cyclophosphamide, chlorambucil, melphalan and ifosfamide

References for pubertal disorders in cancer survivors: Gleeson & Shalet (2004), Cohen (2005) and Nathan & Palmert (2005).

more cumulative damage required for gonadotroph deficiency as compared with precocious puberty (Burstein 1994, Yeung *et al*. 1998). Time-dependency of RIH is another factor that warrants careful monitoring of childhood cancer survivors by an experienced multidisciplinary team.

The treatment of pubertal timing disorders in patients with childhood cancer is esentially the same as in the general population (Gleeson & Shalet 2004). Early, rapid or inappropriate puberty for growth benefit from GnRH analogues, while delayed puberty is best treated by progressive doses of gonadal steroid replacement.

Radiation-induced hypogonadism in the adult

Primary and secondary hypogonadism are among the most common endocrine sequelae in cancer survivors (Skinner *et al*. 2006). Hypogonadism might result from damage at the hypothalamic, pituitary or gonadal level, which is readily discernible through the medical history and basic biochemical evaluation. Cranial radiotherapy, tumoral compression and surgical damage are the most common aetiologies of gonadotroph deficiency, while surgical gonadectomy, chemotherapy and radiotherapy (in pelvic, abdominal and total body irradiation) are the most common determinants of primary gonadal failure. Aetiological investigations are necessary for a tailored management of fertility problems, which can be treated with gonadotroph stimulation in secondary hypogonadism but remain a difficult challenge in primary gonadal failure.

In adult women, hypogonadism results in the inability to ovulate, infertility and decreased oestradiol levels. The initial stages of oestradiol deficiency present with menstrual irregularity, hot flushes, vaginal dryness and atrophy, dyspareunia, loss of libido and fatigue. Chronic oestradiol deficiency is reflected in breast tissue atrophy, weaning of secondary sexual characteristics and osteoporosis (Baird 2002, Conway 2002, Verga 2002). A woman receiving cranial irradiation might develop primary or secondary amenorrhoea, depending on the age of exposure. In patients receiving radiotherapy for tumours of the sellar region, the cause of amenorrhoea is often multifactorial including damage to GnRH releasing hypothalamic cells, ablation of pituitary parenchyma by the tumour or previous surgical procedures and hyperprolactinaemia from stalk disconnection, radiation-related damage to hypothalamic dopamine-secreting cells. The approach to a cancer survivor with amenorrhoea is even more complex. Amenorrhoea may be due to RIH, gonadal damage from radiation or chemotherapy, and primary or secondary hypothyroidism. Malnutrition after cancer therapy can also generate a functional hypothalamic amenorrhoea. All require evaluating in a cancer survivor presenting with amenorrhoea.

In men, radiation-induced secondary hypogonadism results in decreased sperm counts (with secondary infertility) and low testosterone levels. Testosterone deficiency causes reduced libido, poor erection, decreased energy, hot flushes and sweats. Decreased energy, motivation, depressed mood and poor concentration and memory are other symptoms. At later stages, male hypogonadism is accompanied by decreased muscle mass and strength, osteoporosis, excess body fat mass and increased cardiovascular risk. Gynaecomastia can occur as a result of an increased oestradiol/testosterone ratio in hypogonadal patients, although this is far more common in primary hypogonadal patients than in RIH, as FSH and LH stimulate aromatase activity (Bhasin *et al*. 2006). Hypogonadal patients tend to have lower haematocrit values which add to the effects of hypogonadism on functional performance (Ferrucci *et al*. 2006).

ACTH and TSH deficiency

ACTH and TSH deficiencies are the least common among RIH. They are more frequently described in patients with previous tumour or surgical insults to the pituitary gland, and following radiation doses above 50 Gy (Littley *et al*. 1989).

ACTH deficiency in irradiated patients can be mild and subclinical, but without timely recognition it can progress and lead to catastrophic consequences. The most common symptoms are anorexia, weight loss, fatigue, tiredness, weakness, dizziness and postural hypotension, gastrointestinal symptoms, arthralgia and myalgia, intolerance to stress and infection, decreased axillary and pubic hair and reduced libido in women. During stressful situations, cortisol deficiency manifests with hypotension and tachycardia due to vascular collapse and reduced response to inotropic factors. In routine biochemistry, hypoglycaemia, eosinophilia and low sodium levels can be found, but hyperkalaemia is an exclusive feature of primary hypoadrenalism due to mineralocorticoid deficiency (Arlt & Allolio 2003).

The diagnostic tools of routine use for ACTH deficiency include basal 0900 h cortisol, high-dose short Synacthen test (SST), low-dose SST, ITT and metyrapone stimulatory challenge; optimum use of each investigation requires careful assessment of their particular advantages and shortcomings (Table 4), together with periodic and detailed evaluation of clinical signs and symptoms suggesting adrenal failure.

TSH deficiency is the least commonly reported pituitary dysfunction in patients with RIH. When assessed by routine combination of TSH and free thyroxine (FT_4) measurements, 5% of patients receiving radiation for childhood cancer and 6–50% treated with radiotherapy for pituitary adenomas report TSH deficiency (Littley *et al*. 1989, Darzy & Shalet 2005*b*). In the subgroup with FT_4 levels in the lower quartile, 25% show abnormal circadian TSH variation and 32% have a blunted response to TRH stimulation (Rose *et al*. 1999*b*). This has been interpreted as the presence of hidden central hypothyroidism, an early stage in the development of thyrotroph dysfunction. However, it is unclear whether these findings illustrate a clinically significant degree of TSH secretory dysfunction, and whether T_4 replacement improves any outcome measures in patients with these test results. Furthermore, measures of hidden central hypothyroidism have failed to correlate with FT_4 levels and radiotherapy-dependent variables (Romijn & Wiersinga 1990, Adriaanse *et al*. 1992, Adriaanse *et al*. 1993, Darzy & Shalet 2005*a*,*b*). Globally, the standard of practice for the diagnosis and surveillance of suspected central hypothyroidism involves combined measurement of TSH and FT_4 (Lania *et al*. 2008, Yamada & Mori 2008), while replacement therapy should be aimed at restoring FT_4 levels into the upper quartile of the normal range. Although tri-iodothyronine (T_3) represents the most important thyroid hormone in terms of biological activity, the diagnostic use of free T_3 levels is hampered by substantial overlap between healthy and hypothyroid individuals (Ferretti *et al*. 1999, Alexopoulou *et al*. 2004). This overlap is attributed to preferential secretion of T_3 when substantial impairment in TSH stimulatory capacity ensues (Alexopoulou *et al*. 2004).

Hyperprolactinaemia and diabetes insipidus

Radiation-induced hyperprolactinaemia is caused by a depletion of the hypothalamic inhibitory influence on PRL secretion. It is usually mild, more common in adult women receiving doses >40 Gy, with a 14–50% reported incidence of hyperprolactinaemia (Littley *et al*. 1989, Lam *et al*. 1991, Constine *et al*. 1993). In most cases, this is a subclinical finding that resolves spontaneously in the first 5 years after radiation exposure and rarely induces gonadotroph deficiency (Darzy & Shalet 2006). In acromegalic patients, radiation-related hyperprolactinaemia, which tends to resolve spontaneously, should be distinguished from PRL excess derived from somatotroph cell hypersecretion, usually accompanied by GH excess (Ciccarelli *et al*. 1989).

Despite the vicinity of vasopressin-secreting magnocellular neurons to the hypothalamic–adenohypophyseal functional unit, to our knowledge central diabetes insipidus has not been consistently reported as a direct consequence of RT for sellar or extrasellar brain neoplasms, which comes in sharp contrast with the common observation of this disorder after non-adenomatous tumoral or surgical insults to the hypothalamic–pituitary area (Sudhakar *et al*. 2004, Dumont *et al*. 2005). Interestingly, a series described the occurrence of diabetes insipidus in a significant minority of patients (8%) who received pituitary SFR using total doses as high as 140–180 Gy for the treatment of post-stroke intractable thalamic pain (Hayashi *et al*. 2007). Albeit impaired vasopressin secretion remained mostly a transient phenomenon in the series, these findings suggest a much higher dose threshold for radiation-induced diabetes insipidus. However, further research should be encouraged to confirm these findings and possibly shed more light into the pathophysiology of this phenomenon.

Table 6 Radiation-induced brain disorders

	Incidence	Latency	Predisposing factors	Pathophysiology and histology	Clinical presentation	Diagnosis and treatment
Second brain tumours (SBT; Minniti *et al.* 2005)	2.9% Incidence at 30 years from exposure	Median 27 years (2–30 years)	Unknown Radiation thresholds not currently defined	Meningiomas, high-grade gliomas, chondrosarcomas, primary neuroectodermal tumours	Focal neurological symptoms Headache, nausea, photophobia (increased intracranial pressure)	Poor prognosis Diagnosis of SBT requires development within radiation fields, different histology to primary tumour and no genetic predisposition for brain tumours
Cerebrovascular accidents (CVA; Brada *et al.* 1999, 2002, Lindholm *et al.* 2006)	4% (5 years of exposure) 11% at 10 years 21% at 20 years Int J. Radiat. Oncol. Biol. (Brada *et al.* 1999)	Incidence increases with time after radiation exposure	Female sex Older age Aggressive intracranial surgery Radiation total dose >45 Gy Untreated hypogonadism	Type of CVA unknown Radiotoxicity to vascular lining enhances cerebrovascular atherogenesis	Sudden neurological deficit	Major determinant of mortality in patients with hypopituitarism Management does not differ from non-irradiated patients
Radiation optic neuropathy (RON; Kline *et al.* 1985, Minniti *et al.* 2007*a*, Stafford *et al.* 2003)	1–2%, 15 years after exposure for sellar and parasellar tumours	2 months–15 years (more common 3 years after exposure)	Total doses to the optic pathways >8 Gy Higher irradiated volume of optic pathways If radiosurgery, distance of the tumour to optic nerve <3–5 mm Tumoural compression Older age Diabetes mellitus	Radiation-induced microvascular obliteration in optic pathways Considered focal manifestation of radiation brain necrosis	Depending on the radio-necrosed section of optic pathways: Optic nerves (more common): uni or bilateral (synchronic or metachronic) amaurosis Optic chiasm Optic tracts	Mostly avoidable with modern conformal techniques Devastating consequences on vision, no effective treatment Diagnosis requires exclusion of tumoral compression of optic pathways, optic disc oedema and other causes of visual deficit
Radiation brain necrosis (Smith *et al.* 2006)	Very rare with total doses <50 Gy	More common 5 h–1 year after exposure	Previous radiotherapy Total doses >50 Gy	Microvascular obliteration Ischaemic necrosis Demyelination of white matter	Variable severity: cognitive deficits Tiredness Personality changes Neurological focal sequelae: motor impairments, seizures or language problems	Differential diagnosis with SBT (magnetic resonance imaging, positron emission tomography, histology) Treatments: glucocorticoids, anticonvulsants and neurological rehabilitation

Table 7 Endocrine late effects of cancer treatments

	Neoplasms	Risk factors	Clinical sequelae	Preventive strategies	Treatment
Ovarian failure (Lobo 2005, Wallace *et al*. 2005, Marhhome & Cohen 2007)	Haematological malignancies Pelvic and abdominal tumours	Alkylating agents Older age in females Doses >20 Gy to the ovaries (lower doses needed if >30 years of age)	Infertility Premature Ovarian failure ↓Uterine blood flow: gestational risks	Shielding and transposition of the ovaries prior to radiation Avoid gonadotoxic chemotherapy if feasible Oocyte preservation prior to treatment	Hormonal replacement therapy If feasible, address fertility issues prior to start treatment
Testicular damage (Gleeson & Shalet 2004, Cohen 2005)	Haematological malignancies Abdominal tumours Testicular cancer and other pelvic malignancies	Alkylating agents and cisplatin Doses: >2 Gy: oligo-azoospermia, subclinical Leydig dysfunction >20 Gy: pubertal failure >30 Gy: primary hypogonadism in adults	Transient or permanent infertility Hypogonadism: osteoporosis, quality of life, sexual dysfunction, body composition, cardiovascular risk	Sperm storage before treatment Testes shielding	Testosterone replacement If feasible, address fertility issues prior to treatment
Thyroid gland (Sklar *et al*. 2000, Schmiegelow *et al*. 2003*b*)	Haematological malignancies, head and neck tumours, brain tumours, neuroblastomas and phaeochromocytomas (MIBG)	Increasing doses to the thyroid Females Older age at radiation	Primary hypothyroidism (17.1 fold risk) Hyperthyroidism (8-fold risk) Thyroid cancer (18-fold risk; Sklar *et al*. 2000)	Radiation hyperfractionation Thyroid shielding	Hormonal replacement (TSH in lower limit of normal range) Periodic neck palpation or ultrasonography
Hyperparathyroidism (Adami *et al*. 2002, Schneider *et al*. 1995)	Benign conditions (tonsillar hyperthrophy…)	Scattered neck radiation Thyroid dysfunction after radiation	Osteoporosis, renal stones Kidney dysfunction Psychological and cardiovascular morbidity	Avoid radiation therapy in benign conditions	As in non-irradiated patients

Associated disorders in patients with RIH

The follow-up of patients with RIH must also account for the presence of other associated morbidities that are highly dependent on the underlying neoplasm. In the case of tumours arising in the sellar region, these initially result from either surgical or tumour-induced compression of neural structures, most commonly the optic chiasm, cranial nerves and hypothalamus, leading to loss of visual function and symptoms of hypothalamic dysfunction (abnormal drinking and feeding behaviour, poikilothermia and memory and mood problems). Although hypopituitarism is the most common sequelae of radiotherapy for sellar and parasellar tumours, RT may also result in other relatively uncommon radiation-induced brain disorders listed in Table 6. These sequelae include radiation optic neuropathy, radiation brain necrosis, increased incidence of cerebrovascular accidents and second-brain tumours, and they tend to occur for months-to-years after RT. Although rare following conventional radiation doses used for sellar neoplasms, the clinician involved in the management of these patients needs to be aware of them.

The effects of cancer treatments involve systemic as well as local effects. As a result of the direct effect of the tumour, surgical and radiation treatments and chemotherapy regimens, as many as 41% of childhood cancer survivors suffer endocrine sequelae, together with non-endocrine side effects, such as congestive heart failure, second malignancies, cognitive dysfunction, renal failure, coronary artery disease or cerebrovascular accidents (Stevens *et al*. 1998, Oeffinger *et al*. 2006, Skinner *et al*. 2006). The most common endocrine side effects of cancer treatments are shown in Table 7. Awareness of these risks among physicians involved in the long-term care of childhood cancer survivors is an important tool for optimising outcomes.

In most endocrine disorders presenting in cancer survivors, clear correlations have been found between treatment-related variables (i.e. radiation dose, chemotherapy scheme) and their development. Diabetes mellitus represents an exception to this rule. Cancer survivors seem to be at risk of being diagnosed with this disorder (Neville *et al*. 2006, Stava *et al*. 2007), a finding that has been particularly well documented following haematopoietic cell transplant (Taskinen *et al*. 2000, Hoffmeister *et al*. 2004). Increased rates of obesity, sedentary lifestyle, effect of some chemotherapy regimens, glucocorticoid treatments and hormonal deficiencies have been advocated as risk factors for diabetes mellitus in cancer survivors (Neville *et al*. 2006). Radiation-induced β-cell dysfunction was postulated as a causative mechanism in a series of nephroblastoma survivors (Teinturier *et al*. 1996), but to our knowledge these findings have not been reproduced (Hawkins *et al*. 1996). Total body irradiation has been inconsistently associated with increased risk of diabetes mellitus (Lorini *et al*. 1995, Taskinen *et al*. 2000, Hoffmeister *et al*. 2004, Neville *et al*. 2006), but the available evidence does not firmly link part of the diabetes risk to a direct deleterious effect of RT on β-cells. Notwithstanding the aetiology, the burden of diabetes-associated morbidities strongly advocates for routine screening strategies in cancer survivors.

Hypopituitarism and mortality

The prognosis of patients with RIH is in great measure influenced by the underlying disease and other effects of cancer treatment. However, hypopituitarism may be an independent risk factor for mortality, particularly due to cerebrovascular causes (Rosen & Bengtsson 1990, Bates *et al*. 1996, 1999, Bulow *et al*. 1997, Erfurth *et al*. 2000, 2001, Tomlinson *et al*. 2001, Brada *et al*. 2002). Cerebrovascular accidents in cohorts with hypopituitarism are more common in women and in untreated hypogonadal patients of both sexes (Tomlinson *et al*. 2001, Lindholm *et al*. 2006, Nielsen *et al*. 2007). Higher mortality rates in women with hypopituitarism have been attributed to suboptimal sex-hormone replacement strategies and possibly an overlooked decrease in glucocorticoid requirements as compared with their male counterparts. The use of radiotherapy has also been associated with increased cerebrovascular mortality in most (Bates *et al*. 1996, Tomlinson *et al*. 2001, Brada *et al*. 2002) but not all studies (Erfurth *et al*. 2002). Radiation-induced damage to the vascular wall may be the cause of the enhanced cerebrovascular atherogenicity in irradiated patients (Gittoes 2005). These epidemiological findings represent a note of caution in the use of radiotherapy for pituitary tumours until further evidence defines the long-term risk profile of more modern radiation techniques and hormonal replacement practice.

Conclusions

The advent of modern radiotherapy has contributed to improved survival and QoL in patients with a variety of malignancies and benign tumours, albeit with an increased risk of treatment related side effects.

RIH is to be one of the most common sequelae of RT. While hypothalamic–pituitary sparing techniques are being developed, strategies for risk-assessment and early recognition of RIH and other adverse effects should be initiated at completion of radiation treatments. As regards RIH, pathophysiological tailoring of biochemical assessment and current availability of replacement therapies closer to the physiology of the normal pituitary gland is expected to further improve outcomes in this population. However, other possible side effects of the primary neoplasm and its treatments on the pituitary function, its target organs and the general health outcome should also be considered. The recognition and management of radiation-induced brain disorders, endocrine and systemic effects of radiation and chemotherapy and the sequelae of the primary tumour are important tools for optimising outcomes. As the population of cancer survivors continues to increase and cancer treatments evolve in a constant endeavour to improve survival rates, renewed efforts for defining and treating the sequelae of future cancer survivors should be undertaken.

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