REVIEW

The impact of cancer therapy on the endocrine system in survivors of childhood brain tumours

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Abstract

Survival rates are improving following cancer therapy for childhood brain tumours. There is therefore a growing cohort of survivors at risk of late effects of cancer therapy. Endocrine problems are very common in these patients. The recognition and prompt management of these are essential to prevent further morbidity and impairment of quality of life.

Cranial radiation can damage hypothalamic–pituitary function, most frequently affecting GH status; however, higher radiation doses may cause more widespread hypothalamic–pituitary damage. Early puberty secondary to cranial irradiation is now being managed with gonadotrophin-releasing hormone analogues to improve final height. Prompt diagnosis and management of GH deficiency may improve final height outcome; continued GH therapy beyond final height aids the achievement of adult body composition (lean body mass and bone mass) and GH therapy in adulthood improves quality of life. Both cranial irradiation alone and with spinal irradiation can result in radiation damage to the thyroid resulting in hypothyroidism and thyroid nodules, a high proportion of which are malignant. Gonadal damage secondary to spinal irradiation and adjuvant chemotherapy may have long-term consequences including infertility.

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Introduction

Brain tumours are the most common type of solid neoplasms that occur in children (Gurney *et al.* 1996). Survival after a diagnosis of a malignant brain tumour has improved substantially over the last few decades. The 5-year relative survival probability for all brain malignancies combined for children is approximately 65% (de Nully Brown *et al.* 1995, Bleyer 1999, Ries *et al.* 2003). However, the improvement in prognosis has been achieved at the cost of serious late effects. Survivors of childhood brain tumours are at a high risk of adverse medical, neurocognitive and psychosocial late effects (Anderson *et al.* 2001). Endocrine disorders are prominent among the spectrum of long-term conditions that may afflict brain tumour survivors; in one survey 43% had a self-reported endocrine condition (Gurney *et al.* 2003b). These may impact negatively on growth, body composition, fertility, quality of life, morbidity and mortality.

Hypothalamic–pituitary axis

Role of radiation

Neuroendocrine abnormalities may follow cranial irradiation resulting in deficiency of one or more anterior pituitary hormones. The radiobiological impact of a radiation schedule depends on the total dose, fraction size, number of fractions and the duration.

There is a strong correlation between the total radiation dose and the development of pituitary hormone deficits (Shalet *et al.* 1976a, Duffner *et al.* 1985, Littley *et al.* 1989b, Clayton & Shalet 1991b, Constine *et al.* 1993). Thus, after lower radiation doses, as used in the treatment of acute lymphoblastic leukaemia (ALL) or brain tumours (18–50 Gy), isolated growth hormone deficiency (GHD) occurs, while higher doses (> 60 Gy) may produce panhypopituitarism. Interestingly, however, diabetes insipidus is not seen following irradiation to the hypothalamic–

pituitary axis. Also the same total dose given in fewer fractions over a shorter time period is likely to cause a greater incidence of pituitary hormone deficiency than if the schedule is spread over a longer time interval with a greater number of fractions (Shalet *et al.* 1976*b*).

More recently, the degree of anterior pituitary hormone deficit has been correlated with the biological effective dose (BED) of radiation affecting the hypothalamic–pituitary axis. The formula used to calculate the BED incorporates total dose, fraction size and tissue response to radiation (Schmiegelow *et al.* 2000). Calculation of the BED provides a useful method of comparing radiation schedules and predicting the effect on hypothalamic–pituitary function (Schmiegelow *et al.* 2000).

The hypothalamus is more radiosensitive and is damaged by lower doses of cranial radiation than the pituitary. Thus, after lower doses of cranial irradiation (<50 Gy) the primary site of radiation damage is hypothalamic, and is usually associated with isolated GHD (Samaan *et al.* 1975, Chrousos *et al.* 1982, Ahmed *et al.* 1986, Lannering & Albertsson-Wikland 1987, Costin 1988), whereas higher doses may also produce direct anterior pituitary damage which contributes to early and multiple pituitary hormone deficiencies (Samaan *et al.* 1975, 1982).

Hypothalamic–pituitary dysfunction secondary to radiation is also time dependent. There is an increase in the frequency and severity of hormonal deficits with a longer time interval after radiotherapy. The progressive nature of the hormonal deficits following radiation damage to the hypothalamic–pituitary axis can be attributed to the delayed effects of radiotherapy on the axis or the development of secondary pituitary atrophy following previous hypothalamic damage (Spoudeas *et al.* 1996, Clayton & Shalet 1991*b*, Schmiegelow *et al.* 2000). This necessitates prolonged follow-up with yearly testing of pituitary function in patients treated with cranial irradiation for brain tumours.

The damaging effects of radiation on hypothalamic–pituitary axis function are also increased when the hypothalamic–pituitary axis is already affected by another pathology. A radiation dose of 35–42.5 Gy to the hypothalamic–pituitary axis caused isolated GHD in the majority of children treated for non-pituitary brain tumours (Shalet *et al.* 1975, Duffner *et al.* 1985), whereas a similar dose in adult patients irradiated for pituitary adenomas led to multiple pituitary hormone deficits in more than 80% within a similar time scale after radiotherapy (Littley *et al.* 1989*c*).

The difference in the development of the anterior pituitary hormone deficiencies, with growth hormone (GH) being most frequently affected, suggests that selective hypothalamic neuronal and pituitary cell damage

by direct radiation occurs. Consequently, while GHD is prevalent in brain tumour survivors, other pituitary hormone deficits occurred in only 2–6% after almost 10 years following 40–50 Gy (Shalet *et al.* 1977, Livesey *et al.* 1990). Clinical observations reveal that GH is the most radiosensitive followed by gonadotrophin and adrenocorticotrophin (ACTH) with thyrotrophin (TSH) the last hormone to be affected, although variations in this order can occur.

Whether or not the age of the patient at the time of radiotherapy is an additional factor that determines the extent of radiation damage sustained by the hypothalamic–pituitary axis is unknown. Some but not all data suggest that children are more radiosensitive than adults and that older children are less vulnerable than younger children to the risk of developing GHD following radiation to the hypothalamic–pituitary axis (Shalet *et al.* 1976*a*).

There have been reports that suggest that chemotherapy potentiates the deleterious effect of radiation on pituitary function (Spoudeas *et al.* 1996, Achermann *et al.* 1998, Gleeson *et al.* 2004). There is no conclusive evidence to date, however, that chemotherapy alone results in neuroendocrine dysfunction.

Growth hormone deficiency

Current evidence suggests that nearly 100% of children treated with radiation doses in excess of 30 Gy will have blunted GH responses to an insulin tolerance test (ITT), whilst 35% of those receiving less than 30 Gy still show a normal peak GH response to the ITT between 2 and 5 years after radiotherapy (Clayton & Shalet 1991*b*). Prospective studies also suggest that impaired GH responses to provocative tests can occur as early as 3 months and certainly in the first 12 months post-irradiation for brain tumours (Shalet *et al.* 1975, Duffner *et al.* 1985).

Radiation-induced GH neurosecretory dysfunction is well described following radiation injury to the hypothalamic–pituitary axis (Chrousos *et al.* 1982, Blatt *et al.* 1984, Spoudeas *et al.* 1996). It is characterised by diminished spontaneous (physiological) GH secretion in the presence of preserved peak GH responses to provocative tests (Bercu & Diamond 1986). Thus, the reported frequency of radiation-induced GHD is likely to be influenced by the type of investigation used to assess GH secretion, i.e. physiological versus pharmacological tests. Most prospective studies have concentrated on provocative tests and therefore the exact prevalence of radiation-induced GHD may well be underestimated. For example, Albertsson-Wikland *et al.* (1987) showed that spontaneous GH secretion was severely disturbed in all children more than 2 years after they had received cranial

irradiation ($>40\,$Gy) for brain tumours. This is in contrast to the lower incidence of GHD with the same radiation schedules and time scale reported in other studies which relied on stimulation tests. The discrepancy between stimulated and spontaneous GH secretion tends to disappear with time after radiotherapy and it is likely that patients who develop impaired GH responses to provocative tests late after irradiation may have had GH neurosecretory dysfunction at an earlier stage (Darzy *et al.* 2003). Further studies are needed to define the exact incidence of radiation-induced GH neurosecretory dysfunction in children and its clinical relevance.

Abnormalities of gonadotrophin secretion

The effect of cranial irradiation on the hypothalamic–pituitary–gonadal axis is dose dependent. Doses in excess of $50\,$Gy may render a child gonadotrophin deficient whereas lower doses, paradoxically, may result in early puberty.

Early puberty

The mechanism for early puberty following irradiation is thought to be due to the disinhibition of cortical influences on the hypothalamus. Puberty then proceeds through the increased frequency and amplitude of gonadotrophin-releasing hormone (GnRH) pulsatile secretion by the hypothalamus (Roth *et al.* 2000, 2001).

Low-dose cranial irradiation employed in central nervous system prophylaxis for ALL is associated with a higher incidence of early puberty, which predominantly affects girls (Leiper *et al.* 1987). At higher radiation doses employed in the treatment of brain tumours (25–50 Gy) early puberty is not restricted to girls. Ogilvy-Stuart *et al.* (1994) demonstrated that in 46 GHD children previously irradiated for brain tumours (25–47.5 Gy) the onset of puberty occurred at an early age in both sexes and there was a significant linear association between age at irradiation and age at onset of puberty, i.e. the younger the age at irradiation the earlier the onset of puberty (Fig. 1). Subsequently Lannering *et al.* (1997) also showed that boys who received high doses of irradiation for brain tumours entered puberty at a median age of 10.5 years compared with an average age for Swedish boys of 12.4 years; again emphasising the disappearance of sexual dichotomy with higher radiation doses.

Gonadotrophin deficiency

When the dose of cranial irradiation exceeds 50 Gy in the treatment of brain tumours there is a progressive increase in the incidence of gonadotrophin deficiency. Rappaport *et al.* (1982) reported that 14 out of 45 children studied

Figure 1 Age at onset of puberty compared with age at irradiation in children treated for brain tumours (Ogilvy-Stuart *et al.* 1994).

following high-dose cranial irradiation for head and neck tumours showed evidence of partial or severe gonadotrophin deficiency. The prevalence of gonadotrophin deficiency also increases with time post-irradiation, a cumulative incidence of 20–50% has been reported in patients followed long term, making it the second most common anterior pituitary hormone deficit in many series (Rappaport *et al.* 1982, Constine *et al.* 1993).

Gonadotrophin deficiency exists in a range of severity from subtle (subclinical) abnormalities with low normal sex hormone levels to severe impairment associated with subnormal circulating sex hormone levels.

In a study of 30 male survivors of childhood brain tumours who had received 40–60 Gy of cranial irradiation, there was evidence of subtle secondary hypogonadism compared with age-matched normal controls after a median of 18 years follow-up (Schmiegelow *et al.* 2001).

ACTH deficiency

A recent study of 73 patients who were treated with cranial irradiation for childhood brain tumours not directly involving the hypothalamic–pituitary axis observed that 19% had abnormalities of the hypothalamic–pituitary–adrenal axis after 15 years of follow-up (Schmiegelow *et al.* 2003*b*). Previous studies all based on less than 12 years follow-up demonstrated only subtle abnormalities (Livesey *et al.* 1990, Constine *et al.* 1993, Oberfield *et al.* 1997, Spoudeas *et al.* 2003) suggesting that the hypothalamic–pituitary–adrenal axis might be

affected relatively late by irradiation. This was further illustrated in the same study by the relationship between the length of follow-up and the peak cortisol response to an ITT (Schmiegelow *et al.* 2003*b*). Longer follow-up data beyond 15 years in these patients is not available.

Dose of irradiation is important as no damage to the hypothalamic–pituitary–adrenal axis was reported following lower doses of irradiation (18–24 Gy) in the treatment of ALL after 3.6 to 10 years of follow-up (Crowne *et al.* 1993) compared with the higher doses of radiation used in the treatment of brain tumours when subtle abnormalities were identified after a similar period of follow-up (Livesey *et al.* 1990, Constine *et al.* 1993, Oberfield *et al.* 1997). The dose–response relationship was confirmed by the recent follow-up study in brain tumour survivors (Schmiegelow *et al.* 2003*b*).

The manner in which ACTH deficiency is diagnosed in this irradiated cohort is important. The ITT is considered the gold standard; however, it is contraindicated in patients with a history of fits which immediately excludes a proportion of brain tumour survivors. Many centres are also reluctant to perform ITTs at all because of lack of experience and/or suitable levels of supervision. Consequently, many centres employ the well-tolerated glucagon stimulation test (GST) (Leong *et al.* 2001) which allows the assessment of both GH and ACTH reserve. Although compared with the ITT the GST evokes a less pronounced GH response, the cortisol responses to the two tests in healthy individuals (Littley *et al.* 1989*a*) and patients with pituitary disease (Orme *et al.* 1996) appear to be comparable in magnitude.

The short synacthen test (SST) is extensively used in clinical practice; there is, however, controversy surrounding the use of the SST in assessing ACTH deficiency particularly in situations where partial ACTH deficiency may occur, as may be the case following cranial irradiation. Of the 33 patients who had both an SST and an ITT, ten patients had discordant results, i.e. failing the ITT but passing the SST; however, eight of the ten had a peak cortisol between 400 and 500 nmol/l to an ITT (Schmiegelow *et al.* 2003*b*). This is suggestive of partial ACTH deficiency, the implications of which are likely to be less critical than for a patient with severe ACTH deficiency.

In summary, an awareness of ACTH deficiency in brain tumour survivors is essential and monitoring should continue beyond 10 years following irradiation. If reliance is placed on a test other than an ITT, for instance as SST, caution should be maintained in a patient diagnosed as ACTH sufficient following cranial irradiation.

TSH deficiency

The hypothalamic–pituitary–thyroid axis appears to be the least vulnerable to radiation damage. The frequency of radiation-induced TSH deficiency has been clearly shown to be dose related (Constine *et al.* 1993) and also related to the length of time from irradiation (Schmiegelow *et al.* 2003*a*).

Making the diagnosis of central hypothyroidism is important but notoriously difficult. Most clinicians rely on basal thyroid function tests (TFTs; TSH and thyroxine (T4)), making the diagnosis when there is a low normal or subnormal T4 level, particularly if there is evidence of declining T4 levels over time, with a low, normal or mildly raised TSH level with or without symptoms of hypothyroidism.

A survey of 71 childhood brain tumour survivors assessed after a median of 12 years of follow-up using baseline TFTs found that only 6% had evidence of central hypothyroidism (Schmiegelow *et al.* 2003*a*). This is in keeping with previous studies (Livesey & Brook 1989, Oberfield *et al.* 1992). However, another study controversially claimed that the reason TSH deficiency is reported to be the last anterior pituitary hormone to become deficient is due to the insensitivity of baseline TFTs in making the diagnosis and the authors claim that the thyrotrophin-releasing hormone (TRH) test and the presence or absence of a nocturnal TSH surge are more useful diagnostically (Rose *et al.* 1999). This study (Rose *et al.* 1999) examined 208 childhood cancer survivors after a mean of 6 years follow-up and diagnosed 36% as having evidence of hidden central hypothyroidism; however, 20% of the children with non-cranial tumours, who had not received any form of cranial irradiation, had evidence of central hypothyroidism at 5 years and 16% of those with central hypothyroidism had received only chemotherapy. This places huge doubt over the specificity of the TRH test and/or an absent TSH surge to diagnose central hypothyroidism in the presence of a normal T4 level.

Endocrine target organs

Primary gonadal failure

In brain tumour survivors gonadal damage most frequently occurs secondary to adjuvant chemotherapy. Gonadotoxicity is dose dependent and can occur with the following chemotherapy agents: alkylating agents, procarbazine, cisplatin and vinblastine (Ahmed *et al.* 1983, Clayton *et al.* 1989). Scattered radiation from spinal radiotherapy may also be responsible for gonadal damage (Livesey & Brook 1988, Ahmed *et al.* 1983, Schmiegelow *et al.* 2001).

In females, sex steroid production and germ cells are lost in parallel. Loss of sex steroid production may manifest itself early as failure to enter or progress through puberty, or later with symptoms of premature menopause which may place the patient at risk of all the biological

consequences of hypogonadism as well as problems with fertility. In one study of brain tumour survivors after 8 years follow-up, 64% (seven out of eleven) of girls who had received craniospinal irradiation without adjuvant chemotherapy had evidence of primary ovarian damage as determined by elevated gonadotrophins (Livesey & Brook 1988). Another study found that it was only the adjuvant chemotherapy (in particular the alkylating agent, nitrosourea and procarbazine) in combination with craniospinal irradiation that resulted in primary ovarian failure (Ahmed *et al.* 1983).

In males, spermatogenesis is more sensitive to damage by cancer therapy than Leydig cell function, therefore men may be infertile yet have normal levels of testosterone. Scattered radiation from craniospinal irradiation itself has been reported not to damage Leydig cell function (Ahmed *et al.* 1983, Schmiegelow *et al.* 2001), whereas impaired spermatogenesis has been observed in brain tumour survivors secondary to chemotherapy alone and also in combination with spinal irradiation (Ahmed *et al.* 1983, Livesey & Brook 1988, Schmiegelow *et al.* 2001).

Primary thyroid damage

The thyroid gland in children is among the most sensitive organ to damage by radiation. Hypothyroidism, thyroid nodules and hyperthyroidism have been described (Sklar *et al.* 2000). The role of chemotherapy is less clear.

Compensated or frank hypothyroidism has been described in 20–60% of brain tumour survivors depending on treatment modalities and length of follow-up (Livesey *et al.* 1990, Ogilvy-Stuart *et al.* 1991, Schmiegelow *et al.* 2003*a*). Damage can occur in the brain tumour survivor secondary to scattered radiation from craniospinal irradiation as well as from cranial irradiation alone (Schmiegelow *et al.* 2003*a*). Fraction size is also important as it has been observed that hyperfractionation with conventional spinal irradiation schedules results in less damage to the thyroid (Ricardi *et al.* 2001). An increased incidence of hypothyroidism has been observed with adjuvant chemotherapy in combination with irradiation compared with irradiation alone (Livesey & Brook 1989, Ogilvy-Stuart *et al.* 1991, Paulino 2002). However, three recent studies have failed to confirm this finding (Chin *et al.* 1997, van Santen *et al.* 2003, Schmiegelow *et al.* 2003*a*).

Excess thyroid cancer has been reported following treatment for brain tumours (Goldstein *et al.* 1997). Thyroid nodules occur frequently in the irradiated population (Kaplan *et al.* 1983, Tucker *et al.* 1991). The percentage of nodules which contain malignancy in cancer survivors varies from 14% to 40% depending on the method of detection (Crom *et al.* 1997, Acharya *et al.* 2003). Very young children are at higher risk as are

females. At low to moderate doses of radiation there is a linear relationship with risk of developing thyroid cancer which flattens out at higher doses (Ron *et al.* 1995). Radiation-induced tumours begin to appear 5–10 years after irradiation and excess risk persists for decades (Schneider *et al.* 1993). Most of the thyroid cancers are usually well-differentiated papillary carcinomas but follicular tumours also occur.

Clinical assessment has limitations in both detecting and characterising thyroid nodules, and can miss those smaller than 2 cm (Brander *et al.* 1992). Consequently some physicians advocate the use of ultrasound (Healy *et al.* 1996, Crom *et al.* 1997). However, the smaller thyroid nodules are less likely to be malignant and therefore the use of a more sensitive screening strategy may increase patient anxiety without necessarily improving outcome. Therefore the standard practice in many centres is to perform TFTs and thyroid gland palpation annually in brain tumour survivors. If the TSH is found to be only mildly raised, T4 replacement should be instituted as an elevated TSH is known to promote thyroid tumour growth. Thyroid cancer in survivors should be treated in a similar fashion to such tumours arising in the unirradiated patient. The disease-free interval or survival in patients treated for thyroid cancer is uninfluenced by whether or not there is a history of thyroid irradiation (Schneider *et al.* 1986).

Obesity and cardiovascular risk

Obesity is a recognised late effect in cancer survivors. Obesity is a risk factor for morbidity in the general population. It is therefore important to understand the pathogenesis of obesity in this group to treat and prevent further disability and early demise.

Lustig *et al.* (2003*a*), in a study of brain tumour survivors, identified hypothalamic damage from any source of treatment, but in particular radiation doses of 50 Gy or higher were associated with abnormal 10-year post-therapy body mass index (BMI) increases and therefore a primary risk factor for obesity. Young age at diagnosis was also identified as a risk factor (Lustig *et al.* 2003*a*), as has been identified in ALL survivors (Didi *et al.* 1995).

Damage to the hypothalamus is associated with obesity. The mechanism for this phenomenon has been postulated to be due to damage to the ventromedial hypothalamus (VMH) (Gold *et al.* 1972), which normally integrates the blood-borne information from the peripheral hormones leptin, ghrelin and insulin. The VMH translates this information into regulation of energy balance. Dysfunction of the VMH results in excessive caloric intake and decreased caloric expenditure, resulting

in relentless weight gain (Schwartz *et al*. 2000). There are two hypotheses, one proposes that VMH damage results in hyperphagia, resultant obesity and compensatory hyperinsulinaemia, the other that VMH damage disinhibits the efferent output of the vagus nerve, which acts on the pancreatic β cell to promote excessive insulin secretion. Lustig *et al*. (2000*b*) found that reducing the hyperinsulinaemia in 18 cancer survivors with hypothalamic damage by using octreotide resulted in a reduction of weight gain. Octreotide, the long-acting somatostatin analogue, binds to the somatostatin receptor 5 (SSTR5) on the β cell and results in inhibition of intracellular calcium influx and attenuation of insulin release.

Children with brain tumours frequently receive high-dose glucocorticoid treatment to either reduce symptoms of raised intracranial pressure or to limit post-operative oedema. Glucocorticoids could promote obesity by effects on appetite and regulation of energy intake, alterations in substrate oxidation and/or alteration in energy expenditure (Tataranni *et al*. 1996). However, studies in ALL survivors have been unable to conclusively demonstrate a link between weight gain and the dose of steroid used, probably because of small sample sizes (Van Dongen-Melman *et al*. 1995). The recent study by Lustig *et al*. (2003*a*) excluded patients who had received prolonged supraphysiological glucocorticoids.

Radiation to the hypothalamic–pituitary region results in hypopituitarism, with GH the most frequently affected hormone. GH is known to have numerous metabolic effects. When GHD is prolonged, affected individuals are at increased risk of obesity; GH therapy can help to reverse these effects (Salomon *et al*. 1989). In a study examining cardiovascular risk, an elevated systolic blood pressure, increased waist:hip ratio and an adverse lipid profile were more commonly seen in brain tumour survivors than normal controls and these abnormalities were particularly pronounced in those with untreated GHD (Heikens *et al*. 2000).

Intracranial tumours and their treatment are associated with neurological complications that may have adverse effects on motor function which may, in turn, result in significantly reduced physical activity, thus predisposing a child to obesity. Reduced physical activity has been shown to be common in patients treated for ALL both during and after therapy (Reilly *et al*. 1998, Warner *et al*. 1998).

Reassuringly, the Childhood Cancer Survivor Study has published results on self-reported BMI in patients treated for brain tumours and found that the BMI of survivors did not differ appreciably from that of sibling controls with only 15% having a BMI of greater than 30 (Gurney *et al*. 2003*a*).

There is only limited evidence on strategies for prevention or treatment of obesity in children with cancer (Gregory & Reilly 2004). Clearly lifestyle advice on diet and exercise must be employed early; however, true 'hypothalamic' obesity may be resistant to these measures. Where possible, future more focal irradiation schedules for children with tumours in the posterior fossa and temporal lobes may reduce incidental hypothalamic irradiation. There may also be a role for controlling hyperinsulinaemia, for instance, by octreotide in the more severe cases but randomised controlled trials of efficacy are required (Gregory & Reilly 2004).

Growth and attainment of final height

Suboptimal growth in brain tumour survivors is multifactorial in aetiology and may be a consequence of poor nutrition, tumour recurrence, impaired spinal growth due to spinal radiotherapy, chemotherapy, radiation-induced GHD, early puberty and other endocrinopathies.

The Childhood Cancer Survivor Study has published results on self-reported final height in patients with brain tumours and found that 40% were below the tenth percentile for height (Gurney *et al*. 2003*a*). There is a clear association between final height and age at diagnosis (Ogilvy-Stuart & Shalet 1995, Helseth *et al*. 1999, Noorda *et al*. 2001, Gurney *et al*. 2003a, Xu *et al*. 2003). In this most recent study, children diagnosed before the age of 5 years were fivefold more likely to have adult short stature than children diagnosed after the age of 9 years (Gurney *et al*. 2003*a*). There is clear evidence that the degree of impairment of spinal growth is greater the younger the child (Shalet *et al*. 1987), and it is the young irradiated child who is at risk of early puberty. Finally, the possibility remains that the hypothalamic–pituitary axis of the young child is more radiosensitive than in older children.

Spinal irradiation

Spinal irradiation results in a reduction in sitting height resulting in an overall poor adult height (Shalet *et al*. 1987, Clayton & Shalet 1991*a*). Spinal growth exceeds leg length growth during puberty and it is during this time that spinal growth is particularly impaired in those that have received craniospinal irradiation, resulting in an exaggeration of disproportion at final height. The effect on the spine is dependent on the dose of irradiation (Xu *et al*. 2003) and age at irradiation (Probert *et al*. 1973, Shalet *et al*. 1987).

Chemotherapy

Adjuvant chemotherapy has been reported to be associated with risk of short final height. It has been shown

that growth in the first 4 years after treatment with craniospinal irradiation is more profoundly affected in children who have received adjuvant chemotherapy than in those receiving craniospinal irradiation alone, suggesting potentiation of radiation-induced growth failure by chemotherapy (Olshan *et al*. 1992). Ogilvy-Stuart & Shalet (1995) demonstrated that the effect of chemotherapy on final height was as profound as craniospinal irradiation in GH-treated brain tumour survivors. It has been hypothesised that cytotoxic drugs may amplify the damage to the hypothalamic–pituitary axis by irradiation (Spoudeas *et al*. 1996), directly affect the production of insulin-like growth factor-I (IGF-I) by the liver (Nivot *et al*. 1994) and/or impair the action of IGF-I on the growth plate.

Management of endocrine late effects

Growth-promoting strategies

Final height outcome is important in survivors of childhood brain tumours. GH replacement is indicated in those found to be GHD. More recently, GnRH analogues (GnRH*a*) have been introduced to delay early or rapidly progressing puberty to allow more time for linear growth. Studies to final height are important to determine the effectiveness of growth-promoting strategies.

GH replacement

There have been numerous studies of GH replacement in brain tumour survivors with GHD. Unfortunately, meaningful interpretation can be difficult because of the following weaknesses: assessment made before final height is achieved (Clarson & Del Maestro 1999); small sample size; failure to consider familial determinants (Darendeliler *et al*. 1990); data collected from multiple centres introducing variations in oncology therapy, hormonal therapy and auxological assessments (Gurney *et al*. 2003*a*).

In 1995 our unit published final height data in 29 children who had received GH for radiation-induced GHD following therapy for brain tumours and clearly demonstrated the detrimental effect of spinal irradiation and the additive adverse effect of chemotherapy (Ogilvy-Stuart & Shalet 1995). We have recently revisited this topic and published final height data in the largest cohort of brain tumour survivors reported from a single centre (Gleeson *et al*. 2003). Because of the time span of the data collection we have been able to assess differences in practice over the last 25 years and have shown that, over this time, patients have come much closer to achieving target height (Fig. 2) (Gleeson *et al*. 2003).
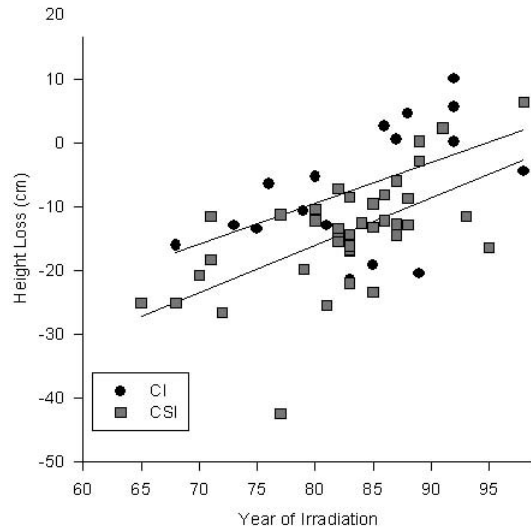

Figure 2 Improvements in height loss in children treated for brain tumours from 1975 to 2000 (Gleeson *et al*. 2003). CI, cranial irradiation; CSI, craniospinal irradiation.

In this study (Gleeson *et al*. 2003), auxological outcomes were affected by age at irradiation. From the perspective of clinical management, age at irradiation was correlated with a longer period of time until first assessment of GH status and consequently a longer time until GH therapy was started. In addition, those children irradiated in the latter time period of the study (after 1988) were first assessed for GHD and started on GH therapy on average 2 years earlier after irradiation than those treated previously despite similar age at irradiation. This change in practice may, in part, explain the improvements in final height outcome. Reassuring safety data (Moshang *et al*. 1996, Swerdlow *et al*. 2000, Packer *et al*. 2001, Sklar *et al*. 2002) have allowed this earlier and bolder approach to GH replacement in cancer survivors.

Another reason for improvement in final height is the effect of the GH treatment protocol. Adan *et al*. (2000) commented that the final height results of a previous study using extracted GH given as 0.1mg/kg intramuscular injections thrice weekly (Sulmont *et al*. 1990) were worse than the results that were achieved using daily subcutaneous injections of GH (0.2 mg/kg per week) (Adan *et al*. 2000). Another study using even higher doses of GH (0.3 mg/kg per week) claimed that their final height results in children treated with craniospinal irradiation were better than in earlier studies (Xu *et al*. 2003). A recently reported dose–response study of GH in children with GHD demonstrated that a dose of 0.35 mg/kg per week significantly improved growth velocity over 2 years, compared with similarly affected children (Cohen *et al*. 2002) randomised to receive 0.15 mg/kg per week. Although to date the use of GH replacement in childhood

cancer survivors has not been associated with increased tumour recurrence, there is a question mark over the possibility of an increased risk of secondary neoplasms that needs to be considered in future epidemiological studies (Moshang *et al.* 1996, Swerdlow *et al.* 2000, Packer *et al.* 2001, Sklar *et al.* 2002). Therefore, long-term safety needs always to be a consideration when using potentially supraphysiological doses of GH.

GnRHa therapy

The effect of GnRHa in children with precocious puberty without organic pathology is clear, with the results from numerous studies demonstrating an improvement in final height compared with untreated patients (Partsch & Sippell 2002). However, there is little information about its impact on final height if used from early puberty onwards. Studies that have investigated the use of GnRHa to delay puberty in GHD children have reported that final height outcome is improved nearly to target height (Mul *et al.* 2001, Saggese *et al.* 2001, Mericq *et al.* 2002). Three studies have looked at the use of GnRHa for the treatment of early puberty in cancer survivors treated with GH for radiation-induced GHD (Adan *et al.* 2000, Gleeson *et al.* 2003, Xu *et al.* 2003).

In patients previously treated with cranial irradiation without spinal irradiation, improvement has been demonstrated in final height in those who received GnRHa. Adan *et al.* (2000) reported improvements in final height in 21 cancer survivors who had received cranial irradiation treated with GnRHa compared with a group of survivors who did not receive GnRHa. The groups, however, were not matched for diagnosis, age at irradiation, dose of irradiation or use of chemotherapy (Adan *et al.* 2000). In GH-replaced brain tumour survivors, Gleeson *et al.* (2003) compared the actual auxological outcome in 11 children (cranial irradiation $n = 5$; craniospinal irradiation $n = 6$) also treated with a GnRHa against the predicted auxological outcome without treatment with GnRHa and demonstrated significant improvements in final height outcome with the use of GnRHa in patients who had received cranial irradiation ($+18\,cm$; $+2.7$ standard deviation score (SDS)) and to a lesser extent craniospinal irradiation ($+3.2\,cm$; $+0.9$ SDS). Overall, however, the benefits of the combination of GnRHa plus GH in cranospinal irradiation-treated children is disputed (Adan *et al.* 2000, Gleeson *et al.* 2003, Xu *et al.* 2003). In interpreting the results of all these studies, it should be remembered that the decision to start GnRHa therapy is partly based on the child having a poorer final height prediction, therefore by comparing the GnRHa-treated group with a group not considered for GnRHa therapy, the effect of GnRHa usage is almost certainly underestimated in all studies.

Although the numbers included in these studies are small these data support the use of combination GnRHa and GH in those children with radiation-induced GHD and early puberty. However further prospective randomised studies are required.

Management of GHD in adolescence and adulthood

Radiation-induced damage to the hypothalamic–pituitary axis persists into adult life and may also continue to evolve in degrees. It is therefore imperative that patients who underwent cranial irradiation in childhood are not lost to follow-up during the transition from paediatric to adult clinics. Continued surveillance of hormone status and management of hormone replacement therapy is required.

Despite the persistence of radiation-induced damage, retesting at final height should still be mandatory to identify those patients with severe GHD, who would then fulfil the criteria to receive continued GH therapy during the 'transition' period from childhood to adulthood. Re-evaluation is essential because the criteria for defining GHD in childhood include all degrees of GHD and differ from those used in adulthood when only patients with severe GHD are considered for GH replacement. Pharmacological tests of GH status also have low reproducibility in childhood (Zadik *et al.* 1990, Ropelato *et al.* 1996) and adulthood (Vestergaard *et al.* 1997, Fisker *et al.* 1998, Hoeck *et al.* 1999, Van den Broeck *et al.* 1999) and therefore an individual testing GHD on one occasion may not do so on a subsequent occasion. Consequently, in a recently published study, only 61% of brain tumour survivors treated with GH during childhood retested severe GHD at final height and would therefore be suitable for consideration for further GH therapy in adult life (Gleeson *et al.* 2004).

Transition

A recent study determined body composition parameters in 92 young adults with childhood-onset GHD with 35 age-matched GH-naïve hypopituitary patients with adult-onset GHD (Attanasio *et al.* 2002). Childhood-onset GHD patients had about 20% less total body mass, lean body mass, fat mass and bone mineral content than adult-onset GHD patients (Attanasio *et al.* 2002). Furthermore, there was a significant relationship between the degree by which a child failed to achieve target height and the impairment of body composition, implying that growth as a goal in treating GHD children is of crucial importance in that it is a surrogate for normalisation of body composition in adult life.
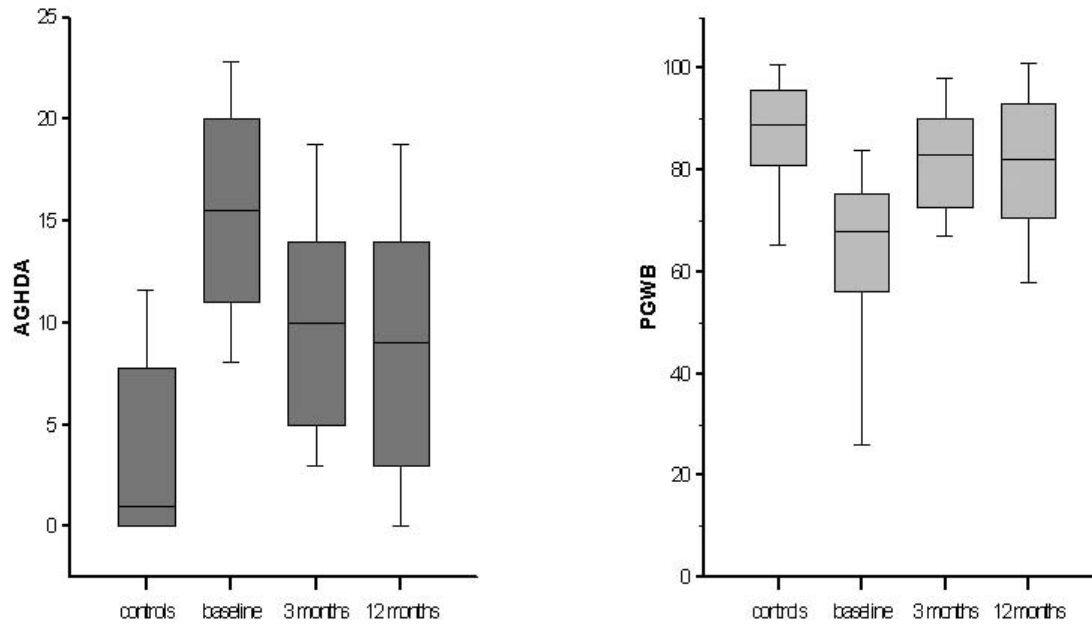
Figure 3 Box and whisker plots, representing quality of life as represented by (left plot) the AGHDA (range 0–25; high values represent greater morbidity) and (right plot) the PGWB (range 0–110; low values represent greater morbidity) in GHD survivors of childhood cancer during 12 months of GH treatment and in healthy control subjects. The lower boundary of the box indicates the 25th percentile, a line within the box marks the median, and the upper boundary of the box indicates the 75th percentile. Error bars above and below the box indicate the 90th and 10th percentiles (Murray *et al.* 2002). AGHDA, quality of life assessment in GHD adults; PGWB, psychological general well being schedule.

Beyond final height, several discontinuation and controlled treatment studies have suggested that by continuing GH therapy favourable body composition is maintained (Vahl *et al.* 2000). A multinational controlled 2-year study in patients, who had terminated GH at final height, randomised patients to GH at two different doses or no GH treatment (Shalet *et al.* 2003). After 2 years, significantly greater increases were seen in total bone mineral content in the GH-treated patients compared with those who were untreated (Shalet *et al.* 2003). The results of this study implied that withdrawal of GH replacement at final height may limit progression to peak bone mass in patients with severe childhood-onset GHD and that adequate GH replacement is required to continue this process.

Therefore, after final height has been achieved, it is now recognised that there are benefits in continuing GH replacement seamlessly in those individuals with severe GHD to achieve both adult body composition and peak bone mass amongst other end-points.

At present, only those with severe GHD are being considered for continued GH therapy in the transition period. At the same time, spontaneous GH secretion is much higher in a teenager compared with an adult, yet the criteria defining severe GHD in adults were derived from studies in middle-aged adults (Hoffman & Ho 1994); thus it may be inappropriate to use the same threshold for diagnosing severe GHD in teenagers. This belief was highlighted recently in a study of patients with partial GHD at retesting who developed a similar deterioration in body composition as that seen in severe GHD individuals when GH was discontinued for 1 year after final height (Tauber *et al.* 2003).

Adulthood

The clinical features of adult GHD have been described over the last 13 years (de Boer *et al.* 1995) and the benefits of GH replacement therapy in GHD adults proven in double-blind, placebo-controlled trials (Carroll *et al.* 1998). These include improvement in quality of life and psychological well-being, body composition (increased lean mass and decreased fat mass), lipid profile and other cardiovascular risk factors and bone mineral density (Carroll *et al.* 1998). Currently, in the UK, impaired quality of life remains the major indication for a trial of GH replacement in adults. Young adult survivors of childhood brain tumours have many of the features that are associated with adult GHD. However, the relative contribution of GHD toward these abnormalities is difficult to disentangle from the direct effects of the primary pathology, irradiation, chemotherapy, high-dose

glucocorticoids, insufficient exercise and excessive caloric intake.

Only one study to date has addressed the role of GH replacement in adult survivors of childhood cancer. Murray *et al.* (2002) analysed the effects of physiological GH replacement therapy for 12–18 months in 27 GHD adult survivors of childhood cancer. Significant improvement in quality of life was observed (Fig. 3), but improvements in body composition, the abnormal lipid profile and bone mineral density were minor. This suggests that either GHD is not the only aetiological factor in the pathogenesis of these abnormalities or that a longer duration of GH replacement would be required to show benefit. Therefore, when considering the use of GH replacement in an adult brain tumour survivor with GHD, quality of life remains the main indication. Further studies of GH replacement over a longer duration are required in this cohort to assess whether, with time, other biological end-points may also be improved.

Conclusions

With the increasing numbers of childhood brain tumour survivors reaching adulthood awareness of endocrine late effects of cancer therapy is essential. These patients should be followed long term after irradiation as endocrine problems evolve over many years. These endocrinopathies may impact on quality of life, morbidity and mortality. A particularly important time is the transition from childhood to adulthood when not only is a patient most likely to be lost to follow-up but there are also important issues with regard to maturational development after final height has been achieved.

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