
Long-Term Follow-Up of Survivors of Childhood Cancer

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Abstract

Today more than 75% of children treated for cancer will be cured, and attention is focusing on the late effects of treatments for these long-term survivors. Treatment-related morbidity is diverse, with potential effects on the endocrine system (growth, puberty, fertility, pituitary, thyroid and other disorders), cardiovascular, pulmonary and renal complications, second tumours, cognitive, education, neuropsychological and social manifestations. Multi-disciplinary long-term follow-up of these patients is essential to monitor, treat, and prevent morbidity. Depending on the nature of the treatment delivered, long-term follow-up of the survivor of childhood cancer can be individualised and delivered by a wide range of health professionals either in hospital or in primary care. In this review we describe the chronic health problems encountered by survivors and discuss the development of a long-term follow-up service for childhood cancer survivors.

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Cancer in childhood is relatively uncommon, with about 1,400 new cases per year in the UK, and a cumulative risk of 1 in 600 by the age of 15 years. Therapeutic advances and specialist cancer centres mean that the majority of children can realistically hope for long-term survival. With survival rates currently in the region of 75%, it has been estimated that by 2010, 1 in 715 of the young adult population will be a long-term survivor of childhood cancer [1]. Cure is generally achieved with multi-agent chemotherapy, plus or minus surgery, radiotherapy and bone marrow or stem cell transplantation, but is frequently associated with late effects and morbidity. The North American Childhood Cancer Survivor Study (CCSS), which has studied long-term health

outcomes in more than 20,000 long-term survivors of childhood cancer, has reported a standardised mortality ratio of 10.8 for the whole cohort when compared to age-matched normal controls, of which cancer recurrence accounted for two thirds of the deaths and about 20% were complications related to treatment [2, 3]. Treatment-related morbidity is diverse and may give rise to endocrine dysfunction (including growth impairment, infertility, hypothyroidism), cardiovascular disease, pulmonary and renal complications, cognitive impairment, educational problems, neuropsychological difficulties, and social problems. It has recently been reported in the UK that almost 75% of childhood cancer survivors have one or more chronic health problems, 40% have suffered at least one life-threatening/disabling event, and 25% of survivors have at least five chronic health problems [4].

Today paediatric oncologists are faced with the challenge of sustaining the excellent survival rates whilst striving to achieve optimal quality of life. Late effects may occur soon after treatment or may not present for many years. Life-long follow-up of survivors is recommended and this will necessitate multidisciplinary collaboration between oncologists and other health professionals to ensure early diagnosis, counselling and, where possible, timely institution of appropriate treatments [5–8]. The need to develop guidelines for the assessment of late effects of cancer therapy is reflected in recently published guidelines from the US Children's Oncology Group, the UK National Institute for Clinical Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN) and the UK Children's Cancer and Leukaemia Group (CCLG).

This chapter will describe the chronic health problems encountered by survivors and discuss strategies for the development of a long-term follow-up service. In particular, we focus on an evidence-based approach developed by SIGN and discuss how this is complemented by other guidelines [9]. The SIGN guideline provides a systematic review of the evidence available in five areas of long-term follow-up [9, 10]. These are: (1) the assessment and achievement of normal growth; (2) achievement of normal progression through puberty and factors affecting fertility; (3) early identification, assessment and treatment of cardiac abnormalities; (4) assessment of thyroid function, and (5) assessment and achievement of optimum neurodevelopment and psychological health. (Based upon the evidence available, SIGN guidance provides a grade of recommendation to guide the management decisions: reflecting the strength of the evidence on which the recommendation is based and does not reflect the clinical importance of the recommendation.) Other important areas not addressed by the guideline include renal, respiratory and liver dysfunction, second malignancies, and visual and hearing impairment. It is planned that a future SIGN guideline will address these issues. Each of the five areas covered in the guideline, with brief mention of the other areas, is discussed below.

Endocrine Function

Disorders of the endocrine system are commonly encountered in up to 50% of childhood cancer survivors following chemotherapy and radiotherapy, and include growth impairment, thyroid dysfunction, disrupted puberty and infertility [11].

Hypothalamic-Pituitary Dysfunction

Children who receive cranial irradiation for brain tumours, nasopharyngeal carcinoma, acute lymphoblastic leukaemia (ALL) or total body irradiation in preparation for bone marrow transplant are at risk of developing hypothalamic-pituitary dysfunction (hypopituitarism) and multiple pituitary hormone deficiencies [11–18]. The extent and timing of onset of these disorders is related to the total dose of irradiation, fractionation schedule and time from treatment. The hypothalamus is more radiosensitive than the pituitary [18, but also see Darzy and Shalet, pp 1–24]. The frequency and severity of hypothalamic-pituitary dysfunction increase with time after irradiation due to secondary pituitary atrophy [15]. Growth hormone (GH) is the most vulnerable anterior pituitary hormone to irradiation, followed by gonadotrophin, corticotrophins and thyrotrophin [15, 16]. Isolated GH deficiency may develop 10 or more years after fractionated doses as low as 10–12 Gy while higher doses (over 60 Gy) may produce panhypopituitarism [17, 18]. Patients treated for ALL with prophylactic cranial irradiation (18–24 Gy) have been found to have abnormalities of GH secretion up to 25 years following treatment. Treatment of nasopharyngeal tumours or brain tumours exposes patients to much higher doses of irradiation and is associated with GH deficiency in 50% of patients within 5 years, and is often compounded by other pituitary deficiencies [19].

Growth Problems

Treatment with chemotherapy and radiotherapy may have a significant impact on the growth and development of the child and short stature is well documented following cranial and craniospinal irradiation. Growth may be impaired as a result of GH insufficiency (compounded by other pituitary hormone deficiencies), impaired spinal growth, disrupted bone mineral homeostasis, immobilisation, and nutritional problems [11–18].

Radiotherapy to the spine (for CNS tumour or abdominal irradiation) may have a direct impact on spinal growth by causing permanent disruption to the

epiphyses. The damage is greater with single dose versus fractionated irradiation and with younger age at the time of treatment [16, 17]. The spinal growth spurt occurs towards the end of secondary sexual development, therefore, radiotherapy to the spine will result in late pubertal growth failure.

Younger children, especially girls, are more likely to develop early or precocious puberty and a pubertal growth spurt can be mistaken for 'catch-up' growth [10]. Obesity can normalise growth at the expense of a disproportionate bone age advance and reduce final height.

Bone development is maximal during puberty and peak bone mass is reached in the third decade of life. Evaluation of bone mineral density in long-term survivors of ALL has shown reduced bone mineral density [20, 21]. Although this is likely to be multifactorial, involving a combination of alterations in calcium absorption, vitamin D metabolism, IGF-binding proteins and GH insufficiency, there is increasing evidence to implicate chemotherapy. At presentation with ALL there is already low bone turnover with reduced levels of collagen formation and resorption markers (PICP, PIIINP and ICTP) [21]. In remission, there is further suppression of bone synthesis (low levels of PICP and PIIINP) and growth suppression that probably relates to glucocorticoid (prednisolone) and high dose methotrexate therapies [22–25]. Reduced bone mineral density will increase the risk of osteopenia, osteoporosis and pathological fractures in later life.

Management of Growth

It is recommended that all children should undergo regular assessment of growth (sitting and standing height, skin folds, weight, BMI and pubertal staging) until final height is reached (SIGN grade B recommendation). Children with craniopharyngioma or impaired growth should undergo assessment of pituitary function with appropriate stimulation tests. Children with impaired growth velocity should have GH levels measured after appropriate stimulation tests (SIGN grade C recommendation). Children with a good prognosis 2 years out from treatment with proven GH deficiency should have GH replacement therapy (SIGN grade B recommendation). The relapse rate is higher in the first 2 years after diagnosis, and there is no evidence that GH is associated with reactivation of the primary lesion [26]. Children with craniopharyngioma may need GH from presentation (SIGN grade B recommendation) and GH response is similar to that seen in children with idiopathic GH deficiency. Where the cause of growth impairment is unclear, a trial of GH may be appropriate (SIGN grade C recommendation). Young girls receiving cranial radiotherapy should be monitored for precocious puberty (SIGN grade B recommendation).

Obesity

Survivors (especially girls and those with ALL, brain tumours and craniopharyngioma) are at risk of obesity in adolescence and adult life. The aetiology is multifactorial (nutritional, psychological, lifestyle including lack of exercise, endocrine and neuroendocrine) and is difficult to identify or treat [27, 28]. The consequences of childhood obesity are multiple, with an adverse impact on educational attainment and interpersonal relationships, especially in males. Monitoring of weight and calculation of BMI should be carried out routinely. Advice on healthy eating and exercise should be given early and reinforced regularly [Gregory, pp 59–76].

Thyroid Disorders

Thyroid disorders are commonly encountered following radiation treatment for cancer, either secondary to disruption of the hypothalamic-pituitary-thyroid axis or following direct damage to the thyroid gland itself. Thyroid gland abnormalities may present as thyroid dysfunction, nodules and, rarely, thyroid cancer [29, 30]. Central hypothyroidism with TSH deficiency, may develop following cranial or craniospinal irradiation, although it is uncommon with doses of <40 Gy. However, there is some evidence to suggest that lower doses may be associated with clinically significant subtle damage to thyrotrophin secretion despite apparently normal biochemical levels of TSH and thyroid hormone. Direct damage to the thyroid gland following radiation of the neck, at a fractionated dose of >18 Gy, most commonly presents as hypothyroidism, with low T₄ and elevated TSH. Risk factors are radiation dose, female sex, and older age at diagnosis, with the highest risk 5 years after irradiation [31]. Chemotherapy is an independent risk factor for thyroid dysfunction and may potentiate radiation-induced damage. Hyperthyroidism may also develop from about 8 years after irradiation at doses of >35 Gy, but this is less common [30].

Irradiation involving the neck also confers an increased risk of developing both benign and malignant thyroid tumours. The risk of developing thyroid tumours increases with radiation dose, younger age at the time of treatment and female gender [32]. In the past, children treated with low dose radiotherapy for a variety of non-thyroid malignant disorders, including lymphoid hyperplasia and various skin conditions, have a significantly increased risk of thyroid cancer (<10% over 35 years) [33]. Radiation-induced thyroid cancers were all too evident following the devastating impact of the radioactive fallout from the Chernobyl nuclear power plant accident in 1986. Thyroid nodules may be benign (adenomas, focal hyperplasia and colloid nodules), or malignant, most frequently papillary carcinoma secondary to irradiation, which is highly curable if detected early.

It is recommended that survivors of childhood cancer who have received radiotherapy to the neck, brain or spine should have thyroid function checked at the end of treatment and at regular intervals thereafter for life (SIGN grade B recommendations). There are no good quality studies that address the question of screening for thyroid nodules or second primary thyroid cancers. At-risk survivors should be advised accordingly and asked to seek urgent medical advice if they notice a palpable neck mass.

Thyroid hormone replacement therapy is safe and effective, although cautious introduction is necessary in patients treated with anthracyclines who are at risk of cardiac dysfunction. There is no evidence to support or refute the use of thyroxine in compensated hypothyroidism, although it is arguable that supplementation is warranted in these patients as hyperstimulation with persistently elevated TSH may theoretically predispose to malignant change.

Hypothalamic-Pituitary-Adrenal Axis

The hypothalamic-pituitary-adrenal axis has been shown to be relatively radio-resistant. ACTH deficiency is potentially a life-threatening condition, often with subtle onset, which although rare following low-dose cranial irradiation must be considered in patients with pituitary tumours or those receiving cranial irradiation doses in excess of 50 Gy [15]. The insulin tolerance test is regarded as the gold standard for assessing the integrity of the hypothalamic-pituitary-adrenal axis, although severe hypoglycaemia may be problematic. Subtle clinical signs and diagnostic difficulties may lead to an underestimation of the true incidence of abnormalities of the hypothalamic-pituitary-adrenal axis. However, once identified, life-long hydrocortisone replacement is required and increased doses may be necessary for surgery or inter-current illness.

Hypothalamic-Pituitary-Gonadal Axis

The impact of cranial irradiation on the hypothalamic-pituitary gonadal axis is complex [Darzy and Shalet, pp 1–24; Armstrong et al., pp 25–39], and the clinical manifestations are dependent upon the dose received and gender of the patient. Relatively high doses of cranial irradiation may disrupt the hypothalamic-pituitary-gonadal axis resulting in hypogonadism. The hypothalamus is more radio-sensitive than the pituitary gland with hypothalamic GnRH deficiency being the most frequent aetiology. Radiation doses of 35–45 Gy are associated with impaired gonadotropin secretion with increasing time following radiation [15, 34]. Clinical manifestations vary from subclinical biochemical abnormalities, detectable only