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Paediatric Update

Commentary

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Endocrine and growth disorders are the most prevalent late effects observed in survivors of childhood cancer. Our institutional experience indicates that some 40% of survivors followed into young adulthood have developed at least one endocrine abnormality and a sizable number ultimately are diagnosed with multiple hormonal deficits [1]. Most, but not all, endocrine disturbances are the consequences of curative therapy, particularly external beam radiation therapy. The groups at greatest risk for endocrine complications are those treated with cranial or craniospinal irradiation, total body irradiation, and those exposed to high-dose, alkylator-based, myeloablative chemotherapy.

As detailed in Dr Spoudeas' comprehensive overview, during the past few decades a great deal has been learned about the various endocrine sequelae that can arise following the successful treatment of cancer in children and adolescents. While many of the endocrine aberrations that occur in cancer survivors affect, unequivocally, the patients' functional status and quality of life, more recent research has brought to light abnormalities that represent more subtle deviations from normal and that have less obvious clinical implications. Thus, at the present time it remains unclear what the clinical ramifications are, if any, for survivors who develop entities such as Leydig cell insufficiency (ie, normal testosterone level combined with raised plasma level of luteinising hormone (LH) [2] or 'hidden' central hypothyroidism (i.e., normal free T_4, but loss of normal thyroid stimulating hormone (TSH) secretory dynamics) [3]. Much work is required to understand fully how best to treat and follow survivors who develop these changes and to understand better the evolution of these perturbations.

It has become increasingly evident over the past several years that, in many instances, endocrine abnormalities may only become manifest many years after the completion of cancer treatment, when the survivor has reached adulthood [4,5]. Survivors at risk for a late-occurring endocrinopathy (e.g., those treated with cranial irradiation, Hodgkin's disease survivors treated with neck irradiation) will require life-long endocrine follow-up with an adult clinician. Unfortunately, this is easier said than done. This requires knowledge and motivation on the part of the survivor, as well as knowledge and experience on the part of the treating endocrinologist. Additional barriers include limited access to appropriate providers and the high costs of this type of specialised care. Overcoming these barriers represents an enormous challenge to all those involved in providing medical care to this vulnerable population.

Until quite recently, 'late effects' research in general and endocrine research in particular has relied heavily on single institution studies. Such studies have been invaluable. They have provided extensive data on the prevalence and risk factors for the endocrine diseases observed after cancer therapy, as well as providing important insights into the mechanistic changes underlying many of the endocrine complications that occur in this setting. Nevertheless, the limited patient numbers and relatively homogenous treatment exposures inherent in single institution studies have made it difficult to discern potential interactions between patient and treatment variables. Additionally, few studies have had adequate power to establish the safety and efficacy of the most common interventions used in childhood cancer survivors (eg, growth hormone replacement therapy, gonadotrophin-releasing hormone (GnRH) agonists to improve final height).

Over the past few years, a few collaborative, multicentre cohorts have been established, including the Childhood Cancer Survivor Study (CCSS) in North America and the equivalent CCSS in the UK. The North American CCSS includes detailed treatment information and extensive data on health-related outcomes in 14,000 5-year survivors of childhood cancer diagnosed and treated from 1970 to 1986 [6]. The North American CCSS has already yielded new data on a number of endocrine issues [5,7]. Most notably, the risk of disease recurrence and second neoplasms was assessed in 361

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childhood cancer survivors treated with growth hormone (GH) compared with 12,000 cancer survivors not so treated [7]. The risk of disease recurrence was not increased in those treated with GH, including individuals previously treated for a brain tumour, acute leukaemia, soft-tissue sarcoma or neuroblastoma. Of some concern, survivors who received GH were at increased risk of developing a second solid tumour. However, given the small number of events (15 second tumours among 361 survivors), it is important that this data on second tumours is interpreted with caution. Data on the prevalence of and risk factors for obesity and early menopause in adult survivors within the CCSS will be available in the near future.

Dr Spoudeas rightly points out that much of the current information on endocrine complications of cancer therapy relates to therapies that often were employed 10–20 years ago; some may not be relevant to the contemporary treatment of oncological diseases. Thus, we must continue to track and evaluate childhood cancer survivors in order to understand the late complications of newer treatment strategies. If we all continue to do our jobs, in the future we will have greater numbers of survivors who suffer fewer side-effects and late adverse events.

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