Endocrine late-effects of cancer treatment 1

Screening and management of adverse endocrine outcomes in adult survivors of childhood and adolescent cancer

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5 year survival for childhood and adolescent cancer in developed countries is now in excess of 80% and the number of survivors of cancer continues to increase worldwide. After completion of therapy, many of these survivors will face a lifelong risk of endocrine late effects. We summarise the available evidence related to the prevalence and risk factors for endocrine late effects among adult survivors of childhood and adolescent cancer. Present screening, surveillance, and treatment recommendations differ by country and region, so we also highlight the continued effort to harmonise the international guidelines for this population.

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This is the first in a Series of three papers about endocrine late-effects of cancer treatment

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For the **International Late Effects of Childhood Cancer Guideline Harmonization Group** see http://www.ighg.org

Introduction

With the 5 year survival rates for childhood and adolescent cancer in developed countries now in excess of 80%,[1,2] the number of cancer survivors continues to increase worldwide. In the UK, an estimated 33 000 survivors of childhood cancer, who were diagnosed before the age of 15 years, are alive and are at least 5 years from diagnosis.[2] The inclusion of patients diagnosed aged 15–19 years increases this number to about 44 000.[3] The National Cancer Institute states that the definition of a cancer survivor starts from the time of diagnosis; with this definition in the USA, more than 420 000 survivors of cancer diagnosed before the age of 21 years exist.[4] Stated another way, about one in every 750 individuals who live in the USA is a survivor of a cancer diagnosed before the age of 21 years.[4]

Many survivors will face lifelong challenges with their health after the cure of their cancer.[5] Several studies[6–8] have characterised the incidence and severity of chronic health disorders in long-term survivors of childhood and adolescent cancer (hereafter collectively referred to as childhood cancer). The cumulative incidence of serious health disorders among survivors does not seem to plateau. Among the childhood cancer survivors who completed therapy and reached the age of 35 years without a new serious health problem, 26% had a subsequent severe, life-threatening or disabling disorder, or died of a chronic health disorder within the next 10 years.[9]

Endocrine late effects are common, diverse, and often lead to other disorders (figure 1).[10] For example, weight gain or increased fat mass associated with cranial radiotherapy can lead to dyslipidaemia, and insulin resistance, which can lead to cardiovascular disease and eventually a cardiac event, such as a myocardial infarction. Moreover, therapy-related endocrinopathies can affect a survivor not only physiologically, but also psychologically. For example, ovarian damage due to pelvic radiotherapy, or alkylating agent chemotherapy, or both, can result in pubertal delay, premature ovarian insufficiency, infertility, and osteoporosis, which can lead to changes in body image, depression, and a diminished quality of life.[11]

Thus, with a goal to reduce the risk of morbidity, prevent premature death, and maximise the quality of life of survivors, the framework of risk-based survivorship health care has evolved. The foundation of risk-based care is anticipatory proactive care that includes a systematic plan of prevention and surveillance that is based on risks associated with the cancer therapy, genetic predispositions, lifestyle behaviours, and comorbid health disorders.[12] To guide clinicians in the delivery of risk-based survivorship care, several organisations have developed screening recommendations, largely based on treatment exposures.[13–17] As a result, the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) was formed. Concurrent with other projects, the IGHG will provide a framework to consolidate the various national and international guidelines for the long-term follow-up of childhood cancer survivors.[18] Of note, efforts are underway to harmonise recommendations for the screening of gonadal dysfunction, thyroid cancer, and metabolic syndrome.

In this Series paper we provide a synopsis of the two accompanying papers[19,20] and integrate information into recommendations to screen for endocrine disorders in the high-risk population of childhood cancer survivors. We report endocrine outcomes according to treatment exposure because this parallels the experience of many clinicians who see childhood cancer survivors in their clinic or office. First, the clinician determines the cancer and the cancer therapy that the survivor had and then identifies which complications the survivor could be at risk of developing. We describe key aspects of risk-based health care that clinicians use to monitor and manage endocrine disorders and that are particularly relevant in childhood cancer survivors.

As is the case for many adverse outcomes from cancer therapy, endocrine complications are often related to treatment. Therefore the total radiation dose and field of exposure, and the total dose and nature of any chemotherapy received by the patient are important to

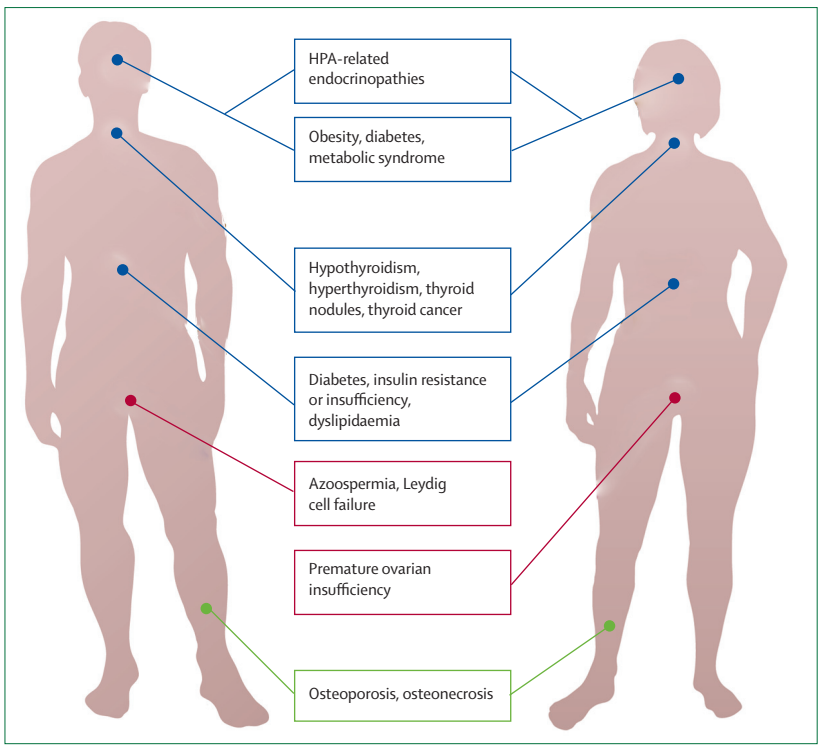

Figure 1: **Endocrine outcomes after treatment for childhood cancer**
HPA=hypothalamic—pituitary axis.

know. Many organs are exposed during total-body irradiation, so we discuss endocrine outcomes specifically associated with this procedure. Because some endocrinopathies are not directly associated with radiation, such as osteoporosis, we review outcomes associated with systemic therapy separately.

Treatment exposures

Cranial irradiation

As a treatment or adjunct in the treatment of childhood cancer, the brain could be exposed to radiotherapy. Radiotherapy that could affect the brain includes the whole-brain, segmental, or regional fields (such as cone down fields radiation, which is used for many brain tumours), and orbital, or head and neck fields (which include parts of the brain in the primary treatment field) or of scatter radiation (table 1). The most common group of childhood cancers that require cranial radiation with contemporary therapy are the CNS tumours, such as medulloblastoma, astrocytoma, and primitive neuroectodermal tumours. Additionally, 18–24 Gy whole-brain irradiation was used for CNS directed therapy in the treatment of childhood acute lymphoblastic leukaemia until the early 1980s. Since then, the total dose and frequency of use of cranial radiotherapy has decreased substantially; presently, less than 5% of children with acute lymphoblastic leukaemia are treated with cranial radiotherapy, although many patients who were given whole-brain irradiation for acute lymphoblastic leukaemia are now adults who need long-term follow-up.[21] Radiation therapy delivered for soft-tissue sarcomas or carcinomas in close proximity to the CNS (such as orbital, nasopharyngeal, or skull-base tumours) could also result in radiation exposure to the brain.

Any radiotherapy to the brain, orbits, or face that includes the hypothalamic–pituitary axis (HPA) puts survivors at risk of neuroendocrine abnormalities. Because the HPA produces several hormones, many important endocrine late effects might result from cranial radiotherapy, especially with radiation doses exceeding 30 Gy. As shown in figure 2,[22] the time to development of hormonal deficiencies after high-dose radiation varies but typically follows a predictable course. Growth-hormone secretion is most sensitive to radiotherapy; the greater the dose of radiation, the greater the prevalence and the shorter the lag time to growth-hormone deficiency. Thus, growth-hormone deficiency is dependent on the dose of the radiation delivered to the HPA and could be the first or only hormone deficiency apparent.[23] Although survivors who received doses greater than 18 Gy are at highest risk, growth-hormone deficiency can be recorded among those who receiv ed radiation doses as low as 8 Gy, especially if the radiation was delivered in a single fraction.[24] Growth-hormone deficiency also can be recorded in patients in which the HPA was exposed to scatter radiation during treatment for non-CNS tumours. Dependent on the clinical scenario, growth-hormone replacement can be offered to children with growth failure and growth-hormone deficiency that has been confirmed by provocative testing. Replacement in adult survivors of childhood cancer is controversial.[25] Growth-hormone deficiency and suggestions for replacement are discussed in detail elsewhere in this Series.[20] Other HPA endocrinopathies, such as gonadotropin (follicle-stimulating hormone and luteinising hormone) deficiency, thyroid-stimulating hormone (TSH) deficiency, and adrenocorticotropin hormone (ACTH) deficiency, might not be apparent until several years after the cancer therapy. The risk of gonadotropin deficiencies increases with radiation doses to the HPA of 30 Gy or higher;[26] these deficiencies result in altered gonadal function, with consequent oligomenorrhoea or amenorrhoea in women, and low testosterone concentrations in men. Notably, doses of 40 Gy or higher can lead to hyperprolactinaemia, which can also cause amenorrhoea or decreased libido. Attention to suggestive symptoms among survivors treated with cranial radiation and clinically appropriate tests is recommended.[15–17] Hormone replacement therapy might provide clinical benefit, dependent upon the sex of the survivor, attained age, pubertal status, and other considerations. Fertility, gonadal function, and hormone replacement are discussed elsewhere in this issue.[19] TSH deficiency manifests as a low or apparently normal TSH in combination with a low free T_4 concentration; screening for TSH deficiency might be necessary among

survivors who are at risk, especially survivors who received more than 40 Gy to the HPA.[15–17] Thyroid replacement tends to be easy to manage and therapy can be titrated to achieve normal free T_4. ACTH deficiency, which is much less common but can be life-threatening, generally results from a radiation dose to the HPA in excess of 30 Gy.[27] Therefore, clinical suspicion for ACTH deficiency among survivors who are at risk, especially for patients who are septic or critically ill, should remain high. Screening for ACTH deficiency might require a referral to an endocrinologist. Typically, tests include an initial screen followed by a stimulation test for confirmation.[15–17] For an adult patient, replacement with hydrocortisone is typically needed, with higher doses during times of illness. Patients with ACTH deficiency should also be provided with an injectable form of hydrocortisone, which can be given in case of critical illness (while awaiting emergency medical response).

Cranial radiotherapy, in addition to other factors, increases the risk of obesity, diabetes, and metabolic syndrome among survivors of childhood acute lymphoblastic leukaemia and CNS tumours.[28–33] Estimates for the prevalence of obesity after acute lymphoblastic leukaemia therapy range from 12% to 47%.[34–36] Risk factors include female sex, low bodyweight at diagnosis, and age under 5 years at time of treatment.[37,38] A dose–response association is absent for risk of these related outcomes.[30,39] Derangements of the leptin–adiponectin system might contribute to the excess body fat reported among these long-term survivors.[39,40] Treatment-related weakness and poor aerobic conditioning might also be contributory.[41,42] Among survivors of craniopharyngioma, hypothalamic obesity has long been a reported sequela of surgery and radiation; these survivors might also become hyperphagic.[43] Survivors with a history of cranial radiotherapy or brain surgery should have periodic assessments of height, weight, BMI, and HbA_{1c} or fasting blood glucose.[15–17]

Several studies[44–47] suggest that adult survivors of childhood cancer with healthy eating and exercise habits could have fewer cardiometabolic late effects. The Mediterranean dietary pattern, which includes a high consumption of vegetables and legumes (pulses), and a low consumption of meat, has been shown to reduce cardiovascular events in the general population,[48] and could also be beneficial for childhood cancer survivors. In a questionnaire survey[44] of 117 adult survivors of childhood acute lymphoblastic leukaemia, those whose diets were consistent with a Mediterranean dietary pattern had lower visceral and subcutaneous adiposity, lower waist circumference, and lower BMI than did those with other dietary patterns.[44] A randomised controlled trial called Exercise and QUality diet After Leukemia: the EQUAL Study (NCT02244411) will help measure whether improvements in diet and physical activity can result in a metabolic benefit among adult survivors of childhood acute lymphoblastic leukaemia.

	Radiotherapy field	Cancer	Outcome*
Cranial	Whole brain, total-body irradiation, orbital	Acute lymphoblastic leukaemia, brain tumours, preconditioning for stem-cell transplantation, soft-tissue sarcoma	HPA-related deficiencies (GH, TSH, ACTH, LH, FSH), obesity, diabetes
Neck	CRT, total-body irradiation, spinal, neck	Acute lymphoblastic leukaemia, brain tumours, Hodgkin's lymphoma, preconditioning for stem-cell transplantation, soft-tissue sarcoma	Hypothyroidism, hyperthyroidism, thyroid nodules, thyroid cancer
Abdomen	Whole abdomen, flank, para-aortic, total-body irradiation	Germ-cell tumours, Hodgkin's lymphoma, leukaemia, neuroblastoma, preconditioning for stem-cell transplantation, Wilms tumour	Insulin resistance, diabetes, fatty liver
Pelvis	Pelvis, total-body irradiation	Ewing sarcoma, Hodgkin's lymphoma, non-Hodgkin lymphoma, pelvic sarcoma, preconditioning for stem-cell transplantation, soft-tissue sarcoma	Premature ovarian insufficiency, impaired spermatogenesis, Leydig cell failure

HPA=hypothalamic–pituitary axis. GH=growth hormone. TSH=thyroid-stimulating hormone. ACTH=adrenocorticotropic hormone. LH=luteinising hormone. FSH=follicle-stimulating hormone. CRT=cranial radiotherapy. *Risk for outcome can be dose-dependent.

Table 1: **Radiation treatment fields and common endocrine outcomes**

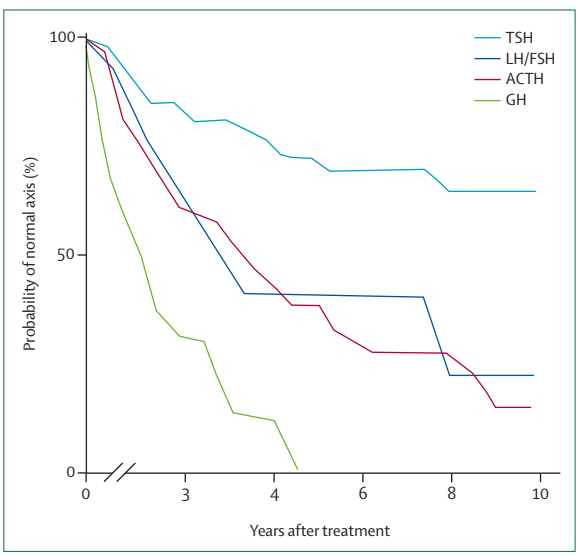

Figure 2: **Life-table analysis of probabilities of initially normal hypothalamic—pituitary—target gland axes remaining normal after radiotherapy**
TSH=thyroid stimulating hormone. LH=luteinising hormone. FSH=follicle-stimulating hormone. ACTH=adrenocorticotropic hormone. GH=gonadotropin hormone. Reproduced with permission from Darzy and Shalet.[22]

Neck irradiation

Radiation delivered in the course of treatment for childhood cancer might expose the thyroid gland when treatment fields include the neck. As a result, children given nasopharyngeal, oropharyngeal, Waldeyer, cervical and supraclavicular, cervical spine, and mantle irradiation are at risk for a range of thyroid disorders (table 1).[49–53] These locations are most often used in the treatment of CNS tumours, Hodgkin's lymphoma, acute lymphoblastic leukaemia, and head and neck sarcomas.

Thyroid abnormalities linked to neck irradiation include primary hypothyroidism, hyperthyroidism, and

thyroid neoplasia. The most common of these abnormalities is primary hypothyroidism, which varies widely in prevalence among reported cohorts because of the differences in radiation treatment variables, frequency and adequacy of follow-up, method of ascertainment, and definition of outcome.[49–53] Compensated hypothyroidism is characterised by a raised concentration of TSH in the presence of normal free T_4; if persistent, the laboratory profile is deemed to represent an imminent thyroid-gland failure and a suggestion for the initiation of thyroid-hormone replacement. Clinical primary hypothyroidism presents with a low free T_4 and high TSH. Non-specific symptoms of thyroid dysfunction include: fatigue, weight gain, cold intolerance, constipation, oedema, myalgia, dry skin, and depression. Primary hypothyroidism after radiation for childhood malignancies often manifests within 5 years post-treatment, but new cases can occur much later.[49,50,52] Risk factors for primary hypothyroidism recorded among paediatric cohorts include female sex,[52,53] white race,[54] older age at exposure,[51,52] and a high radiation dose to the thyroid gland,[49–53] with radiation dose being the most consistently identified risk factor. Among 1791 survivors of Hodgkin's lymphoma who participated in the Childhood Cancer Survivor Study,[52] the 20 year actuarial risk of hypothyroidism was 20% for patients who received less than 35 Gy, 30% for patients who received 35–44·9 Gy, and 50% for patients who received more than 45 Gy to the thyroid gland.

Childhood cancer patients given neck irradiation are also at an increased risk for hyperthyroidism coompared with the general population.[50–53] The clinical presentation is characterised by a diffusely enlarged thyroid gland, a raised concentration of thyroid hormone, suppressed TSH concentrations, an increased thyroidal uptake of radioactive iodine, and the development of thyroid autoantibodies, which are features similar to those of Graves' disease. Delineation of risk factors for hyperthyroidism has been difficult because of the low prevalence of this complication in paediatric cancer cohorts. Several groups have reported a high risk of hyperthyroidism among Hodgkin's lymphoma survivors given radiation doses of 35 Gy or greater, but no difference related to sex.[50,52]

Thyroid neoplasia is another well established adverse effect of neck irradiation that includes both benign and malignant lesions.[50,52,55–59] The clinical manifestation ranges from occult asymptomatic nodules to large, multinodular goitre. The reported incidence of thyroid nodules varies substantially dependent on length of follow-up and method of ascertainment (thyroid palpation *vs* ultrasonography).[50,52,56,57] Most nodules that arise in an irradiated gland show an indolent course, although a proportion will undergo malignant transformation.[57] Thyroid cancer, most often a well differentiated, papillary carcinoma, is among the common subsequent neoplasms reported in survivors given neck radiation;[50,52,55,58,59] thyroid cancer has also been reported in neuroblastoma survivors given ^{131}I-metaiodobenzylguanidine.[60] Risk factors for the development of benign or malignant thyroid lesions recorded among paediatric cancer cohorts include: a younger age at cancer diagnosis, female sex, and a longer relapsed time from radiation exposure.[52,55] Radiation dose to the thyroid affects the risk of these outcomes. High thyroid radiation doses have been correlated with greater risk of the development of benign thyroid nodules than low doses,[52] whereas a linear dose–response association between radiation exposure and thyroid cancer is recorded only up to 29 Gy, with a decline in the risk at high doses consistent with a cytotoxic effect.[58,59] The long latency period, effective therapy, and uniformly good outcomes among survivors who develop radiation-induced thyroid carcinoma have prompted debate about the risks, harms, and benefits associated with ultrasonography surveillance for occult malignancy.[57] At present, most groups do not recommend routine-screening thyroid ultrasonography for long-term childhood cancer survivors given neck irradiation; the IGHG continue to harmonise international guidelines for thyroid cancer screening.[18]

Abdominal irradiation

The abdomen is exposed to radiation therapy during the course of treatment for many cancers (table 1). Historically, the para-aortic field was used to treat children with Hodgkin's lymphoma with infradiaphragmatic disease, which often included a splenic field (or splenic pedicle if the individual had a splenectomy).[21] With contemporary multimodality therapy, para-aortic radiation is used infrequently. By contrast, whole abdomen, hemiabdomen, or flank radiation continues to be the mainstay of local control for children with advanced-stage Wilms tumour and high-risk neuroblastoma.

Many studies[28,61] have substantiated an increased risk of diabetes in long-term survivors of childhood cancer who were given radiotherapy to different abdominal fields. Meacham and colleagues[28] reported that childhood cancer survivors given abdominal irradiation had increased risk for diabetes, compared with siblings. Survivors of neuroblastoma had a seven-times increased risk, whereas those treated for Wilms tumour and Hodgkin's lymphoma had double the risk.[28] When multivariate models were adjusted for BMI, estimates of risk were higher. When survivors of these three cancer groups who were not given abdominal irradiation were compared with siblings, no increased risk of diabetes was noted.[28] A retrospective analysis[62] reported on the association between pancreatic radiation dose and the subsequent development of diabetes among 2520 survivors of childhood cancer in France and the UK. In that study, radiation dosimetry was done on all participants to calculate the dose of radiation to the different sections of the pancreas, and cases of diabetes were validated by a physician's report. Excess risks of both type 1 and type 2 diabetes were reported, with an apparent dose–response association between

radiation exposure to the tail of the pancreas, with a range of 20–29 Gy, and a subsequent risk of diabetes. The cumulative incidence of diabetes was 5·5% by the age of 45 years in survivors given abdominal radiation.[62] Another study[63] of more than 2000 long-term survivors of Hodgkin's lymphoma who had had para-aortic radiation (with or without the splenic pedicle) were compared with patients whose treatment did not include the para-aortic field. Irradiation with 36 Gy or more to the para-aortic lymph nodes and spleen was associated with a 2·3-times increased risk of diabetes. When the para-aortic field did not include the spleen, doses of 36 Gy or more were associated with a 1·82-times increased risk of diabetes; the mean dose to the pancreatic tail was significantly correlated with the risk of diabetes.

Diabetes is uncommon in the early interval after abdominal irradiation; rather it generally occurs many years later. We, and others,[64,65] have postulated the various pathways that lead to an excess risk of diabetes in this population. Diabetes after abdominal radiation is partly related to damage to the β cells of the pancreas that occurs during treatment, which results in insulin insufficiency. However, adaptive responses during the childhood years result in maintenance of glucose homoeostasis. As the body ages, and new fat mass is added, there seems to be a disproportionate amount of fat deposited in the visceral depots, the result of which is compounded by the sarcopenic phenotype that these survivors often manifest. Thus, as visceral adiposity increases, β cell insufficiency becomes a problem and the adaptive responses are no longer adequate to maintain glucose homoeostasis. Clinically, these survivors often have low fasting insulin and C-peptide concentrations that are inappropriately low for the fasting glucose concentrations.

Pelvic irradiation and high-dose alkylating agent chemotherapy

Radiation to the pelvis or high-dose alkylating agent chemotherapy, or both, are often essential components of therapy for childhood cancers including pelvic, soft tissue, or Ewing sarcoma, and Hodgkin's and non-Hodgkin lymphoma (table 1). Historically, the inverted-Y radiation technique, which was used independently or as part of total nodal irradiation for lymphoma, also included the pelvis.[21]

Among female survivors, abdominal, pelvic, or flank radiation therapy or high-dose alkylating agent chemotherapy, or both, strongly increase the risk of premature ovarian insufficiency (figure 1). Because the hormonal and reproductive roles of the ovary are closely interconnected, radiation therapy and high-dose alkylating agent chemotherapy can affect both functions. The risk for premature ovarian insufficiency increases with increasing age at treatment, and with high doses of therapy.[66,67] Radiation therapy is directly toxic to oocytes, which includes oocytes that are dormant or in the non-growing follicle pool. Chemotherapy, by contrast, seems to cause ovarian injury and damage through several different mechanisms.[68] High-dose alkylating agents are known to cause injury to the oocytes directly,[59,60] whereas other chemotherapeutic agents, such as docetaxel, might mainly damage ovarian-somatic cells, with oocyte death as a secondary outcome.[69] When given as preconditioning for the haemopoietic stem-cell transplantation, alkylating agents are nearly uniformly toxic to ovarian function.[68,70] As with hypogonadotropic hypogonadism due to cranial radiotherapy, hypogonadism after pelvic radiotherapy or high-dose alkylating agents might require oral or transdermal replacement of the female sex hormones with use of oestrogen and progesterone.[15–17] The risk of primary hypogonadism is discussed elsewhere in this Series.

In male patients, high-dose alkylating agent chemotherapy also increases the risk for hypogonadism and impaired fertility (azoospermia). As in female patients, the risk for hypogonadism increases with an increase in doses of chemotherapy, although age of the patient at the time of treatment might not be as relevant.[71] Leydig cells, which respond to luteinising hormone and produce testosterone, seem to be less sensitive to chemotherapy than are germ cells, which bring about spermatogenesis, or Sertoli cells, which support germ-cell development.[72] Nonetheless, reports suggest that 10–57% of male survivors will show increased luteinising hormone concentrations,[70–74] although fewer survivors will show decreased testosterone concentrations or need testosterone replacement.[75,76] If testosterone is measured, survivorship guidelines recommend the measurement of early morning testosterone concentration to avoid the effect of diurnal variation.[15–17]

Total-body irradiation

Total-body irradiation is widely used for preconditioning before haemopoietic stem-cell transplantation, particularly in individuals with acute lymphoblastic leukaemia. Several studies[77–81] have recorded an association between total-body irradiation and dyslipidaemia, insulin resistance, or diabetes. Majhail and colleagues[82] reported findings from the comprehensive metabolic assessment of 106 children and young adults with a history of haemopoietic stem-cell transplantation and 72 sibling controls. Survivors with a history of total-body irradiation (with or without additional cranial radiation) had significantly higher total cholesterol, low-density lipoprotein, and triglycerides, and significantly lower high-density lipoprotein concentrations, than did controls. No differences were noted between survivors without a history of total-body irradiation and controls. Additionally, survivors conditioned with total-body irradiation and lymphoid irradiation before haemopoietic stem-cell transplantation might have thyroid dysfunction,[83] and growth-hormone deficiency, premature ovarian failure, and infertility.[84,85]

Systemic chemotherapy

Systemic chemotherapy, which includes corticosteroids and methotrexate, predisposes individuals to skeletal toxicities that develop during the period of active cancer treatment. Deficits in bone mineral density are typically subclinical in most children, by contrast with osteonecrosis that might manifest as asymptomatic radiographical abnormalities, or chronic joint pain, and swelling associated with reduced function, and lower quality of life.[86] Survivors of haematological malignancies and bone tumours, and patients given haemopoietic stem-cell transplants, are at risk of skeletal toxicities due to the routine inclusion of corticosteroids and methotrexate in treatment regimens. Bone mineral density deficits have also been reported in survivors of solid malignancies and recipients of haemopoietic stem-cell transplants, but these studies are restricted by incomplete ascertainment of deficits in bone mineral density in small, clinically heterogeneous cohorts, precluding statistical power to assess confounding variables, like hypogonadism.[87] The most robust data on long-term bone health are largely derived from studies of survivors of childhood leukaemia. At diagnosis, many factors contribute to an increased risk of deficits in bone mineral density in childhood survivors, including suboptimum nutrition, sedentary behaviour, and tumour infiltration of the bone marrow. The cytotoxic effect of methotrexate on osteoblasts results in a reduction of bone volume and new bone formation that could be exacerbated by chronic corticosteroid treatment.[88] Treatment-related risk factors for low bone mineral density include high-cumulative doses of methotrexate (>40 g/m²), high-cumulative doses of corticosteroids (>9 g/m²), use of potent glucocorticoids such as dexamethasone, and among survivors of childhood acute lymphoblastic leukaemia, cranial irradiation.[89,90] Collectively, lifestyle and treatment factors could compromise attainment of maximum peak bone mass, which has been identified as an important factor that affects the risk of osteoporosis and fracture associated with ageing. In long-term survivors, growth-hormone deficiency, hypogonadism, and vitamin D deficiency contribute to a sustained bone mineral loss.[91] Assessment of adult survivors of childhood acute lymphoblastic leukaemia provides support that bone mineral density deficits improve after a discontinuation of therapy.[92,93] In a study of 845 survivors of more than 10 years of childhood acute lymphoblastic leukaemia (median age 31 years), very low bone mineral density was uncommon (5·7% with bone mineral density *Z* scores less than or equal to –2·0 and 23·8% with scores between –1·0 and –2·0).[92] The primary predictor for suboptimum bone mineral density was a high-dose (≥24 Gy) cranial or craniospinal radiation exposure, which provides support for the contribution of radiation-related endocrinopathies to this adverse outcome.

Osteonecrosis is a well established complication of persistent corticosteroid therapy that can result in the development of articular surface collapse and subsequent debilitating arthritis. Studies[86,89,90,94–96] on osteonecrosis have reported varying prevalences dependent on the study population, treatment protocol, and method of ascertainment (clinical *vs* radiographic). A substantial proportion of patients with symptomatic osteonecrosis has persistent-progressive symptoms after the completion of therapy that require surgical intervention, such as core decompression, osteotomy, and arthroplasty.[97] Risk factors for the development of osteonecrosis reported in cohorts of survivors of childhood leukaemia and recipients of haemopoietic stem-cell transplants include older age (≥10 years) at diagnosis or transplantation,[95,96,98,99] female sex,[94,97,100] and white skin colour.[100,101] Among these characteristics, older age is the most consistent demographic risk factor reported across studies. In the Children's Oncology Group-1961 trial[98] for high-risk acute lymphoblastic leukaemia, the 5 year cumulative incidence of symptomatic osteonecrosis varied significantly by age at treatment: 1·0% for patients aged 1–9 years, 9·9% for those aged 10–15 years, and 20% for patients aged 16–21 years. Treatment-related risk factors for osteonecrosis include the type and duration of corticosteroid therapy, and the corticosteroid dosing schedule. The incidence of osteonecrosis in patients with acute lymphoblastic leukaemia is higher with the use of dexamethasone than with prednisone.[99] Among high-risk patients with acute lymphoblastic leukaemia who were randomly assigned to receive either continuous (daily) dexamethasone or an alternate-week schedule of dexamethasone during the delayed intensification phase, children assigned to the alternate-week corticosteroid dose schedule had a statistically lower incidence of osteonecrosis than did the continuous corticosteroid group.[98] Additionally, the contribution of genomic variations has been studied, which shows the effect of antifolate and glucocorticoid metabolism on osteonecrosis risk.[100,101] In survivors of acute lymphoblastic leukaemia, polymorphism of the *ACP1* gene, which regulates lipid concentrations and osteoblast differentiation, was associated with an almost six-times (OR 5·6, 95% CI 2·7–11·3) excess risk of osteonecrosis.[102]

Evidence has emerged that supports an excess risk of thyroid disorders in individuals given chemotherapy alone.[103] Among recipients of transplants, the prevalence of thyroid dysfunction did not differ among survivors conditioned with busulfan-based and total-body-irradiation-based regimens, and this was a significantly greater proportion than that recorded among survivors who were given regimens that contained only cyclophosphamide.[83] An increased risk of thyroid cancer has also been reported in association with chemotherapy, independent of radiation exposure, although surveillance bias might be relevant in these reports.[55,56,59] In a pooled cohort study[59] of 16757 survivors, including 187 with secondary thyroid cancer, individuals given anthracyclines without radiation exposure to the thyroid had an increased risk of thyroid cancer. A subgroup analysis of

patients who received both anthracyclines and radiotherapy revealed that the relative contribution of the anthracycline chemotherapy to the risk of thyroid cancer diminished as the dose of radiotherapy increased, such that, as doses approached 20 Gy, radiotherapy represented the primary risk factor.

Risk-based health care

Guidelines and guidance

Several groups around the world have developed guidelines for surveillance of late effects after childhood cancer. The Children's Oncology Group (COG) from North America has reported long-term guidelines for the follow-up of survivors of childhood, adolescent, and young adult cancers.[15] The UK Children's Cancer Study Group (UKCCSG) Late Effects Group produced a therapy-based statement for long-term follow-up practice.[17] The guideline includes mainly recommendations for surveillance. The Scottish Intercollegiate Guidelines Network (SIGN) produced an evidence-based national clinical guideline on the long-term follow-up of survivors of childhood cancer,[16] and updated it in 2013.[104] The Late Effects Taskforce of the Dutch Childhood Oncology Group (DCOG LATER) has developed evidence-based multidisciplinary guidelines for follow-up after childhood cancer more than 5 years after diagnosis.[14] Many other groups developed recommendations for childhood cancer survivors mainly based on the recommendations of the COG and UKCCSG guidelines.[105] The present guidelines have been produced within different groups and different methods, leading to duplication in investigations and a high variation in the recommendations for the same health problems in survivors of childhood cancer.[13]

To avoid duplication in effort and to harmonise recommendations, several representatives from the guideline groups formed IGHG.[18] The IGHG is a collaborative effort between the guideline groups from COG, UKCCSG, SIGN, DCOG LATER, and PanCare (a European collaboration on care for survivors of childhood cancer). Furthermore, many experts from around the world contribute to this group. Despite the potentially varied needs of different countries and health-care settings, an increasing recognition exists of the advantages and efficiencies of collaborative efforts to share evidence and the workload in guideline development for the follow-up care of survivors.[13] The IGHG aims to produce evidence-based guidelines.[18] First the concordances and discordances among existing international guidelines were assessed with selected topics about the following key issues: (1) Who needs surveillance? (2) At what age or time from exposure should surveillance be initiated? (3) At what frequency should surveillance be performed? (4) What surveillance modality should be used? And (5) what effective treatments are available if health problems are identified? Based on the discordant areas, the collaborative group's formulation focuses on clinical questions to assess the evidence. The topic groups then undertake systematic scientific literature searches to make comprehensive evidence summaries. A common system is used to grade the levels of evidence. Recommendations are formulated with regard to the quality of the evidence, the benefits versus harms of the screening intervention, and the need to maintain flexibility across health-care systems. An essential focus of the IGHG is that surveillance will only be recommended for high-risk groups by use of a validated diagnostic test and only for health problems in which effective treatment is available. Ideally, randomised trials will establish whether screening for the specific late effects in survivors will lead to improvements in outcomes. So far, however, these randomised trials have been restricted because of the smaller sample of survivors available for any particular question.

Investigations done by the IGHG have led to the development of guidelines for surveillance of breast cancer[106] and cardiomyopathy[107] in survivors of childhood cancer. The recommendations have been developed in such a manner as to allow implementation in different health-care and resource settings. The collaboration is now working on the development of guidelines for male and female gonadal toxic effects surveillance, and thyroid cancer surveillance. Over the next 5 years, other endocrine outcomes, such as metabolic syndrome, will be addressed by the IGHG, in a sequence defined by a panel of experts with use of a Delphi survey.[18]

Care delivery

As time from treatment increases, the proportion of childhood cancer survivors returning to a cancer centre for follow-up decreases.[108] Possible explanations for failure to participate in long-term follow-up include patient-based reasons, such as little awareness of risks, desire to move on with life,[109] and systems-based reasons, such as scarcity of appropriate adult services.[110,111] As a result, survivors typically receive routine medical care from non-specialty primary care providers.[111] Unfortunately, these providers have various degrees of knowledge and comfort with long-term follow-up care.[112–114] Shared care is an intrinsically appealing option as a care model in which the oncologist and primary care provider collaborate.[12,115] A study[116] from the Netherlands reported that patients were willing to see a family doctor for long-term follow-up, the family doctors were interested in sharing care, and family doctors were willing to return the necessary medical information needed for continued follow-up.

The treatment summary and survivorship care plan, known as the Health Passport in the UK and elsewhere, has been proposed as a technique to improve provider communication,[117] quality of care,[5] patient satisfaction and quality of life,[118–120] and adherence to guidelines.[121,122] As noted, many country-specific guidelines for the long-term follow-up of childhood cancer have been developed;[13,15–17,104] a continuing international harmonisation effort will unify

	Treatment	Method	Frequency
1	Surgery alone, low risk chemotherapy	Postal or telephone	Every 1–2 years
2	Chemotherapy, low-dose cranial radiation (≤24 Gy)	Primary-care nurse (using protocols)	Every 1–2 years
3	Radiotherapy, except low-dose cranial, megatherapy*	Medically supervised late-effects clinics	Every year

Reproduced with permission from Wallace and colleagues.[124] *Megatherapy refers to haemopoietic stem-cell transplantation, treatment for multiply relapsed cancers, or other combination therapy regimens.

Table 2: **Levels of follow-up care for survivors of childhood and adolescent cancer**

Search strategy and selection criteria

We searched PubMed, Scopus, and Google Scholar for articles published in English within 2009–14 with the search terms "child", "adolescent", "neoplasm", "survivor", "endocrine", "cancer", "onco*", "tumour", "survivorship", "endocrinopathy", and "paediatric". A search for (child OR adolescent) AND neoplasms AND endocrine identified 11 616 manuscripts; addition of the term "survivor" restricted the search to 435 manuscripts. Of these studies, 113 were reported in the past 5 years. On the basis of search results, and input from the authors and expert advisers, we included 125 studies for endocrine late effects after treatment for childhood cancer.

and clarify these recommendations.[18,105,123] Therefore, continued enhancements to survivorship care via the survivorship care plan, the Survivorship Passport work of the European Network for Cancer Research in Children and Adolescents,[120] and the harmonised guidelines[18,105,123] should result in improvements in care for survivors of childhood cancer. Nonetheless, cancer therapy, long-term follow-up recommendations, and individual provider and patient needs might be substantially heterogeneous.

High-quality, risk-based care in a clinical setting is likely to be improved on via the risk-stratified approach, which uses treatment history to divide survivors by risk for late effects (table 2).[110,124] Edgar and colleagues[125] attempted to identify whether this approach was effective at separating survivors at high, moderate, and low risk for late effects.[125] Long-term childhood cancer survivors from one institution were retrospectively stratified with the categories outlined in table 2.[125] Roughly half (45%) of survivors were deemed at moderate risk and 41% were classified as at high risk of developing late effects. Importantly, the prevalence and severity of late effects increased as expected; the highest-risk group showed the highest prevalence of late effects.[125] Thus, stratification by treatment history seems to correctly identify patients who need the highest intensity of follow-up care. The practice of the risk-stratification guidelines, a supply of a survivorship care plan upon completion of therapy, and adherence to risk-based care strategies should improve quality and reduce the use of unnecessary tests in all risk groups.

Conclusions

Adult survivors of childhood cancer are at risk of several treatment-related adverse endocrine late effects. As outlined above, risk for endocrine late effects can be effectively delineated from treatment history. Providers should review previous cancer therapy to identify relevant risks and should be attentive to suggestive symptoms. Although country-specific guidelines for screening and surveillance have been developed, the continued international harmonisation effort will bring clarity and concordance to these recommendations. Finally, although survivors might be reluctant to engage in care, a risk-based approach, as has been outlined here, can be applied under most clinical scenarios, with the ultimate goal of survivor health and wellbeing.

Contributors

EST did the literature search, provided the figures, interpreted the data, and wrote the manuscript. MMH did the literature search, collected and interpreted the data, and wrote the manuscript. AE and LCK did the literature search, interpreted the data, and wrote the manuscript. CAS interpreted the data, and wrote and revised the manuscript. WHW and KCO conceived and designed the study, interpreted the data, and wrote the manuscript.

Declaration of interests

We declare no competing interests.

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