J R Coll Physicians Edinb 2008; 38:246–50

Long-term follow-up of survivors of childhood cancer

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ABSTRACT Today, more than 70% 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; and cognitive, educational, neuropsychological and social manifestations. Multidisciplinary long-term follow-up of these patients is essential to monitor, treat and prevent morbidity. In this review the authors describe the chronic health problems encountered by survivors and discuss the development of a long-term follow-up service for childhood cancer survivors.

KEYWORDS Childhood cancer survivors, growth and development of cancer survivors, long-term follow-up service

DECLARATION OF INTERESTS No conflict of interests declared.

Published online ***May 2008***

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INTRODUCTION

Childhood cancer is rare, with about 1,400 new cases per year in the UK and a cumulative risk of 1 in 600 by 15 years. Contemporary treatment is associated with a five-year survival rate of about 75% and, consequently, the population of long-term survivors continues to increase steadily. In Scotland, more than 26,000 people, constituting 1 in 715 of the young adult population, are survivors of childhood cancer. Increased mortality has been reported by the North American Childhood Cancer Survivor Study, where 20,000 long-term survivors had a standardised mortality ratio of 10.8, of which about 20% was due to treatment-related late complications.

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.

Multidisciplinary long-term follow-up of survivors is essential to monitor, treat and, where possible, prevent morbidity. An awareness of the need to develop a service for long-term follow-up of survivors of childhood cancer is reflected in recently published guidelines from the National Institute for Health and Clinical Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN) and the Children's Cancer and Leukaemia Group (CCLG). However, the implementation of guidelines is variable throughout the country. We describe the evidence-based approach in five main areas of long-term follow-up as developed by SIGN, and discuss how this is complemented by the other guidelines.

LATE COMPLICATIONS OF TREATMENT

The Scottish Intercollegiate Guidelines Network (see Further Reading) provides a systematic review of the evidence available in the following areas of long-term follow-up: growth, fertility, cardiotoxicity, thyroid function, neurodevelopment and psychological health. Table 1 shows the key to evidence statements and the grades of recommendation.

GROWTH PROBLEMS

Cancer therapy may have a significant impact on a child's growth and development. Children who receive cranial irradiation for brain tumours, nasopharyngeal carcinoma, acute lymphoblastic leukaemia (ALL) or total body irradiation (TBI) pre-bone marrow transplantation (BMT) are at risk of pituitary failure. Growth hormone is the most vulnerable pituitary hormone, followed by gonadotrophins, corticotrophins and thyrotrophin, dependent upon the irradiation dose, fractionation schedule and time from treatment. Cranial irradiation doses >30 Gy are associated with growth hormone deficiency within two years of treatment. Lower doses (18–24 Gy), used as central nervous system-directed therapy in previous national UK trials of childhood ALL, may lead to isolated growth hormone deficiency. Low-

TABLE 1 Key to evidence statements and grades of recommendation

Levels of evidence	SIGN grades of recommendation
1++ High quality meta-analyses, systematic reviews of randomised control trials (RCTs) or RCTs with a very low risk of bias. **1+** Well-conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias. **1–** Meta-analyses, systematic reviews of RCTs or RCTs with a high risk of bias.	**A** At least one meta-analysis, systematic review of RCTs or RCTs rated as 1++ and directly applicable to the target population; or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results.
2++ High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a moderate probability that the relationship is causal.	**B** A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+.
2– Case control or cohort studies with a high risk of confounding or bias, and a significant risk that the relationship is not causal.	**C** A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated 2++.
3 Non-analytical studies, e.g. case reports, case series.	**D** Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+.
4 Expert opinion	

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

dose radiotherapy for TBI (7.5–15.75 Gy) may also be associated with pubertal growth hormone (GH) insufficiency, thyroid dysfunction and radiation-induced skeletal dysplasia.

Spinal irradiation (such as TBI, craniospinal or abdominal irradiation) may cause epiphyseal disruption. The effect is greater with single dose versus fractionated irradiation and with younger age at the time of treatment. The spinal growth spurt occurs towards the end of secondary sexual development, so radiotherapy to the spine will result in late pubertal growth failure. Long-term survivors of ALL have also been shown to have reduced bone mineral density, which increases the risk of osteopenia, osteoporosis and pathological fractures in later life.

TABLE 2 Gonadotoxic chemotherapy agents

Alkylating agents	Others
Busulfan	Cisplatin
Chlorambucil	Cytarabine
Cyclophosphamide	Procarbazine
Ifosfamide	Vinblastine
Melphalan	
Nitrosoureas, e.g. BCNU, CCNU	

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

Survivors (especially girls and those with ALL, brain tumours and craniopharyngioma) are at risk of obesity in adolescence and adult life. The aetiology is multi-factorial (nutritional, psychological, lifestyle including lack of exercise, endocrinal and neuro-endocrinal) and is difficult to identify or treat. The consequences of childhood obesity are multiple, with an adverse impact on educational attainment and interpersonal relationships, especially in males.

SIGN Grade B recommendations include the following:

- All children should undergo regular measurements of height (until final adult height is reached), sitting height (if received spinal irradiation), skin folds, weight, body mass index (BMI) and pubertal staging.
- Pituitary hormones should be monitored regularly and treated appropriately.
- Children with a good prognosis two years out from treatment, with proven GH deficiency, should have GH replacement therapy.
- The relapse rate for brain tumours is higher in the first two years after diagnosis, but there is no evidence that GH is associated with reactivation of the primary lesion. Children with craniopharyngioma may need growth hormone from presentation.

Where the cause of growth impairment is unclear, a trial of GH may be appropriate (see SIGN Grade C recommendations).

THYROID DISORDERS

Abnormalities of thyroid function are common following treatment for childhood cancer, either due to direct or indirect radiation damage to the thyroid gland, or damage to the hypothalamic–pituitary–thyroid axis by cranial irradiation. Children with Hodgkin's lymphoma treated with radiotherapy to the neck have a significantly

TABLE 3 Best assessment of risk of sub-fertility following current treatment for childhood cancer, by disease

Low risk (<20%)	Medium risk	High risk (>80%)
Acute lymphoblastic leukaemia (ALL)	Acute myeloblastic leukaemia (AML)	Total body irradiation
Wilms' tumour	Hepatoblastoma	Localised radiotherapy; pelvic/ testicular
Soft tissue sarcoma stage I	Osteosarcoma	Chemotherapy conditioning for bone marrow transplant
Germ cell tumours (with gonadal preservation and no radiotherapy)	Ewing's sarcoma	Hodgkin's lymphoma – alkylating agent-based therapy
Retinoblastoma	Soft tissue sarcoma	Soft tissue sarcoma – metastatic
Brain tumour surgery only with cranial irradiation <24 Gy	Neuroblastoma	
	Hodgkin's lymphoma – anthracycline-based therapy	
	Brain tumour craniospinal radiotherapy with cranial irradiation >24 Gy	

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increased risk of hypothyroidism, thyroid nodules and thyroid cancer, compared to those treated with chemotherapy alone. Transient abnormal thyroid function tests are common in the first few years after treatment and may resolve spontaneously, but hypothyroidism may develop many years later. Thyroid function should be checked at the end of treatment and at regular intervals thereafter for life in these patients (see SIGN Grade B recommendations). 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.

PUBERTAL DEVELOPMENT, REPRODUCTIVE FUNCTION AND HEALTH OF OFFSPRING

Cytotoxic therapy may damage gonadal tissue at all ages and result in permanent sterility in both males and females. A number of chemotherapy agents are known to be gonadotoxic and modern treatment regimens are being introduced to minimise the risk of infertility (see Table 2). Previous treatment of Hodgkin's lymphoma in the UK with 'ChlVPP' (chlorambucil, vinblastine, procarbazine and prednisolone) was associated with almost universal permanent sterility in males and raised gonadotrophins of around 50% in females, which in due course could lead to a premature menopause. Current UK treatment with OEPA (vincristine, etoposide, prednisolone and doxorubicin) +/- radiotherapy is likely to be less gonadotoxic.

The extent of radiation damage to the reproductive tissue depends on the radiation dose, fractionation schedule and age at time of treatment. In males, testicular germinal epithelium is more susceptible than the testosterone-producing Leydig cells. Permanent azoospermia may follow a single fraction of 4 Gy, while testosterone insufficiency ensues post doses of >20 Gy in pre-pubertal boys and >30 Gy in post-pubertal men.

TABLE 4 Assessment of pubertal status and reproductive function in males and females

Males	Females
Tanner staging of secondary sexual characteristics	Tanner staging of secondary sexual characteristics
Assessment of testicular volumes using the Prader orchidometer	Menstrual history
Measurement of serum FSH/ LH, testosterone/inhibin B (if available)	Measurement of serum FSH/ LH/oestrogen/progesterone/ inhibin B
Semen analysis	Ultrasound assessment of ovarian follicles/uterus

Therefore, secondary sexual development and potency may be preserved despite infertility. Advances in assisted reproductive techniques, particularly intracytoplasmic sperm injection (ICSI), make paternity achievable for men with low sperm counts. Reassuringly, despite cancer therapy-induced oligozoospermia, the healthy sperm DNA is comparable to the normal population. The female oocyte is very sensitive to radiation, with an estimated LD_{50} of <2 Gy. The number of primordial follicles present at the time of treatment and dose received will determine the fertile 'window' and influence the age of premature ovarian failure. Uterine radiation in childhood increases the incidence of nulliparity, spontaneous miscarriage and intrauterine growth retardation, probably attributable to reduced uterine musculature elasticity and vascular damage.

The majority of childhood cancer survivors will be fertile; however, counselling patients and families appropriately can be difficult given the varied nature of the treatment (Table 3). All patients should undergo age-appropriate pubertal staging and further assessment of reproductive function as indicated (see Table 4). In post-

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TABLE 5 Suggested levels of follow-up for long-term survivors of childhood cancer

Level	Treatment	Method of follow-up	Frequency	Examples of tumours
1	Surgery alone Low-risk chemotherapy	Postal or telephone	1–2 years	Wilms' stage I or II, LCH (single-system), germ cell (surgery only)
2	Chemotherapy Low-dose cranial irradiation (<24 Gy)	Nurse or primary care-led (after appropriate training)	1–2 years	Majority of patients (e.g. ALL in first remission)
3	Radiotherapy, except low-dose cranial irradiation, megatherapy	Medically supervised long-term follow-up clinic	Annual	Brain tumours Post BMT Any Stage 4 patients

pubertal males, testicular volume <12 ml, in association with elevated follicle-stimulating hormone (FSH) and normal serum testosterone levels, strongly correlates with impaired spermatogenesis. In females, early follicular phase assay of FSH, oestradiol and ovarian ultrasound are potential tools to assess ovarian reserve (Table 4). If there is evidence of ovarian failure, sex steroid replacement therapy is necessary from puberty to at least the fifth decade for optimal bone mineralisation and cardiovascular protection. In young adult women, physiological sex steroid replacement therapy improves uterine function (blood flow and endometrial thickness) and may potentially enable these women to benefit from assisted reproductive technologies.

CARDIAC PROBLEMS

Early and late cardiac effects following chemotherapy and radiotherapy include cardiomyopathy, pericarditis, valvular lesions and coronary artery stenosis. Anthracyclines, such as daunorubicin and doxorubicin, cause cardiac damage in a cumulative dose-related fashion, due to focal myocyte death with replacement fibrosis. There is probably no 'safe' anthracycline dose as cardiac dysfunction is reported with relatively low doses and adverse effects increase with time. Higher anthracycline doses are associated with prolongation of the Q–T interval. Younger age at treatment and female gender are risk factors.

Mediastinal irradiation increases the risk of coronary artery disease and myocardial infarction by inducing atheromatous lesions of the proximal coronary arteries. Risk factors include high dose (>30 Gy), minimal protective cardiac blocking, young age at irradiation and length of follow-up. Radiation damage has an additive effect to anthracycline cardiotoxicity.

Echocardiography at diagnosis and at regular intervals thereafter is recommended in survivors exposed to anthracyclines or mediastinal irradiation. Cardiovascular risk factors, including blood pressure, BMI and lipid profile, should be monitored routinely as survivors are at risk of premature evolution of the metabolic syndrome.

COGNITIVE AND PSYCHOSOCIAL OUTCOMES

During therapy, children may miss substantial amounts of schooling, but a decline in cognitive function is neither frequent nor inevitable. However, there is a strong association between cranial irradiation and structural brain abnormalities (disruption of frontal lobe/basal ganglia connections, temporal lobe calcification and cortical atrophy). The functional significance of this is difficult to determine but may be associated with vasculopathy, calcification and electro-encephalogram (EEG) abnormalities. Treatment (particularly high dose irradiation and treatment at a young age) may have an impact on neurological function in later life. Regular review for such a deficit should be part of routine follow-up for at-risk patients (see SIGN Grade D recommendations).

DEVELOPING A LONG-TERM FOLLOW-UP SERVICE FOR CHILDHOOD CANCER SURVIVORS

It is clear that many survivors are at risk of multiple chronic problems throughout life, and long-term follow-up in a paediatric environment is neither sustainable for the paediatric NHS services nor age-appropriate for adult survivors. There is no evidence available to define the optimum follow-up for long-term survivors, and there is wide variation in when survivors are currently discharged from hospital follow-up. The best solution is a multidisciplinary team approach between primary and secondary health professionals, depending upon the individual treatment received. It is important that a summary is provided for the patient, parents and general practitioner to outline the child's diagnosis, treatment and list of potential late effects, as the side-effects profile will be dictated by the treatment regimen. The NICE guidance *Improving outcomes in children and young people with cancer* recommends that the long-term follow-up (LTFU) multidisciplinary team (MDT) should include a lead clinician with expertise in LTFU (usually an oncologist, but not necessarily paediatric), a specialist nurse, an endocrinologist, a general practitioner, an allied health professional (e.g. social worker) and a psychologist, with the identification of a 'key worker' for each patient (probably the nurse specialist) to coordinate care.

Based upon the limited evidence available, SIGN has developed risk-stratified recommendations for the intensity and frequency of follow-up. The long-term risks depend on the site of the underlying malignancy, the type and intensity of treatment and the age at treatment. Three levels of follow-up have been recommended, assigned at five years after treatment, and are summarised in Table 5. With increasing time since treatment, the risk of developing late complications may diminish and patients may be reassigned an intensity of follow-up at 10 and 15 years after treatment, by which time most survivors will be independent adults.

The Children's Cancer and Leukaemia Group (CCLG) Late Effects Group recently published a practice statement on therapy-based long-term follow-up, designed to inform and guide clinicians responsible for the long-term follow-up of childhood cancer survivors. The practice statement recommends follow-up assessments and investigations based on the treatment that the individual has received, and complements the recommendations made by SIGN. In addition, the CCLG has developed a website called Aftercure (http://www.aftercure.org), for survivors of childhood cancer. This provides helpful information on the importance of LTFU, fact sheets on therapy-related late effects, health promotion and guidance on education, employment and other social issues. This resource should be introduced to patients in the LTFU clinics, with ongoing support from the patient's key worker or nurse specialist.

CONCLUSIONS

Survivors of childhood cancer are at significant risk of developing late complications following the successful treatment of their cancer. Increasing awareness of the late complications of therapy dictates vigilant long-term follow-up of these patients with early intervention, treatment and appropriate counselling. In the UK, strategies are being developed to define a comprehensive programme for follow-up. There is little evidence to guide these, and current best practice is that all survivors should be monitored for life.

KEY POINTS

- All survivors of childhood cancer should be actively followed up for life by a multidisciplinary team to monitor, treat and, where possible, prevent morbidity. Intensity and frequency of follow-up will depend upon the underlying cancer diagnosis, treatment received and the age at time of treatment.
- Treatment of cancer with radiotherapy involving the neck (e.g. Hodgkin's lymphoma) may lead to hypothyroidism many years later. Patients at risk will need annual thyroid function tests.
- Many treatments may lead to premature ovarian failure in girls, and this should be taken into consideration when counselling for contraception. Premature ovarian failure requires treatment with sex steroid replacement therapy until the age of 50.
- Men with reduced sperm counts may still be fertile, and the sperm has been shown to contain as much healthy DNA as sperm produced by the normal population.
- Survivors of childhood cancer are not at increased risk of having children with cancer unless there is a known genetic predisposition (e.g. retinoblastoma).
- Long-term survivors are at greater risk of developing metabolic syndrome with obesity and hypertension.

FURTHER READING

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Originally published as part of the Haematology module in the RCPE Online Continuing Medical Education Programme. Online CME, including self-asessment MCQs, is available to Fellows and Members at: http://www.rcpe.ac.uk