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Long-term follow-up of survivors of childhood cancer (SIGN Clinical Guideline 132)

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BACKGROUND

Five-year childhood cancer survival rates have increased to 80–90% for some tumours due to intensified treatments and better supportive care imposed on an incidence stable over four decades.^{1 2} Between 2005 and 2012, the number of UK survivors has risen from 26 000 to 33 000, or from 1:1000 to 1:715 UK adults.^{3 4} However, 40% experience chronic severe or life-threatening consequences ('late effects') of their tumour and/or its treatment.⁵ The recent National Cancer Survivorship Initiative (NCSI) has highlighted the unmet need in service provision for adult childhood cancer survivors, with a proposed survivorship framework and stratified care pathways modelled on >20 years' prior experience.^{6 7}

In March 2013, the Scottish Intercollegiate Guidelines Network (SIGN) published updated guidance on long-term follow-up of childhood cancer survivors to aid the 'identification, assessment and management of late effects' aimed at primary, secondary and tertiary healthcare practitioners.⁸ The Guideline Development Group (GDG) included representatives from paediatric haematology, oncology, endocrinology, reproductive medicine, cardiology, general paediatrics and general practice, as well as a survivor.

PREVIOUS AND OTHER ASSOCIATED GUIDELINES

The previous SIGN 76 guideline was published in 2004. This revision updates information on fertility preservation, cardiac late effects and patient information provision, and provides new sections on subsequent primary cancers (SPCs), bone health and metabolic syndrome. The UK Children's Cancer Study Group's (UK CCSG) best practice statement⁹ is a

potentially valuable companion guideline for tertiary care practitioners requiring details of therapeutic regimens and their toxicity profiles to individualise care for those most affected.

KEY ISSUES

- ▶ *Section 11: long-term follow-up* provides a useful summary of the recommendations. It recognises the multisystemic and evolving nature of late effects over decades of survival, concluding a need for lifelong multidisciplinary follow-up (table 1). The authors suggest a three-tiered follow-up stratified by disease-related and/or treatment-related morbidity risk (table 2) and list the key multidisciplinary professionals required (box 1).
- ▶ *Subsequent primary cancers (SPCs)*—The British Childhood Cancer Survivor Study¹⁰ and others have shown an excess SPC risk—>50% due to gastrointestinal, genitourinary, breast and lung cancers—persisting into old age.
- ▶ *Fertility*—The impact of cancer treatment on the pituitary–gonadal axis, reproductive capacity and options for pretreatment fertility preservation are complex and differ between the sexes (see British Fertility Society review for a fuller discussion¹¹). In boys, post-treatment sub/infertility may exist despite a normal puberty and potency.¹² With intracytoplasmic sperm injection, oligospermia is no barrier to fertility preservation, while long-term spermatogenic recovery is possible.¹³ By contrast, pubertal delay or secondary amenorrhoea may herald sub/infertility in girls whose options are more limited. Pretreatment gonadotropin-releasing hormone analogues, ovarian transposition and oocyte collection are unproven and/or impracticable. Prepubertal children of either sex have no recommended options outside a clinical trial. Miscarriage rates are increased, but



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Table 1 Summary of SIGN recommendations on long-term follow-up of survivors of childhood cancer

Late effect	High-risk factors	Specific late effects	Screening methods/ management	Evidence level/grade
Subsequent primary cancers (SPCs)	Genetic predisposition, eg, NF-1 Radiotherapy	Dependent on syndrome Delayed presentation >5 years from treatment, at edge of radiation field (eg, mediastinal radiotherapy and breast SPCs)	As per guidance for specific syndromes No consensus Promote healthy lifestyle behaviours	3/C
	Chemotherapy* (alkylating agents, epipodophyllotoxins)	Increased risk of all SPCs	No consensus Promote healthy lifestyle behaviours	3/C
Sub-/infertility	<i>Both sexes</i> Cranial radiotherapy	Hypogonadotropic hypogonadism (pubertal arrest/ delay)	See individual sections for assessment depending on sex	3
	Pelvic radiotherapy	Sexual dysfunction	Consider psychological referral	3–4/D
	<i>Boys</i> Chemotherapy* (alkylating agents) Gonadal radiotherapy/ total body irradiation (TBI)	Azoospermia Azoospermia Hypergonadotropic hypogonadism (less likely—pubertal arrest/ delay, sexual dysfunction)	Semen analysis±cryopreservation, FSH, inhibin B Semen analysis±cryopreservation, FSH, inhibin B Regular pubertal assessment, LH, testosterone ±pubertal induction/ testosterone supplementation	3/D 2±3/D
	<i>Girls</i> Chemotherapy* (alkylating agents)	Hypergonadotropic hypogonadism (pubertal arrest/ delay/ oligoamenorrhoea)	Regular pubertal assessment, FSH, AMH ±pubertal induction/ female hormone replacement therapy	3/D
	Abdominopelvic radiotherapy	Hypergonadotropic hypogonadism Uterine dysfunction (premature delivery, low birth weight)	±oocyte cryopreservation if postpubertal	
Cardiac effects	Chemotherapy (anthracyclines)	Congestive heart failure	<i>Echocardiography:</i> Fractional shortening (FS) and ejection fraction (EF) measurements 2–3 yearly if anthracycline dose >250 mg/m ²	3–4/D 3/D
	Cardiac/mediastinal radiotherapy	Cardiovascular (especially coronary artery) disease	5 yearly if anthracycline dose <250 mg/m ² Treat as per regular heart failure/cardiovascular disease guidelines Promote healthy lifestyle behaviours	
Bone health	Chemotherapy (glucocorticoids, high dose methotrexate, 6-mercaptopurine) Cranial radiotherapy Bone marrow transplantation Endocrine dysfunction (GH deficiency, hypogonadism, hypothyroidism)	Osteoporosis (osteonecrosis with glucocorticoids)	<i>Dual energy X-ray absorptiometry (DXA)/ peripheral quantitative CT/ quantitative ultrasound:</i> BMD or bone mineral content (BMC) Z-scores adjusted for age, sex and height 2 years post-end of treatment Serial measurements not required unless abnormal or clinical change Sex steroid replacement Promote healthy lifestyle behaviours	3/D
Metabolic syndrome	ALL (especially after bone marrow transplantation) Brain tumours (especially after cranial radiotherapy and growth hormone deficiency)	Obesity Dyslipidaemia Insulin resistance Cardiovascular disease	<i>BP and BMI:</i> Annually in all survivors <i>Fasting glucose, insulin, lipid profile:</i> 2-yearly if obese/ overweight 5-yearly if normal weight Treat as per regular obesity guidelines	3–4/D
Cognitive outcomes	Cranial radiotherapy	Cognitive decline Psychosocial dysfunction	<i>Neuropsychological assessment:</i> Pretreatment and then annually	3/D

Continued

Table 1 Continued

Late effect	High-risk factors	Specific late effects	Screening methods/ management	Evidence level/grade
Growth	Craniopharyngiomas (and other hypothalamic/pituitary tumours) Cranial radiotherapy	Growth hormone deficiency Pubertal delay/ arrest Growth hormone deficiency Precocious puberty Pubertal delay/ arrest Other pituitary hormone deficiencies Spinal growth retardation	Regular height monitoring Pituitary function testing at diagnosis and regularly thereafter Regular height monitoring and pubertal assessment Paediatric endocrinology referral if reduced height velocity	2+/B-C 2+-2++/B-C
Thyroid dysfunction	(Cranio) spinal radiotherapy Neck, (cranio) spinal and total body irradiation MIBG therapy Cranial radiotherapy Chemotherapy	Primary hypothyroidism Thyroid nodules Thyroid cancer Secondary/tertiary hypothyroidism ?Unclear mechanism	Regular height monitoring+sitting height <i>Thyroid function tests:</i> At end of treatment and then annually Thyroid hormone replacement No consensus about thyroid nodules/ cancer—patient education	2+/B 2±2++/D

*Clinicians should note that all chemotherapy may be associated with an increased risk of SPCs and sub-/infertility. ALL, acute lymphoblastic leukaemia; AMH, anti-Müllerian hormone; BMD, bone mineral density; BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinising hormone; MIBG, metaiodobenzylguanidine; NF-1, neurofibromatosis type 1; SIGN, Scottish Intercollegiate Guidelines Network.

- there is no excess of congenital or genetic disorders in offspring.
- ▶ *Cardiac effects*—Anthracycline-induced heart failure and mediastinal irradiation-induced cardiovascular disease may take years to manifest and may be additive. There is limited evidence for prophylactic ACE inhibitors or β-blockers, hence standard heart failure management is recommended.
 - ▶ *Bone health*—Bone mineral density (BMD) as measured by DEXA is age-dependent, sex-dependent, puberty-dependent and height-dependent, thus Z-scores rather than T-scores need cautious interpretation. The only evidence-based treatment for osteopenia is sex steroid replacement, although its effect on fracture risk is unknown.
 - ▶ *Metabolic syndrome*—Studies are limited to acute lymphoblastic leukaemia (ALL) and brain tumour survivors. A normal body mass index (BMI) does not preclude insulin resistance and dyslipidaemia.¹⁴ Annual blood pressure and BMI assessments are recommended.
 - ▶ *Cognitive/ psychosocial issues*—Cranial irradiation-induced cognitive decline is age-dependent, sex-dependent and dose-dependent and compounded by adjuvant chemotherapy.¹⁵ All survivors are at increased risk of psychosocial maladjustment and warrant consideration for extra educational support.
 - ▶ *Growth*—All new cancer patients require accurate auxology at diagnosis and regularly thereafter to adult height, although the feasibility of performing this means that low-risk patients will need monitoring in primary or secondary care. Growth velocity requires interpreting in light of puberty and hormone replacement. Growth hormone (GH) replacement—important for bone mineralisation and childhood growth—does not increase cancer recurrence and should be substituted early particularly after spinal irradiation as it cannot fully reverse the detriment on adult height.^{16 17}
 - ▶ *Thyroid dysfunction*—Low-dose irradiation scatter can cause compensated and frank primary hypothyroidism years after treatment. Secondary hypothyroidism (thyroid-stimulating hormone deficiency) attributed to cranial irradiation is, in our experience, unusual outside the context of suprasellar tumours. Lifelong monitoring is recommended alongside education on self-examination.
 - ▶ *Information provision*—Information on healthy lifestyle, support networks and the importance of long-term follow-up should be given to all survivors.

UNDERLYING EVIDENCE BASE

These SIGN guidelines represent a synthesis of systematic reviews summarising the best available evidence in accordance with standardised methodology.¹⁸ Unlike the National Institute for Health and Care Excellence (NICE), SIGN does not require a mandatory cost-effectiveness analysis. Recommendations graded A–D are based on a

Table 2 Suggested risk stratification of levels of follow-up for 5-year childhood cancer survivors after completion of treatment (reproduced from SIGN 132: Long term follow up of survivors of childhood cancer by kind permission)⁸

Level	Treatment	Follow-up	Frequency	Examples
1	Surgery alone Low-risk chemotherapy	Postal/ telephone	1–2 yearly	Survivors of Wilms' tumour stage I/II Langerhans cell histiocytosis (single system disease) Germ cell tumours (surgery only)
2	Chemotherapy Cranial radiotherapy ≤24 Gy	Nurse/ primary care-led	1–2 yearly	Majority of survivors
3	Any other radiotherapy (cranial radiotherapy >24 Gy) Megatherapy (ie, high-dose chemotherapy)	Medically supervised dedicated long-term follow-up clinic	Annually	Survivors of Any brain tumour Bone marrow transplantation Stage 4 patients of any tumour type

SIGN, Scottish Intercollegiate Guidelines Network.

hierarchy of evidence from level 1 (meta-analyses, systematic reviews or randomised controlled trials) to level 4 (expert opinion).

HOW DO I IMPLEMENT THESE GUIDELINES IN MY PRACTICE?

- ▶ *Primary care practitioners* need to be alert to the many late organ toxicities incurred by increasing treatment intensity that may manifest decades after treatment. Lifelong surveillance for endocrinopathies, subfertility,

Box 1 Suggested members of the multidisciplinary follow-up team (with one member nominated as the key worker) (reproduced by kind permission from *Scottish Intercollegiate Guidelines Network (SIGN) 132: Long term follow up of survivors of childhood cancer*)⁸

- ▶ Adult oncologist
- ▶ Paediatric oncologist
- ▶ Radiation oncologist
- ▶ Paediatric neurosurgery
- ▶ Paediatric endocrinologist
- ▶ Paediatric neurologist
- ▶ Specialist nurse/nurse practitioner
- ▶ Clinical psychologist
- ▶ General practitioner
- ▶ Dentist
- ▶ Optician
- ▶ Social worker

Clinical bottom line

- ▶ Childhood cancer survivors require lifelong monitoring to limit late consequences of their tumour and/or treatment, but the optimum service delivery model remains incompletely defined.
- ▶ While risk factors associated with certain late effects are known, many evolve over decades, with data interpretation confounded by retrospective and cross-sectional study designs.
- ▶ Tertiary centres are developing one-stop age-appropriate multidisciplinary services for those at highest risk, but the majority will remain in primary and secondary care.
- ▶ All practitioners must thus be aware of consequences of cancer cure and thresholds for referral. In this respect, the SIGN guidance provides a helpful way forward for much needed service development and summarises the current evidence base.
- ▶ More prospective long-term morbidity outcome studies are required from current interventional trials to define the balance between improving survival with increasing treatment intensity and the quality of survivorship.

SPCs, cardiovascular disease, obesity and metabolic syndrome particularly in low-risk patients can only realistically occur in primary care, alongside supporting healthy lifestyle behaviours (including monitoring vitamin D status) and participation in secondary/tertiary follow-up. Young adult survivors may seek support for psychological illness or subfertility.

- ▶ *Secondary care practitioners* will monitor growth, puberty, thyroid function and neurocognitive development until adulthood, with appropriate specialist referral. Letters of support may be required for missed school attendances, statementing and disability living allowance applications. Adult physicians will be responsible for life-long monitoring of cardiovascular disease, obesity, thyroid function, bone and sexual health, fertility and SPCs.
- ▶ *Tertiary care practitioners* should see all those at highest risk (brain, pelvic, bone tumour and transplant survivors) for hypothalamopituitary hormone dysfunction, fertility counselling, cardiac and cognitive assessments and psychological support. Clear end-of-treatment summaries with information regarding long-term surveillance needs and likely consequences are required. Implicit in the latter are the increased resources needed for such age-appropriate tertiary assessment and rehabilitation services.

CONTROVERSIES AND UNADDRESSED ISSUES

The level of care provided to childhood cancer survivors remains highly variable across the UK,¹⁹ and controlled trials on the optimum frequency, duration and

quality of follow-up are still needed to determine the effectiveness of secondary prevention of, for example, congestive cardiac failure or hypocortisolaemic

(Addisonian) crises. A pan-European prospective cohort study of ~80 000 childhood cancer survivors (PanCareSurFup) is currently examining risk factors for cardiac disease, SPCs and late mortality.²⁰ Several issues not discussed in the guideline are summarised in box 2.

Box 2 Critical review

- ▶ Timely update limited by absence of high-quality evidence for the cost effectiveness of the recommended lifelong three-tiered follow-up framework. Evidence graded mainly C–D (none above B) consisting largely of uncontrolled qualitative studies of patient/family satisfaction, not morbidity or mortality.²¹
- ▶ Inherent bias in Guideline Development Group (GDG) composition—no renal, respiratory or neurology/neuropsychology representatives with consequent omissions of important treatment-related renal, neurological and pulmonary toxicities (detailed in the UK CCSG Best Practice Statement).
- ▶ The Human Fertilisation and Embryology Act (2008)²² governing storage and use of haploid gametes and embryos is not mentioned. It mandates personal (not proxy) consent, even in children; hence an intellectual ('Gillick') competency assessment is required. Blood-borne virus (HIV, hepatitis B & C) testing prior to storage and written consent regarding use after death is also necessary.
- ▶ The endocrine and cognitive outcomes sections have not been updated (cited references are over 15 years old). As a result:
 - The cited data on pituitary craniopharyngiomas and hypothalamic obesity have been superseded by prospective outcome studies,²³ retrospective reviews²⁴ and guidelines,²⁵ not identified by the GDG search strategy.
 - The recommendation that all cranially irradiated patients receive annual cognitive assessments has never been achieved even in the context of a prospective trial.¹⁵
 - The perception that cranial irradiation per se causes eventual life-threatening pituitary deficits (eg, adrenocorticotrophic hormone deficiency deficiency) persists from 1987 data on adult pituitary tumours; newer evidence suggests pituitary dysfunction is confined to GH deficiency and precocious puberty except in the presence of a suprasellar tumour, which is most likely causative.²⁶
 - Given the risk of radiation-associated subsequent primary cancers (1% lifetime risk of thyroid cancer), the carcinogenicity of nuclear fallouts and an elevated thyroid-stimulating hormone (TSH)²⁷ and the long-term cardiovascular mortality risk of subclinical hypothyroidism,²⁸ few clinicians would overlook screening for and treating compensated hypothyroidism (raised TSH, normal free T₄) after neck irradiation.

FURTHER RESOURCES

- ▶ *Scottish Intercollegiate Guidelines Network (SIGN) 132: Long-term follow-up of survivors of childhood cancer* <http://www.sign.ac.uk/pdf/sign132.pdf>
- ▶ *UK Children's Cancer Study Group (UKCCSG) Best Practice Statement: Therapy-Based Long-Term Follow-Up (2nd ed.)* http://www.cclg.org.uk/dynamic_files/LTFU-full.pdf
- ▶ *National Cancer Survivorship Initiative (NCSI) website* <http://www.ncsi.org.uk/>
- ▶ *Pan-European Network for Care of Survivors after Childhood and Adolescent Cancer (PanCare)* <http://www.pancare.eu/en/>
- ▶ *British Fertility Society (BFS) Consultation Paper on Fertility in Childhood Cancer* <http://www.britishtfertilitysociety.org.uk/practicepolicy/documents/fccpaper.pdf>

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