GUIDE LINE REVIEW

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

<table>
<thead>
<tr>
<th>Late effect</th>
<th>High-risk factors</th>
<th>Specific late effects</th>
<th>Screening methods/ management</th>
<th>Evidence level/grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subsequent primary cancers</td>
<td>Genetic predisposition, eg, NF-1</td>
<td>Delayed presentation &gt;5 years from treatment, at edge of radiation field (eg, mediastinal radiotherapy and breast SPCs)</td>
<td>No consensus</td>
<td>3/C</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>Chemotherapy* (alkylating agents, epipodophyllotoxins)</td>
<td>Increased risk of all SPCs</td>
<td>No consensus</td>
<td>3/C</td>
</tr>
<tr>
<td>Sub-/infertility</td>
<td>Both sexes</td>
<td>Hypogonadotropic hypogonadism (pubertal arrest/ delay)</td>
<td>See individual sections for assessment depending on sex</td>
<td>3</td>
</tr>
<tr>
<td>Cranial radiotherapy</td>
<td>Pelvic radiotherapy Boys</td>
<td>Sexual dysfunction</td>
<td>Consider psychological referral</td>
<td>3–4/D</td>
</tr>
<tr>
<td>Chemotherapy* (alkylating agents)</td>
<td>Aoospermia</td>
<td>Azoospermia</td>
<td>Semen analysis±cryopreservation, FSH, inhibin B</td>
<td>3/D</td>
</tr>
<tr>
<td>Gonadal radiotherapy/ total body irradiation (TBI)</td>
<td>Hypergonadotropic hypogonadism (less likely— pubertal arrest/ delay, sexual dysfunction)</td>
<td>Regular pubertal assessment, LH, testosterone ±pubertal induction/ testosterone supplementation</td>
<td>2–3/D</td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td>Chemotherapy* (alkylating agents)</td>
<td>Hypergonadotropic hypogonadism (pubertal arrest/ delay/ oligoamenorrhoea)</td>
<td>Regular pubertal assessment, FSH, AMH ±pubertal induction/ female hormone replacement therapy ±oocyte cryopreservation if postpubertal</td>
<td>3/D</td>
</tr>
<tr>
<td>Abdominopelvic radiotherapy</td>
<td>Hypergonadotropic hypogonadism</td>
<td>Uterine dysfunction (premature delivery, low birth weight)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac effects</td>
<td>Chemotherapy (anthracyclines)</td>
<td>Congestive heart failure</td>
<td>Echocardiography: Fractional shortening (FS) and ejection fraction (EF) measurements</td>
<td>3–4/D</td>
</tr>
<tr>
<td>Cardiac/m Mediastinal radiotherapy</td>
<td>Congestive heart failure</td>
<td>Cardiovascular (especially coronary artery) disease</td>
<td>2–3 yearly if anthracycline dose &gt;250 mg/m²</td>
<td>3/D</td>
</tr>
<tr>
<td>Bone health</td>
<td>Chemotherapy (glucocorticoids, high dose methotrexate, 6-mercaptopurine)</td>
<td>Osteoporosis (osteonecrosis with glucocorticoids)</td>
<td>Dual energy X-ray absorptiometry (DXA)/ peripheral quantitative CT/ quantitative ultrasound: BMD or bone mineral content (BMC) Z-scores adjusted for age, sex and height. 2 years post-end of treatment</td>
<td>3/D</td>
</tr>
<tr>
<td>Cranial radiotherapy</td>
<td>Bone marrow transplantation</td>
<td>Endocrine dysfunction (GH deficiency, hypogonadism, hypothryoidism)</td>
<td>Serial measurements not required unless abnormal or clinical change</td>
<td></td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>ALL (especially after bone marrow transplantation)</td>
<td>Obesity</td>
<td>BP and BMI: Annually in all survivors</td>
<td>3–4/D</td>
</tr>
<tr>
<td>Brain tumours (especially after cranial radiotherapy and growth hormone deficiency)</td>
<td>Dyslipidaemia</td>
<td>Insulin resistance</td>
<td>Fasting glucose, insulin, lipid profile: 2-yearly if obese/ overweight</td>
<td></td>
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<tr>
<td>Cognitive outcomes</td>
<td>Cranial radiotherapy</td>
<td>Cognitive decline</td>
<td>Neuropsychological assessment: Pretreatment and then annually</td>
<td>3/D</td>
</tr>
</tbody>
</table>

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Table 1  Continued

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

*Clinicians should note that all chemotherapy may be associated with an increased risk of SPCs and sub-fertility.

ALL, acute lymphoblastic leukaemia; AMH, anti-Mullerian 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.
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 lifelong 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 hypothalamic-pituitary 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, and controlled trials on the optimum frequency, duration and

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

SIGN, Scottish Intercollegiate Guidelines Network.
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.

**REFERENCES**

20 Hjorth L, Kvarnstrom E. Pancreatic Childhood and Adolescent Cancer Survivor Care and Follow-up Studies. 2013. [cited 2013 2 December 2013]; http://www.pancaresurfup.eu