### Levels of Evidence

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</tr>
</thead>
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<td>1++</td>
<td>High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias</td>
</tr>
<tr>
<td>1+</td>
<td>Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias</td>
</tr>
<tr>
<td>1</td>
<td>Meta-analyses, systematic reviews, or RCTs with a high risk of bias</td>
</tr>
<tr>
<td>2++</td>
<td>High quality systematic reviews of case control or cohort studies</td>
</tr>
<tr>
<td>2+</td>
<td>Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal</td>
</tr>
<tr>
<td>2</td>
<td>Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal</td>
</tr>
<tr>
<td>3</td>
<td>Non-analytic studies, eg case reports, case series</td>
</tr>
<tr>
<td>4</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>

### Grades of Recommendation

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.

<table>
<thead>
<tr>
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<th>Description</th>
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<td>A</td>
<td>At least one meta-analysis, systematic review, or RCT 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</td>
</tr>
<tr>
<td>B</td>
<td>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+</td>
</tr>
<tr>
<td>C</td>
<td>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 2++</td>
</tr>
<tr>
<td>D</td>
<td>Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+</td>
</tr>
</tbody>
</table>

### Good Practice Points

- Recommended best practice based on the clinical experience of the guideline development group

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NHS Evidence has accredited the process used by Scottish Intercollegiate Guidelines Network to produce guidelines. Accreditation is valid for three years from 2009 and is applicable to guidance produced using the processes described in SIGN 50: a guideline developer’s handbook, 2008 edition ([www.sign.ac.uk/guidelines/fulltext/50/index.html](http://www.sign.ac.uk/guidelines/fulltext/50/index.html)). More information on accreditation can be viewed at [www.evidence.nhs.uk](http://www.evidence.nhs.uk).

Healthcare Improvement Scotland (HIS) is committed to equality and diversity and assesses all its publications for likely impact on the six equality groups defined by age, disability, gender, race, religion/belief and sexual orientation.

SIGN guidelines are produced using a standard methodology that has been equality impact assessed to ensure that these equality aims are addressed in every guideline. This methodology is set out in the current version of SIGN 50, our guideline manual, which can be found at [www.sign.ac.uk/guidelines/fulltext/50/index.html](http://www.sign.ac.uk/guidelines/fulltext/50/index.html). The EQIA assessment of the manual can be seen at [www.sign.ac.uk/pdf/sign50eqia.pdf](http://www.sign.ac.uk/pdf/sign50eqia.pdf). The full report in paper form and/or alternative format is available on request from the Healthcare Improvement Scotland Equality and Diversity Officer.

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Scottish Intercollegiate Guidelines Network

Long term follow up of survivors of childhood cancer
A national clinical guideline

March 2013
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1 Introduction

1.1 THE NEED FOR A GUIDELINE

Cancer is diagnosed in 1,600 children each year in the UK, with a cumulative risk of 1 in 600 by the age of 15. For teenagers, although cancer is rare – around 1,500 cases a year in the UK – it is second only to accidents as the leading cause of death. In Scotland, between 1983 and 2007, there were 3,235 children under the age of 15 diagnosed with some form of cancer, representing an average of 130 cases per year.

Of all childhood cancers, approximately:

- one third are leukaemias, of which 80% are acute lymphoblastic leukaemia (ALL)
- 25% are brain and spinal tumours
- 15% are embryonal tumours (neuroblastoma, retinoblastoma, Wilms’ tumour and hepatoblastoma)
- 11% are lymphomas (Hodgkin’s and non-Hodgkin’s lymphomas)

The remainder is comprised of bone (osteosarcoma and Ewing’s sarcoma), soft tissue tumours (rhabdomyosarcoma), and a variety of more rare tumours.¹

While the diagnosis is important in that the disease type may be associated with ongoing consequences, it is likely that the risk of late effects will be defined by the treatment received. Consideration must be given to the dramatic changes in treatment modalities since the 1950s.

For all childhood cancers the five-year survival rate has improved over recent decades due to advances in treatment regimens and supportive care. Five-year survival rate has increased from around 30% in the 1960s to around 80% for children diagnosed between 2001 and 2005. This increased survival rate has led to a rapidly increasing population of adult survivors of childhood cancer and it is estimated that there are around 33,000 childhood cancer survivors in the UK. These survivors have higher premature death rates and are at increased risk of a range of physical and psychosocial problems when compared with the general population.² ³

Late effects related to treatment for cancer may occur soon after treatment is completed or may not present for many years or decades. Lifelong follow up of survivors is recommended as current best practice (see section 11) and this will necessitate multidisciplinary collaboration between patients and their families, oncologists and other health professionals including those in primary care to ensure early diagnosis, counselling and, where possible, timely initiation of appropriate treatments.

Guidance for primary care practitioners is required to increase knowledge around late effects and the needs of survivors of childhood cancer whose health behaviours and socioeconomic circumstances, such as access to work and education, may be adversely affected by their experiences. This patient group may attract particular benefit from interventions to encourage healthy lifestyle behaviours with emphasis on diet, exercise, maintenance of a healthy weight and avoidance of smoking (see section 12.2).

A Managed Service Network for Children and Young People with Cancer in Scotland was established in 2011. Within this, there is a Survivorship Initiative which aims to develop a national, comprehensive survivorship programme for children and young people who have been treated for cancer. This will involve developing a risk-based approach to follow up, in an age-appropriate environment, with the introduction of key workers and nurse-led services, supported by a web-based electronic system. This service will provide health surveillance, together with psychosocial support and education of survivors to encourage them to develop into independent adults.⁴
1.1.1 UPDATING THE EVIDENCE

This guideline updates SIGN 76: Long term follow up of survivors of childhood cancer, to reflect the most recent evidence.

For those sections which have not been updated, text and recommendations are reproduced verbatim from SIGN 76. The original supporting evidence was not re-appraised by the current guideline development group.

1.1.2 SUMMARY OF UPDATES TO THE GUIDELINE, BY SECTION

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<td>4 Fertility issues</td>
<td>Completely revised</td>
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<td>5 Cardiac effects</td>
<td>Completely revised</td>
</tr>
<tr>
<td>6 Bone health</td>
<td>New</td>
</tr>
<tr>
<td>7 Metabolic syndrome</td>
<td>New</td>
</tr>
<tr>
<td>8 Cognitive and psychosocial outcomes</td>
<td>Minor changes. Interventions section removed. No new evidence examined.</td>
</tr>
<tr>
<td>12 Provision of information</td>
<td>Completely revised</td>
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</table>

1.2 REMIT OF THE GUIDELINE

1.2.1 OVERALL OBJECTIVES

This guideline provides recommendations based on current evidence for best practice in identification, assessment and management of late effects in survivors of childhood cancer.

It is applicable to everyone who has been treated for cancer as a child or teenager, who may be at risk of developing late effects that are largely, but not exclusively, related to the treatment they received for their cancer.

1.2.2 DEFINITIONS

Survivors of childhood cancer are defined by age at cancer diagnosis and treatment. Across studies this varies from age less than 15 to age less than 24 years. Survival is commonly defined in studies as from two or five or more years post-treatment.

1.2.3 TARGET USERS OF THE GUIDELINE

This guideline is aimed at primary care staff who provide health care for cancer survivors, as well as secondary care and long term follow-up (late effects) clinic staff who assess patients and manage the long term care of this group.

This guideline will be of relevance to general practitioners and other primary care practitioners, specialist nurses, oncologists, haematologists, endocrinologists, reproductive medicine specialists, cardiologists and radiation oncologists. It will also be relevant to counsellors, psychologists, dietitians, physiotherapists and dentists as well as to patients and their families.

1.3 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only


be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient’s case notes at the time the relevant decision is taken.

1.3.1 PRESCRIBING OF LICENSED MEDICINES OUTWITH THEIR MARKETING AUTHORISATION

Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (MA) also known as product licence. This is known as ‘off label’ use.

Medicines may be prescribed off label in the following circumstances:

- for an indication not specified within the marketing authorisation
- for administration via a different route
- for administration of a different dose
- for a different patient population.

An unlicensed medicine is a medicine which does not have MA for medicinal use in humans.

Generally the off label use of medicines becomes necessary if the clinical need cannot be met by licensed medicines within the marketing authorisation. Such use should be supported by appropriate evidence and experience.

“Prescribing medicines outside the conditions of their marketing authorisation alters (and probably increases) the prescribers’ professional responsibility and potential liability”.5

The General Medical Council (GMC) recommends that when prescribing a medicine off-label, doctors should:

- be satisfied that such use would better serve the patient’s needs than an authorised alternative (if one exists)
- be satisfied that there is sufficient evidence/experience of using the medicines to show its safety and efficacy, seeking the necessary information from appropriate sources.
- record in the patient’s clinical notes the medicine prescribed and, when not following common practice, the reasons for the choice.
- take responsibility for prescribing the medicine and for overseeing the patient’s care, including monitoring the effects of the medicine.

Non-medical prescribers should ensure that they are familiar with the legislative framework and their own professional prescribing standards.

Prior to any prescribing, the licensing status of a medication should be checked in the current version of the British National Formulary (BNF).5 The prescriber must be competent, operate within the professional code of ethics of their statutory body and the prescribing practices of their employer.6

1.3.2 ADDITIONAL ADVICE TO NHSScotLAND FROM HEALTHCARE IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

Healthcare Improvement Scotland processes multiple technology appraisals (MTAs) for NHSScotland that have been produced by the National Institute for Health and Clinical Excellence (NICE) in England and Wales. No relevant appraisals were identified.

The Scottish Medicines Consortium (SMC) provides advice to NHS Boards and their Area Drug and Therapeutics Committees about the status of all newly licensed medicines and any major new indications for established products.

No SMC advice relevant to this guideline was identified.
2  Key recommendations

The following were highlighted by the guideline development group as the key clinical recommendations that should be prioritised for implementation. The grade of recommendation relates to the strength of the supporting evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

2.1  SUBSEQUENT PRIMARY CANCERS

**C** Healthcare professionals should be aware that survivors of childhood cancer are at particular and lifelong increased risk of developing a subsequent primary cancer and that this may occur at any site on the body.

2.2  FERTILITY ISSUES

**D** The potential impact of cytotoxic treatment in young male patients with cancer should be considered in discussion with the patient and their parents in order to offer appropriate fertility preservation options.

**D** Assessment of adult ovarian function should be offered to women who have received abdominopelvic radiotherapy or cytotoxic therapy.

**D** Teenage boys should be referred for semen cryopreservation if their fertility is considered to be at risk.

**C** Healthcare professionals should provide reassurance to survivors of childhood cancer that their offspring are not at increased risk of congenital abnormality.

2.3  CARDIAC EFFECTS

**C** Survivors of childhood cancer who received either anthracyclines or radiation to a field that included the heart should be assessed with respect to cardiac muscle function.

**D** Healthcare professionals should reassure survivors of childhood cancer who did not receive anthracyclines or radiation to a field that included the heart that the lifelong risk of treatment-related cardiac problems is very low.

2.4  BONE HEALTH

**D** Survivors of childhood cancer who have had the following interventions are at increased risk of BMD deficits and should have a baseline evaluation of BMD at around two years after completion of treatment:

- high cumulative doses of steroids
- high cumulative doses of methotrexate
- cranial irradiation
- bone marrow transplantation.

Evaluation of bone mineral density should also be undertaken in survivors whose treatment puts them at risk of endocrine dysfunction.
2.5 METABOLIC SYNDROME

Survivors of childhood cancer (particularly those who have been treated for acute lymphoblastic leukaemia or brain tumours) should be advised that they may be at higher risk of developing metabolic syndrome than the general population.
3 Subsequent primary cancers

3.1 TERMINOLOGY

In this guideline, the term subsequent primary cancer (SPC) is used to indicate malignancies which are histologically distinct from the childhood cancer. A range of other terms are used in the literature to describe these, including second malignant neoplasms, second cancers and new primary neoplasms.

3.2 THE EVIDENCE BASE

3.2.1 KEY REGISTRIES

Data on the incidence of SPCs in survivors of childhood cancers come from population level registries and studies which examine outcomes from specific treatment centres. The value of the studies will be dependent on the follow-up interval and duration and how complete the data sets are. The era of treatment is an important factor in analysis; prior to 1970 surgery and radiotherapy were the main treatment modalities with chemotherapy increasingly developing from the early 1970s onwards. Study populations may be pooled to examine outcomes following treatment for a specific type of childhood malignancy. Some studies encompass benign tumours within their inclusion criteria. One notable tumour is meningioma; while benign these tumours can have significant effects because of their location. Nested case control studies within the large population registries allow exploration of how outcomes are associated with treatment modalities, patient characteristics and temporal issues. Parameters of the key studies are outlined in Table 1.

3.2.2 OUTCOME MEASURES

Three main outcome measures are encountered in the evidence base.

- **Standardised incidence ratio (SIR).** The ratio of the incident number of cases of a specified condition in the study population to the incident number that would be expected if the study population had the same incidence rate as a standard or other population for which the incidence rate is known. Since cancer rates increase with age, the SIR takes into account whether a community's population is older or younger than the reference population by comparing observed incidence of further tumours with the expected incidence.

- **Excess absolute risk (EAR).** A measure of the number of disease cases associated with exposure to a putative cause of the disease in the population. It is the difference between the rates of disease in the entire population and among the non-exposed.

- **Cumulative incidence.** The number or proportion of a group (cohort) of people who experience the onset of a health-related event during a specified time interval/duration of follow up.
Table 1: National registries and cohorts for assessing risk of subsequent primary cancers in childhood cancer survivors.

<table>
<thead>
<tr>
<th>Registry/Study</th>
<th>Age at diagnosis (years)</th>
<th>Treatment Era</th>
<th>Entry point</th>
<th>n</th>
<th>Overall SIR</th>
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<tr>
<td>British Childhood Cancer Survivor Study8-10</td>
<td>≤15</td>
<td>1940-1991</td>
<td>Survival of at least 5 years</td>
<td>17,981</td>
<td>3.9</td>
</tr>
<tr>
<td>Nordic Countries Registry11</td>
<td>≤19</td>
<td>1943-2005 (some variation)</td>
<td>Diagnosis of initial malignancy</td>
<td>47,697</td>
<td>3.3</td>
</tr>
<tr>
<td>British Columbia Registry12</td>
<td>≤19</td>
<td>1970-1995</td>
<td>Survival of at least 5 years</td>
<td>2,322</td>
<td>5.0</td>
</tr>
<tr>
<td>German Cancer Registry13</td>
<td>≤15</td>
<td>1980-2008</td>
<td>Diagnosis of original malignancy</td>
<td>37,291</td>
<td>(odds ratio 2.1)</td>
</tr>
<tr>
<td>North American Childhood Cancer Survivor Study Cohort14</td>
<td>&lt;21</td>
<td>1970-1986</td>
<td>Survival of at least 5 years</td>
<td>13,581</td>
<td>6.4</td>
</tr>
<tr>
<td>Dutch Single Centre Study15</td>
<td>≤18</td>
<td>1966-1996</td>
<td>Survival of at least 5 years</td>
<td>1,368</td>
<td>11.2</td>
</tr>
</tbody>
</table>

3.2.3 POTENTIAL CONFOUNDING FACTORS

Children with certain underlying genetic abnormalities have an increased risk of childhood malignancy. Examples include retinoblastoma and neurofibromatosis type 1. These genetic abnormalities persist and affected individuals have an increased risk of developing SPC compared with other survivors of childhood cancer. Environmental factors such as smoke exposure, nutritional and hormonal factors are also potential confounders in observational studies.

3.3 OVERALL RISK

The British childhood cancer survivor study reported an overall SIR of 3.9 (95% confidence interval (CI) 3.6 to 4.2) for SPCs. The EAR of SPC was 1.7 per 1,000 person-years. In order of frequency the commonest SPC sites were; central nervous system, non-melanoma skin cancer, gastrointestinal, genitourinary, breast then bone. The greatest risk for older survivors aged over 40 years was for gastrointestinal and genitourinary malignancies, with 52% of the total EAR attributable to gastrointestinal, genitourinary, breast, or respiratory sites, reflecting the most common cancers in adulthood generally.8

The Nordic countries registry study reported an overall SIR of 3.3 (95% CI 3.1 to 3.5) for SPCs. There was some variation across countries in the era of treatment and the inclusion of meningioma or non-melanoma skin cancer.11 The EAR increased from one case (in age group 0-19 years) to six cases (in age group 60-69 years) per 1,000 person-years.

In a British Columbia registry an overall SIR of 5.0 (95% CI 3.8 to 6.5) was reported for survivors diagnosed with their first tumour between 1970 and 1995. The EAR was 1.7 deaths per 1,000 person-years and the cumulative incidence of SPC was 5.1% at 25 years.12

In a German cancer registry follow up is still relatively short. After 25 years the cumulative incidence was estimated at 1.4% with wide variation across childhood tumour types.16

In a German cancer registry follow up is still relatively short. After 25 years the cumulative incidence was estimated at 1.4% with wide variation across childhood tumour types.16

The North American childhood cancers survivors study (CCSS) is a large cohort study based on self reported cases verified using case note review. The overall SIR was 6.4 (95% CI 5.7 to 7.1), Cumulative incidence at 30 years follow up was 7.9% (95% CI 7.2% to 8.5%) when non-melanoma skin cancer was excluded14,17,18.
A Dutch single centre study found an overall SIR for SPC of 11.2 (95% CI 8.5 to 14.4). There is consistent evidence that the risk of developing an SPC following treatment for cancer in childhood is substantially higher than that expected from the underlying general population (see Table 1).

Healthcare professionals should be aware that survivors of childhood cancer are at particular and lifelong increased risk of developing a subsequent primary cancer and that this may occur at any site on the body.

3.4 ONSET AND DURATION OF INCREASED RISK

Analysis of the profile of SPCs recorded in the German cancer registry between 1980 and 2008, suggested that the delay between the primary and the subsequent cancer is longer for new solid tumours when compared with that for leukaemias or lymphomas, with a median delay of seven years for the former and two and a half years for the latter. This means that studies which take three or five year survival as the entry point may not include such cases.

In the population with the longest follow up (up to age 79 years) the increased risk of developing an SPC has been shown to continue throughout the survivor’s lifetime, including old age.

Figure 1 provides a schematic representation of the onset and duration of risk for subsequent leukaemias and solid tumours up to 30 years following treatment for childhood cancer.

Figure 1: Schematic representation of the onset and duration of risk for subsequent leukaemias and solid tumours up to 30 years following treatment for childhood cancer.
3.5 RISKS ASSOCIATED WITH PARTICULAR TREATMENT MODALITIES

3.5.1 INTRODUCTION

Analysis of the relationship between treatment of childhood cancer and which type of SPCs develop over what timescale is complex and influenced particularly by the era of treatment. The late 1970s and early 1980s saw the increasing development of cytotoxic agents and multiagent regimens. In the large North American study risks of developing solid cancers were higher for patients whose initial treatments included radiotherapy whilst development of subsequent acute non-lymphoblastic leukaemia was strongly related to chemotherapy.18

3.5.2 RISK ASSOCIATED WITH RADIOTHERAPY

Survivors of childhood cancer who have had radiotherapy are at greater risk of an SPC than those who have not.17 Although the risk increases with dose13,19-23 there is not a direct linear relationship between risk and integral dose received and there appears to be a risk even at very low doses.24

Studies looking specifically at breast cancer as an SPC have reported increased risk following radiotherapy to the breast region in childhood.10,20,25

Studies looking specifically at the risk of subsequent thyroid tumours following irradiation of the neck region have shown that at radiotherapy dose > 3,000 cGy SPC of the thyroid becomes unlikely.26

Whilst most SPC occur within the radiotherapy field, there is no demonstrable link between the volume of the body irradiated and development of SPC.27

In one analysis the cumulative incidence of colorectal cancer for survivors treated with abdominopelvic irradiation was 1.4% (95% CI 0.7% to 2.6%) by age 50 years, which the authors concluded was comparable with the 1.2% cumulative incidence in individuals with at least two first degree relatives affected by colorectal cancer.8

Radiotherapy induced tumours are unlikely earlier than five years after treatment but then increase in incidence with length of follow up to around 30 years. Data are limited for follow up of more than 30 years and the pattern of risk with longer follow up is not consistent.19,23

The risk of developing a subsequent tumour is greatest within or just at the edge of the originally irradiated area, 50-75% occurring in these locations.22,28,29

It is important to remember which regions of the body have been exposed by being in the path of the beam entry or exit. For example, the mediastinum and abdomen are irradiated in conventional craniospinal radiotherapy, where the target is the brain and spinal cord.

There is evidence of increased risk of meningioma following radiotherapy to the brain.30

Healthcare professionals should be aware that all survivors of childhood cancer who were treated with radiotherapy are at risk of subsequent primary cancer and should adopt a high index of suspicion when assessing health concerns.

3.5.3 RISK ASSOCIATED WITH CHEMOTHERAPY

Mortality

The CCSS reported an increased risk of death from SPC following exposure to alkylating agents (relative risk (RR) 2.2, 95% CI 1.6 to 3.0) and epipodophyllotoxins (such as etoposide) (RR 2.3, 95% CI 1.2 to 4.5) but not anthracyclines or bleomycin. This study examined death records in a survivor population up to 30 years post-diagnosis.31

Risk of subsequent primary cancer

Several studies have demonstrated an increase in both leukaemia and solid SPCs over the past decades (1940 to 1990, 1960 to 2005 and 1970 to 2000) which the authors have attributed to increasing intensity of chemotherapy.11,32,33
In the CCSS there was an overall increased risk of SPCs with increasing dose of anthracyclines and epipodophyllotoxins (p=0.002 for the trend) but not alkylating agents or platinum.\textsuperscript{14}

One study on the incidence of SPCs following chemotherapy for treatment of osteosarcoma found that the incidence of SPC after follow up of between four and 33 years was not associated with which type of chemotherapy (adjuvant versus neoadjuvant), the drugs which were used nor dose intensity of the treatment.\textsuperscript{32}

One study found an association between SPC, at a median of 13 years follow up, and the cumulative dose of cyclophosphamide (p=0.009) and etoposide (p<0.001) in patients who had relapsed acute lymphocytic leukaemia at age up to 18 years.\textsuperscript{34}

A German case control study reported an OR for SPC for any chemotherapy of 2.5 (95% CI 1.4 to 4.5). For alkylating agents the OR was 2.6 (95% CI 1.7 to 3.9), 2.0 (95% CI, 1.4 to 2.9) for platinum agents, 1.8 (95% CI 1.2 to 2.6) for vinca alkaloids and 1.4 (95% CI 1.0 to1.8), for both epipodophyllotoxins and antimetabolites There was no increased risk with anthracyclines or asparaginase.\textsuperscript{35}

A combined British/French study reported an association between increased risk of SPCs and exposure to alkylating agents (RR 2.04, 95% CI 1.40 to 2.96) and intercalating agents (RR 1.69, 95% CI 1.17 to 2.45).\textsuperscript{24}

3.5.4 RISKS ASSOCIATED WITH COMBINED CHEMOTHERAPY AND RADIOTHERAPY

In a study of children with soft tissue sarcoma, treatment with radiation and chemotherapy was associated with a significantly higher risk of SPC compared with surgery alone (observed/expected ratio of 15.2 versus 1.4; p<0.0001).\textsuperscript{36}

A meta-analysis of 9,312 patients of all ages treated for Hodgkin's lymphoma found a significantly greater risk of SPCs following radiotherapy than combined radiotherapy/chemotherapy and a higher risk for combined treatment than chemotherapy alone.\textsuperscript{27}

One study found an increased risk of SPC of any type with combined modality treatment in childhood Hodgkin's lymphoma patients (p= 0.047).\textsuperscript{37}

A Nordic case control study showed no increased risk with chemotherapy alone but the RR for radiotherapy alone was 2.3 (95% CI 1.4 to 3.7) compared with 4.3 (95% CI 2.6 to 7.0) for combined chemotherapy and radiotherapy.\textsuperscript{35}

A Dutch study found an SIR for SPC for chemotherapy alone of 6.78 (95% CI 3.61 to 11.6), radiotherapy alone 15.4 (95% CI 7.41 to 28.4) and combined modality treatment 15.7( 95% CI 7.17 to 29.8).\textsuperscript{15}

Summary

The evidence examining the risk of SPC in patients receiving combined modality treatment is inconclusive. Radiotherapy alone is generally associated with higher risk of SPC than chemotherapy alone but the data for combined radiotherapy/chemotherapy are conflicting with a number of studies finding combined therapies are associated with a higher risk of SPC than radiotherapy alone but one systematic review, across all ages reporting a magnitude of risk lower than with radiotherapy alone.\textsuperscript{25} This finding may be a tumour-specific effect where chemotherapy-induced menopause is protective against the carcinogenic effect of radiotherapy on breast tissue in young women treated for Hodgkin's lymphoma.\textsuperscript{25}
3.6 CANCER SCREENING AND SURVEILLANCE IN SURVIVORS OF CHILDHOOD CANCER

No studies were identified which explored any benefits or harms of specific screening programmes for survivors of childhood cancer, nor were any studies identified on outcomes for survivors of childhood cancer entering national screening programmes at an earlier age than for general population groups.

In 2003, the Department of Health launched a UK-wide patient notification exercise in which women who had a diagnosis of Hodgkin's lymphoma after 1962 and before the age of 35 years, and who had mantle radiotherapy were offered regular check ups (including scanning and mammography) until they were old enough to be routinely screened as part of the NHS Breast Screening Programme. Women with a known history of breast cancer were excluded. Implementation and screening results from one cancer network concluded that the programme appeared to detect breast cancers at an early stage with an acceptable negative biopsy rate but that evaluation at a national level is required.

No evidence was identified on the potential value of advice to avoid unnecessary diagnostic radiation exposure.

General practitioners should:

- use practice information systems to actively identify survivors of childhood cancer
- be aware that those survivors of childhood cancer who have underlying genetic abnormalities are at additional increased risk of subsequent primary cancer
- provide regular review focusing on patient awareness and early identification of health problems
- be aware of patterns of presentation of subsequent primary cancers and have a lower threshold for referral to specialist services in this patient group, indicating their concerns on that referral
- promote participation in national screening programmes and emphasise the importance of healthy lifestyle behaviours in this patient group.

End of treatment summaries for patients with childhood cancer should provide guidance around the lifelong increased risk of subsequent primary cancers.
4 Fertility issues

4.1 INTRODUCTION

An important issue for survivors of childhood cancer is the impact of their disease and its treatment on reproductive function and the implications for the health of their offspring.

In both girls and boys, the pre-pubertal gonad is not protected against the adverse effects of chemotherapy or radiotherapy. The degree of damage is related to agent and dose. Age is also a factor; adolescent girls have a higher risk of ovarian failure after abdominopelvic radiotherapy than younger girls.

The UK Royal Colleges have produced a guideline on the management of the effects of cancer treatment on reproductive function in adults.

Specialist referral should be considered where there is patient or professional concern around fertility in survivors of childhood cancer.

Fertility counselling should be provided for survivors of childhood cancer.

4.2 RISKS TO FERTILITY ASSOCIATED WITH TREATMENT FOR CHILDHOOD CANCER IN MALES

4.2.1 NORMAL PHYSIOLOGY

The seminiferous epithelium of healthy infant and child testes consists of immature Sertoli cells and spermatogonia. Primary spermatocytes, which degenerate and do not progress to spermatozoa, have been identified in some boys between the ages of four and 13 years. Spermarche occurs at a median age of 13.4 years (range 11.7-15.3) at a time when median testicular size is 11.5 ml (range 4.7-19.6). The pre-pubertal testis is approximately 2 ml in volume. The onset of puberty begins with enlargement of the testis at approximately 11.4 years. The longitudinal growth spurt starts when the testes are approximately of 8 ml volume and maximal at approximately 12 ml. The healthy adult testis volume is 15-25 ml. Azoospermia is likely if the volume of each adult testis is 10 ml or less. As the endocrine function of the testis (Leydig cell activity) is relatively independent of Sertoli cell function and spermatogenesis, spontaneous progression through puberty is not a guarantee of future fertility.

4.2.2 SPERMATOGENESIS

While fertility is a key outcome of importance to patients, it is challenging to study in childhood cancer survivors. Surrogate markers are therefore often used. These include semen analysis, and, less directly, the hormones, follicle stimulating hormone (FSH) and inhibin B.

Inhibin B is secreted by Sertoli cells and in adulthood its serum concentrations are quantitatively related to sperm production. Inhibin B and FSH can therefore be used as indirect markers of spermatogenesis, particularly where detailed semen analysis is not available.

Testicular volume <10 ml is associated with impaired spermatogenesis in the post-pubertal male. Testicular damage is also associated with elevated FSH and reduced serum inhibin B.

Both pre- and post-pubertal testes are susceptible to cytotoxic treatment by alkylating agents or radiotherapy to the gonads. Sertoli cells and germ cells are more susceptible than Leydig cells to chemotherapeutic or radiotherapeutic damage. Direct irradiation to the testes causes permanently impaired spermatogenesis.

Conditioning treatment (alkylating agent-based chemotherapy or total body irradiation) for a bone marrow transplant carries a high risk of spermatogenic damage, with most (70%, n=64) young adult patients becoming azoospermic following treatment. Some will show recovery: this was demonstrated in 90% of patients conditioned with cyclophosphamide, in 50% of patients with cyclophosphamide plus busulphan or thiotepa but in only 17% of patients with cyclophosphamide plus total body irradiation (TBI) or thoracoabdominal irradiation. Recovery can take several years, particularly after TBI.
The risk to spermatogenesis is related to the chemotherapy agent administered, and the cumulative dose received by the patient. Cumulative doses of alkylating agent-based chemotherapy (cyclophosphamide and procarbazine) have been shown to be related to abnormal inhibin B and FSH concentrations. Age at treatment was not a significant factor.69 In a study of males treated for osteosarcoma that included some pre-pubertal boys, ifosfamide dose was related to risk of azoospermia. Only one semen sample was obtained from a patient who was treated pre-pubertally; this showed azoospermia.70

Although there is evidence for impaired spermatogenesis after treatment for childhood cancer, it appears that the sperm that is produced, carries as much healthy DNA as sperm produced by the healthy population.71 Most studies suggest that fertility outcomes are good for young people treated for leukaemia, and solid tumours except Hodgkin’s lymphoma. Treatment for Hodgkin’s lymphoma with multiple courses of alkylating agent-based chemotherapy, irrespective of stage of puberty at treatment, is likely to be sterilising.49, 72-75 Recovery of spermatogenesis has been documented after anthracycline-based treatment alone.76

It is not possible to protect the pre-pubertal testes from potentially toxic chemotherapy nor is it appropriate outside of an ethically approved clinical study, to obtain germ cells for later use.

4.2.3 FERTILITY

A retrospective cohort study examined the fertility of 213 men treated for ALL before the age of 18 in comparison with sibling controls. Using the self reported measure of ever having fathered a child, there was no difference in the fertility between the study groups. In subgroup analysis, treatment with high dose (2,400 cGy) cranial radiotherapy without spinal radiotherapy before the age of 10 was associated with reduced fertility (RR 0.09, 95% CI 0.01 to 0.82).77

In an analysis of semen quality and fertility in 51 adult survivors of childhood ALL none of the survivors of high cumulative dose of cyclophosphamide and testicular irradiation had fathered a child.78

D The potential impact of cytotoxic treatment in young male patients with cancer should be considered in discussion with the patient and their parents in order to offer appropriate fertility preservation options.

D Men who have received cytotoxic treatment or gonadal radiotherapy should be offered access to fertility testing.

✓ Men who have evidence of impaired fertility should be referred for specialist assessment as they could benefit from assisted reproductive technology. This may include specialist psychological support.

4.2.4 RISK TO OFFSPRING OF MALE CANCER SURVIVORS

Pregnancy and infant outcomes for the first live birth were compared for fathers who had a cancer diagnosis at age 20 or younger. Compared with infants born to partners of matched males who had not undergone cancer treatment there was no increased risk of being small for gestational age or having malformations. Male to female infant ratios were unaffected.79

Pregnancy outcomes were reviewed for a self selected cohort of 4,106 sexually active male survivors of childhood cancer from the North American Childhood Cancer Survival Study. The proportion of the pregnancies which resulted in a live birth was significantly lower than the sibling comparison group (RR 0.79, 95% CI 0.65 to 0.96) with increased risk of miscarriage (particularly associated with procarbazine but not cyclophosphamide dose) and induced abortion.80

4.2.5 TESTOSTERONE PRODUCTION

Testosterone production by the Leydig cells of the testis is relatively resistant to the adverse effects of chemotherapy. Total body irradiation and other radiotherapy to the testis carries a risk of Leydig cell failure with hypergonadotrophic hypogonadism.81 Partial loss of Leydig cell function may manifest with normal testosterone but elevated luteinising hormone (LH) concentrations.82 Such individuals are likely to be at risk of progressive decline in testosterone production but the timescale and degree of risk are unknown.
In a cohort of eleven pre-pubertal boys treated with high dose alkylating agent for osteosarcoma, all progressed through puberty normally.\(^7\)

Pubertal onset should be closely monitored in boys who have received radiotherapy to the testes, with early testosterone supplementation considered.

### 4.2.6 Sexual Function

In a systematic review there was some evidence of an increase in prevalence of sexual dysfunction in men treated for lymphoma in comparison to the general population, although most studies were poor quality. Sexual dysfunction was associated with depression, relapse, and low testosterone concentrations.\(^8\)

Treatment of some genitourinary childhood cancers (eg pelvic rhabdomyosarcoma) involves extensive local therapy which can adversely affect sexual function.\(^9\) Other than in such cases, no evidence was identified on the prevalence of sexual dysfunction in male survivors of childhood cancer, but similar risk factors are likely to be relevant to those in adults.

### 4.3 Risks to Fertility Associated with Treatment for Childhood Cancer in Females

#### 4.3.1 Normal Physiology

It is currently understood that the ovary establishes a non-renewable reserve of several million non-growing follicles (NGFs) at around five months of gestational age which is followed by a decline to the menopause when approximately 1,000 remain at an average age of 50–51 years.\(^1\)

Primordial follicles consist of an immature oocyte surrounded by a single layer of spindle-shaped cells, and a small proportion are constantly entering the growth phase throughout life, including in childhood. Accurate measurement of the number of NGFs in the human ovary in life (the ovarian reserve) is not possible. Anti-Mullerian hormone (AMH) is a product of growing ovarian follicles and can be used as an indirect marker of the ovarian reserve in women attending for investigation and management of infertility. A recent model of AMH from birth to menopause shows that serum AMH concentrations rise slowly through childhood and adolescence, with a peak at age 24.5 years followed by a steady decline thereafter.\(^2\)

The onset of female puberty is characterised by the appearance of breast buds (breast stage 2, B2) which may be as early as 8.4 years of age or delayed until 13.5 years of age. Any girl with breast buds before the age of 8.4 years has precocious puberty, whilst the absence of breast development in a girl older than 13.5 years requires endocrine assessment to ascertain the cause of the delay.\(^3\)

Ovarian follicles are both hormone-producing and the site of gamete development, thus their depletion results in both infertility and oestrogen deficiency.

#### 4.3.2 Ovarian Function

Both chemotherapy and radiotherapy can affect ovarian function. A retrospective study of 3,390 childhood cancer survivors found that 6.3% developed acute ovarian failure (AOF) (defined as never menstruating or ceasing menses within five years of their diagnosis) as a result of cancer treatment. The treatments most associated with AOF were; ovarian irradiation with a dose of at least 1,000 cGy, exposure to procarbazine and exposure to cyclophosphamide.\(^4\)

Radiotherapy to the pelvis/abdomen is associated with ovarian failure. This is related to age at treatment.\(^4,8\) A review reported the effective sterilising dose (ESD: dose of fractionated radiotherapy (cGy) at which premature ovarian failure occurs immediately after treatment in 97.5% of patients). The ESD decreases with increasing age at treatment, being 2,030 cGy at birth, falling at 10 years to 1,840 cGy, at 20 years to 1,650 cGy and at 30 years to 1,430 cGy.\(^9\)

Assessment of pre-pubertal ovarian function has been problematic due to the physiological quiescence of the hypothalamo-pituitary-ovarian axis. The measurement of AMH is possible at all ages but further data are required to demonstrate its utility in clinical practice.\(^10\)
AMH concentration in blood may reflect gonadal damage in pre-pubertal and pubertal girls, with absent recovery in girls treated with high-risk regimens. In adults, pre-treatment AMH is predictive of post-chemotherapy ovarian function but this has not been demonstrated in girls or adolescents.

4.3.3 HORMONE DEFICIENCY

Gonadal failure causes hormone deficiency with consequences for bone, cardiovascular and cognitive health. There is some evidence that hormone replacement therapy (HRT) based on physiological rather than pharmacological doses may be beneficial to cardiovascular health.

Pubertal induction with appropriate sex steroid replacement therapy should be managed by a paediatric endocrinologist.

4.3.4 FERTILITY

In a retrospective study of fertility in 5,149 female childhood cancer survivors compared with randomly selected siblings, the relative risk of ever being pregnant was 0.81 (95% CI 0.73 to 0.90). Infertility was most associated with hypothalamic or pituitary radiation dose ≥3,000 cGy or ovarian or uterine dose >500 cGy. Females with a summed alkylating agent dose score of three or four or who were treated with lomustine or cyclophosphamide were also at risk of infertility.

Pubertal onset should be closely monitored in girls who have received abdominopelvic radiotherapy or cytotoxic therapy.

Assessment of adult ovarian function should be offered to women who have received abdominopelvic radiotherapy or cytotoxic therapy.

Women who have evidence of impaired fertility should be referred for specialist assessment as they could benefit from assisted reproductive technology. This may include specialist psychological support.

4.3.5 PREGNANCY AND BIRTH

For cardiac issues related to pregnancy see section 5

Most studies show that chemotherapy does not have adverse effects on uterine function or pregnancy outcomes, other than increased risk of miscarriage shortly after chemotherapy, related to damage to oocytes. In contrast, abdominopelvic radiotherapy is associated with adverse effects on uterine function with increased risk of late miscarriage, prematurity, low birth weight, stillbirth, neonatal haemorrhage and postpartum haemorrhage. The effect is age related, the younger the patient at treatment the greater the adverse effect on uterine function.

An increased risk of prematurity and low birth weight was demonstrated in an analysis of 2,201 children of 1,264 survivors. The prevalence of prematurity was 21.1% versus 12.6% in siblings' children; OR 1.9, 95% CI 1.4 to 2.4. Radiotherapy to the uterus (>500 cGy) was associated with an increased risk of being born preterm (50.0% versus 19.6% OR 3.5, 95% CI 1.5 to 8.0), with low birth weight (36.2% versus 7.6%; OR 6.8, 95% CI 2.1 to 22.2), and small for gestational age (SGA) (18.2% versus 7.8%; OR 4.0, 95% CI 1.6 to 9.8) compared with the children of survivors who did not receive any radiotherapy. At lower uterine radiotherapy doses there was association with increased risks of both pre-term birth (doses from 50 cGy) and low birth weight (from 250 cGy). Chemotherapy (both alkylating and non-alkylating) was not associated with increased risk of prematurity or low birth weight.

In a US cancer registry based study of 1,898 female childhood cancer survivors, compared with women who had no history of cancer, the relative risk of pre-term birth was 1.54 (95% CI 1.30 to 1.83) and RR of weighing less than 2,500 g was 1.31 (95% CI 1.10 to 1.57) although the risk of SGA was not increased. Chemotherapy and any radiotherapy were both associated with increased risk of pre-term birth and low birth weight. There was no increased risk of infant death or malformations. Caesarean section was not more common in women who had had abdominal or pelvic cancer. The increased obstetric risks related to chemotherapy reported in this study are novel findings that need to be confirmed in larger well controlled studies.
Women who have had radiotherapy treatment to a field which included the uterus are at increased risk of adverse pregnancy outcome. Pre-conception counselling may be appropriate and women should be advised that pregnancy should be supervised in a high risk obstetric unit.

4.3.6 SEXUAL FUNCTION

Pelvic radiotherapy is associated with sexual dysfunction in adult women, and a systematic review found some limited evidence for benefit of psychological intervention. This is likely to be relevant to the treatment of girls and adolescents, but no direct evidence was identified.

4.4 PROTECTING FERTILITY

4.4.1 PRINCIPLES

Pre-treatment assessment requires individualised evaluation of the risk of treatment to fertility. See Table 2 for a system of risk assessment.

<table>
<thead>
<tr>
<th>Table 2: Risk assessment for fertility preservation</th>
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<tbody>
<tr>
<td><strong>Intrinsic factors</strong></td>
</tr>
<tr>
<td>Health status of patient</td>
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<tr>
<td>Consent (patient/parent)</td>
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<tr>
<td>Assessment of pubertal stage in boys/young men (including testicular volume)</td>
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<tr>
<td>Assessment of ovarian reserve in girls/young women</td>
</tr>
<tr>
<td><strong>Extrinsic factors</strong></td>
</tr>
<tr>
<td>Nature of predicted treatment (high/medium/low/uncertain risk)</td>
</tr>
<tr>
<td>Time available</td>
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<tr>
<td>Expertise available</td>
</tr>
</tbody>
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Good links are required between paediatric and adolescent oncology units and fertility services to promote rapid referral and pre-treatment assessment of young patients who may benefit from fertility preservation.

4.4.2 PROTECTING FERTILITY IN BOYS UNDERGOING TREATMENT FOR CHILDHOOD CANCER

Fertility preservation in post-pubertal males involves freezing and storing of samples of semen for future use in assisted conception. Successful storage has been reported in a high proportion (67%) of post-pubertal boys. In young teenage patients semen collection may be restricted by willingness or ability to masturbate.

With modern assisted reproductive technology, in particular intracytoplasmic sperm injection, a low sperm count should not preclude fertility.

Teenage boys should be referred for semen cryopreservation if their fertility is considered to be at risk.

Assessment of male pubertal development and fertility should include: assessment of testicular volume using the Prader orchidometer, Tanner staging of secondary sexual development, measurement of serum FSH, luteinising hormone, testosterone and semen analysis.

Cryopreservation of testicular tissue has been proposed for pre-pubertal boys. Data from surveys demonstrate that this may be acceptable to patients and their parents. At present there is no technique sufficiently established to offer to pre-pubertal boys outwith a clinical trial.
4.4.3 PROTECTING FERTILITY IN GIRLS UNDERGOING TREATMENT FOR CHILDHOOD CANCER

Oocyte cryopreservation is increasingly used for fertility preservation in adult women.\(^\text{107}\) This may also be an option in post-pubertal girls.

Several case series of ovarian cortex cryopreservation in girls and young women have been reported. These demonstrate that such surgery is safe and feasible by laparoscopy without delaying cancer treatment\(^\text{108,109}\) but this approach remains experimental. It should only be considered in the context of a clinical trial.

No pregnancies have been achieved following reimplantation of ovarian tissue harvested before puberty although pregnancies obtained after implantation of frozen thawed ovarian tissue in adults have validated this approach.\(^\text{102}\)

**D** Cryopreservation of ovarian tissue (within the context of a clinical trial) should be considered in girls at high risk of premature ovarian insufficiency.

Hormonal suppression of ovarian activity by gonadotropin-releasing hormone analogues to protect the ovary against cytotoxic insult has been proposed in adults. Randomised controlled trials in adults have produced conflicting results and there are no data demonstrating efficacy in girls and adolescents.\(^\text{5,110,111}\)

Ovarian transposition has also been used in adults to move the ovaries out of a proposed radiation field.\(^\text{40}\) There are no data on the efficacy of this approach in girls and adolescents.

4.5 RISK OF CONGENITAL ABNORMALITIES IN OFFSPRING OF SURVIVORS OF CHILDHOOD CANCER TREATMENT

A Danish population based cohort examined the association between gonadal and uterine radiation doses received by 3,963 parents and risk of malformation in offspring. The prevalence of congenital malformations in offspring of cancer survivors was not statistically different from that in offspring of sibling controls (prevalence proportion ratio 1.1, 95% CI 0.8 to 1.5) or offspring of the general population (observed to expected ratio 1.2, 95% CI 0.9 to 1.6). This held true when including malformations diagnosed later in life.\(^\text{112}\)

Data from the CCSS also provide strong evidence that neither chemotherapy nor gonadal radiotherapy increase the risk of congenital abnormality in children of childhood cancer survivors.\(^\text{113}\) In 4,699 children of cancer survivors, the prevalence of abnormality was 2.7%. Regression analysis found no statistically significant dose effect of chemotherapy with alkylating agents or radiotherapy to the testes or ovaries and the risk of congenital abnormality in offspring.

Genetic disease and pregnancy outcomes were reported in a population based cohort of 472 Danish survivors of cancer in childhood and adolescence (1,037 pregnancies). This study found no significant association between genetic disease in children and parental treatment with alkylating agents or pre-conception radiation to the gonads in males or females. The risk of genetic disease was similar among the children of irradiated survivors compared with the children of non-irradiated survivors (RR 1.02, 95% CI 0.59 to 1.44). The risk was unchanged amongst those who received alkylating agents both when compared with those who did not receive chemotherapy (RR 0.9, 95% CI 0.5 to 1.3) and those without any potential mutagenic treatment (RR 0.8, 95% CI 0.3 to 2.1).\(^\text{114}\)

**C** Healthcare professionals should provide reassurance to survivors of childhood cancer that their offspring are not at increased risk of congenital abnormality.
5 Cardiac effects

5.1 INTRODUCTION

Evidence on the cardiotoxic effects of chemotherapy and/or radiotherapy in the treatment of children with cancer comes from retrospective cohort studies, which cover a wide range of ages and heterogeneous treatments. A variety of tools are used for assessment and definitions of subclinical and clinical disease vary. Most studies reflect the effects of historic treatment schedules.

5.2 TREATMENT-RELATED EFFECTS

5.2.1 ASSOCIATION WITH CHEMOTHERAPY

There is an association between exposure to anthracyclines and chronic cardiotoxicity and heart failure in children and in adults. A systematic review found that the risk of late-onset cardiotoxicity increased with higher cumulative doses of anthracyclines, younger age (< 5 years) at exposure, female gender, combination therapy with other agents (cyclophosphamide and amascrin) and mediastinal radiation. Efforts to limit this potential cardiotoxicity with cardioprotective agents, liposomal preparations and prolonged anthracycline infusions have yielded mixed results.

Anthracycline-associated heart damage is now thought to occur largely at the time of exposure, but may take many years to manifest clinically. Patients should therefore be counselled to pay strict attention to risk factors for cardiac morbidity such as smoking, hypertension, obesity and coronary heart disease.

In a long term follow-up study, data from 830 children in a Dutch registry were used to examine the risk of anthracycline-induced congestive heart failure (A-CHF). The risk of A-CHF was strongly dose dependent. While the overall estimated risk of A-CHF was low; rising from 2% at two years to 5.5% at 20 years post-treatment, the risk for those receiving doses >300 mg/m² was 10% at 20 years. In patients treated with doses <300 mg/m² the estimated risk of A-CHF at two years was 0.5% and this did not significantly increase with further follow up. In this study 76% of cases of A-CHF developed within the first year of commencing anthracycline therapy. Of 53 patients in the cohort who became pregnant none developed peripartum A-CHF.

Similar data were presented in a retrospective review of clinical and subclinical cardiotoxicity in children with acute myeloid leukaemia (AML) treated with 300-450 mg/m² equivalent dose daunorubicin. Early cardiotoxicity (within one year of treatment) was reported in 4.3% of patients and late cardiotoxicity in 2.9% Subclinical disease was defined as fractional shortening (FS) <30% by echocardiogram.

An anthracycline dose >250 mg/m² was associated with symptomatic congestive cardiac failure (5.2-fold excess risk, p<0.001) in the CCSS. There were methodological limitations to this questionnaire based survey.

In a comparison of childhood cancer survivors exposed to anthracyclines with normal healthy controls, there was a 4.5-fold excess risk of abnormal non-invasive cardiac tests (including FS) with cumulative anthracycline doses of ≥ 270 mg/m² with uncertain clinical significance.

A study of pregnancy outcomes in women treated with doxorubicin for childhood malignancy found that there was no further deterioration in cardiac function in those with FS in the normal range but in those with FS < 30% there was a median 19% decrease in FS, although this was not statistically significant ( p=0.08 ). This indicates that, while pregnancy is unlikely to induce A-CHF, it may exacerbate any cardiac dysfunction which is present.

✔ Women who are pregnant or planning a pregnancy do not require repeat echocardiograph if they have had a normal test result in the previous three years.
5.2.2 ASSOCIATION WITH RADIOTHERAPY

There is a lack of consistency in published data with respect to methodology, study population and control groups when examining the association of radiotherapy with cardiac adverse effects. Most studies report an increased risk of cardiovascular events and cardiovascular disease following cardiac irradiation and this risk is dose dependent. In a systematic review, the estimated cumulative incidence of cardiovascular events and cardiovascular mortality in those exposed to cardiac irradiation during treatment for childhood cancer, ranges from 0.3-22.8% and 0-3.5% respectively. Across studies the standardised (for duration of follow up, age and gender) cardiovascular mortality ratio compared to the general population ranged from 0 to 68, data from four studies were meta-analysed giving a pooled standardised mortality ratio of 28.4.125

 Mediastinal irradiation as treatment for Hodgkin's lymphoma increases the incidence of coronary artery disease, myocardial infarction, valvular problems and pericardial disease.126,127 The risk increases with high mediastinal doses (≥3,000 cGy), minimal protective cardiac blocking and young age at irradiation.127,128 These observations support the use of combined modality, high dose irradiation regimens in children and adolescents and suggest the need for cardiac screening of treated patients.

Whilst there is evidence that irradiation at levels over 3,000 to 3,500 cGy is a risk factor for cardiac disease in later life, there is insufficient evidence to comment on the lower dose range of 2,000 to 2,500 cGy. Irradiation induces atheromatous lesions of the proximal part of the coronary arteries. There is some evidence that high density lipoprotein blood levels may be altered after radiotherapy.126-135

5.2.3 RECOMMENDATIONS

C Survivors of childhood cancer who received either anthracyclines or radiation to a field that included the heart should be assessed with respect to cardiac muscle function.

D Healthcare professionals should reassure survivors of childhood cancer who did not receive anthracyclines or radiation to a field that included the heart that the lifelong risk of treatment-related cardiac problems is very low.

5.3 ASSESSMENT FOR CARDIAC PROBLEMS

Exposure to cardiotoxic chemotherapeutic agents is an indication for baseline and subsequent re-evaluation. Echocardiography is non-invasive and has the added advantage of evaluating structural changes in the valves and pericardium that may develop secondary to radiotherapy. Several parameters have been used to assess left ventricular function on echocardiography. Of these, FS and ejection fraction (EF) are the most frequently used parameters.117

In addition to systolic dysfunction, reduced diastolic function has also been demonstrated during anthracycline therapy, but controversy exists about the value of these diastolic measures. New echo techniques such as tissue Doppler may offer increased sensitivity.136

Biochemical markers such as troponin, atrial and brain natriuretic peptides have been shown in adult and paediatric studies to be elevated in patients after they received chemotherapy. While some of these studies have shown an increased incidence of subclinical cardiac dysfunction, they have not been proven to correlate with clinical cardiac dysfunction at a later stage. Serum markers of cardiac injury as predictor of future dysfunction remain investigational and cannot be recommended as part of routine monitoring.117

US guidelines provide a conservative recommendation for periodic screening based on age, cumulative dose of anthracycline and chest radiation but these recommendations based on expert opinion cannot be validated.137 Dutch guidelines also recommend risk-based screening.138

No studies were identified which assessed the effectiveness of screening programmes on outcomes for survivors of childhood cancers.
Survivors of childhood cancer who have had anthracyclines or radiation to a field that includes the heart should have long term monitoring for cardiac dysfunction using echocardiography to determine fractional shortening and ejection fraction.

患者无症状的左心室功能障碍（LV dysfunction）后，要求长期的超声心动图监测，因为预后是不确定的。

超声心动图的频率应根据低风险患者亚群的累积剂量和风险因素来个体化，对于低风险患者，使用累积剂量少于250 mg/m²的人，最大间隔为五年。

高风险人群，累积剂量大于250 mg/m²，或已经接受过心脏区域的放疗，应每隔2-3年进行筛查。

5.4 TREATMENT OF CARDIAC PROBLEMS

有有限的证据支持使用依那普利（enalapril）和β-阻断剂（carvedilol）等药物来治疗蒽环类药物诱导的心肌病。一项研究发现，接受早期治疗的亚临床心脏功能障碍的患者，其心脏功能比延迟治疗或未接受治疗的患者有所改善。

一项针对儿童癌症幸存者的研究表明，虽然依那普利治疗可以为无症状左心室功能障碍（LV dysfunction）的患者带来6-10年的益处，但这只是暂时延迟了自然历史，最终会恢复至基线水平。在心脏衰竭的患者中，依那普利的益处为2-6年，但管理失败后，预后较差。

依那普利并不能解决心室壁厚度的问题，而是通过降低血压和左心室（LV）的直径来降低阻力。

患者发生心力衰竭时，应根据心力衰竭治疗的证据指南进行治疗。

患者应被告知健康生活方式的重要性，特别注意吸烟行为、锻炼和避免肥胖。

医护人员应监测冠状动脉疾病的风险因素，如高血压和高脂血症，这些因素可能影响心脏对心力衰竭的易感性。

长期内随访幸存者

- 患者应被告知健康生活方式的重要性，特别注意吸烟行为、锻炼和避免肥胖。
- 医护人员应监测冠状动脉疾病的风险因素，如高血压和高脂血症，这些因素可能影响心脏对心力衰竭的易感性。
6 Bone health

6.1 BONE PHYSIOLOGY AND DIAGNOSTIC APPROACHES

6.1.1 OSTEOPOROSIS

Bone mass increases rapidly during growth and puberty and reaches its peak in the third decade of life. Children treated for cancer during the period of normal accrual of bone mass may be at risk of reduced peak bone mass due to the disease process itself or the treatment received.\(^{140}\)

Bone is a dynamic tissue, in which bone formation (via osteoblast cells) and bone resorption (via osteoclast cells) takes place throughout life in response to mechanical and metabolic influences. If osteoclast production is increased or if osteoblast production is decreased, bone mass is decreased. Osteoporosis (low bone mineral density (BMD)) may result in susceptibility to bone fractures.\(^{141}\)

Three diagnostic approaches are commonly used to assess bone parameters in children; dual energy X-ray absorptiometry (DXA), peripheral quantitative computed tomography and quantitative ultrasound. It is recommended that a single modality be used to evaluate BMD as results are not directly comparable across methods.\(^{142}\)

In adults, the definition of osteoporosis is dependent on a T score, which is the standard deviation (SD) score of the observed areal BMD compared with that of a healthy young adult at peak bone density (T score \(<-1\) SD indicates osteopenia whereas T score \(<-2.5\) SD indicates osteoporosis). This is not appropriate in children. Age-and sex-matched standards may not be sufficient in children with chronic disease, who often suffer from growth retardation and pubertal delay. The International Society for Clinical Densitometry stated that secondary osteoporosis should not be diagnosed in children based solely on DXA BMD.\(^{143}\) The Society’s position is that the diagnosis of osteoporosis in children necessitates the co-existence of a clinically significant fracture and a low BMD or bone mineral content (BMC). Long bone fractures of the lower limbs, compression fractures of vertebrae and two or more long bone fractures of upper limbs are considered significant clinical history of fracture. Low BMC or BMD is defined as a BMC or areal BMD Z-score \(\leq -2.0\), adjusted for age, gender and body size, as appropriate.\(^{144}\)

6.1.2 OSTEONECROSIS

Osteonecrosis, also known as avascular necrosis, occurs as a result of interruption of blood flow to an area of bone. This leads to necrosis at one or more bone sites, usually affecting weight bearing joints, with hips and knees most affected. The exact pathogenesis is unclear, however high dose steroids have been identified as a major cause.\(^{145}\) Osteonecrosis commonly occurs during chemotherapy or within the first years after completing treatment. It may result in long term pain and immobility.\(^{146,147}\)

6.2 MECHANISM OF EFFECTS OF CANCER TREATMENTS

Glucocorticoids are essential components in treating cancer. Glucocorticoids have an inhibitory effect on osteoblast number, increasing osteoblast and osteocyte apoptosis. A study in children receiving chemotherapy for leukaemia demonstrated an imbalance between markers of bone formation and bone resorption and reversibility.\(^{148}\) This is particularly marked during periods of high dose glucocorticoids therapy. As well as glucocorticoids, high dose methotrexate is also likely to have an adverse effect on bone turnover in favour of bone resorption.\(^{149}\)

The dose-dependent effects of radiotherapy on BMD may be due to disruption in the hypothalamic-pituitary axis, which leads to growth hormone deficiency and gonadal dysfunction.\(^{150}\)
6.2.1 STUDIES ACROSS CANCER TYPES

In a cross-sectional study, childhood cancer survivors more than five years post diagnosis but still under 18 years of age, had lower total body and lumbar spine BMD (BMD Z-scores ≤-1) compared with their siblings. Children with BMD Z-scores ≤-1 are likely to have a lower peak bone density that may predispose them to early osteoporosis and increased risk of fracture later in life. There is uncertainty as to whether survivors of childhood cancer continue to have a low BMD in the long term. A large cohort study (n=7,414), found no significant increase in the fracture rates among survivors when compared with healthy siblings at median follow up of 23 years.

6.2.2 STUDIES IN SPECIFIC PATIENT GROUPS

**Acute lymphoblastic leukaemia**

Low BMD in survivors of childhood ALL (age ranges from 10 to 45 years) who completed therapy at least 1.5 years earlier, is described in a large number of studies. One study of survivors of ALL (n=56, mean age 13.5 years and mean time since completion of therapy 6.1 years) found that, 12% and 8% had low lumbar spine BMC Z score (<-1.0) and total body BMC Z score(<-2) (corrected for size) respectively. There is some evidence that BMD improves with time in this group.

**Hodgkin's lymphoma**

Observational studies of survivors of Hodgkin's lymphoma have conflicting results with three studies reporting a decreased BMD and one study reporting only negligible BMD deficits.

**Solid tumours**

Survivors of solid tumours (lymphoma, sarcoma, Wilms' tumour, and neuroblastoma) in childhood are reported to have reduced BMD. In one study there was a statistically significant positive correlation between the number of chemotherapy drugs administered and BMD Z score in the lower extremities. In survivors of brain tumours there was a loss of bone mineral and a positive correlation between BMD Z score of the lumbar spine and overall health and quality of life. One study suggests that bone deficit may be due to other factors such as inadequate vitamin D and calcium intake.

6.3 RISK FACTORS ASSOCIATED WITH LOW BONE MINERAL DENSITY

6.3.1 BONE MARROW TRANSPLANTATION

Survivors of childhood allogeneic bone marrow transplantation are at risk of reduced BMD and osteonecrosis. It is unclear if this is related to the transplantation itself or associated with disease factors or treatment interventions such as steroid use.

6.3.2 CHEMOTHERAPY/GLUCOCORTICOIDS

In ALL survivors, lower BMD was associated with treatment with higher cumulative doses of glucocorticoids (GCs) (>9,080 mg/m² prednisone equivalent) methotrexate (MTX) (>25,000 mg/m²) and 6-mercaptopurine. It has also been found that children who received chemotherapy with no central nervous system (CNS) irradiation in their protocol have a slight reduction in lumbar spine BMD and apparently normal femoral neck-BMD. Femoral neck BMD is affected in those children who received high dose of MTX and GCs compared with age matched healthy controls.

6.3.3 CRANIAL IRRADIATION

Cranial irradiation is reported to have a detrimental effect on BMD and bone growth in ALL survivors. This may result from damage to the hypothalamic-pituitary axis, which leads to growth hormone deficiency (GHD). Some data show that cranial radiation exposure of ≥2,400 cGy is associated with low BMD (Z-score ≤-1). This effect is dose dependent. Within the modern era of leukaemia therapy, the CNS irradiation dose (1,800 cGy) has shown a minimum effect on BMD as the incidence of growth hormone dysfunction in those children who received CNS irradiation has dropped significantly.
6.3.4 ENDOCRINE DYSFUNCTION

Childhood cancer survivors with hypogonadism and hypothyroidism\(^{151}\) together with GHD\(^{170}\) are more likely to have low BMD.

6.3.5 GENETIC/FAMILIAL FACTORS

Genetic polymorphisms in certain receptors of the corticotrophin-releasing hormone receptor-1 gene\(^{171}\) and the vitamin D receptor gene\(^{172}\) are associated with a lower BMD in ALL survivors. Caucasian race is another independent factor associated with low BMD in ALL survivors.\(^{153}\)

6.3.6 GENDER AND AGE

Some studies have reported that male ALL survivors and those older than 10 years at diagnosis are at higher risk of developing low BMD.\(^{150, 153, 171}\) Although males have higher incidence of low BMD than females, shorter females are at greater risk of developing low BMD than shorter males.\(^{156}\) In survivors of Hodgkin’s lymphoma who were diagnosed at median age 14 years, male sex was a risk factor for reduced BMD.\(^{160}\)

6.3.7 PHYSICAL INACTIVITY

Physical inactivity has a negative effect on BMD.\(^{173}\) There are conflicting data as to whether or not physical activity is reduced\(^{153, 154, 174}\) in ALL survivors when compared to healthy controls. Muscle strength in upper and lower extremities is positively correlated with BMD in long term survivors of childhood ALL.\(^{175}\) Decreased physical activity may be due to increased weight or obesity in ALL survivors particularly those younger than 19 years.\(^{176}\)

6.3.8 NUTRITIONAL FACTORS

Poor nutritional intake and reduced vitamin D level may have an impact on bone development in ALL survivors. In one study around one third of ALL survivors were not receiving the recommended dietary intake of calcium, vitamin D, magnesium and potassium.\(^{176}\) This finding must be interpreted in the context that most American children and adolescents did not meet recommended dietary intake of calcium.\(^{173}\) Furthermore, around 9% and 61% of the US healthy adolescent population have vitamin D deficiency (<15 ng/dl) and insufficiency (15-29 ng/dl) respectively.\(^{177}\) These results are similar to ALL survivors with the prevalence of vitamin deficiency at 11.5% and vitamin D insufficiency at 52%.\(^{178}\)

No studies were identified on the development of rickets in survivors of childhood cancer.

6.4 ASSESSMENT OF BONE HEALTH

No evidence based guidelines for assessment of bone health in childhood cancer survivors were identified. Long term follow-up guidelines based on expert consensus recommend a baseline evaluation of BMD at two years after completion of chemotherapy in those at high risk of BMD deficits.\(^{173}\)

Survivors of childhood cancer who have had the following interventions are at increased risk of BMD deficits and should have a baseline evaluation of BMD at around two years after completion of treatment:

- high cumulative doses of steroids
- high cumulative doses of methotrexate
- cranial irradiation
- bone marrow transplantation.

Evaluation of bone mineral density should also be undertaken in survivors whose treatment puts them at risk of endocrine dysfunction.
Repeat measures in patients with results within the normal range are not required unless there is a change in the clinical situation.

Interpretation of bone mineral density measurements should include consideration of whether a patient’s final height is compromised and the possibility of pubertal delay.

6.5 TREATMENT OF LOW BONE MINERAL DENSITY

6.5.1 LIFESTYLE MODIFICATION

No evidence was identified on the effectiveness of lifestyle modifications such as improving nutritional intake and physical activity levels, avoiding alcohol, caffeine and smoking in improving BMD in childhood cancer survivors. A small observational study in childhood ALL survivors found that BMD was correlated favourably with exercise and unfavourably with reporting positive for alcohol use.153

6.5.2 ENDOCRINE THERAPY

Childhood cancer survivors are at risk of hypogonadism and sex steroid replacement therapy should be optimised. It has been reported that sex steroid administration in premature ovarian failure has a beneficial effect on bone density.179

BMD in response to growth hormone therapy shows conflicting results.170,180

Endocrine evaluation is recommended for childhood cancer survivors who have a significant reduction in bone mineral density and/or recurrent fractures.

6.5.3 BISPHOSPHONATES

No evidence was identified on the use of bisphosphonates in childhood cancer survivors.
7 Metabolic syndrome

7.1 INTRODUCTION

Metabolic syndrome is associated with premature death due to macrovascular disease and diabetes. It is characterized by a number of features, but generally considered to include the triad of central adiposity/obesity, hypertension, and dyslipidaemia. Insulin resistance is also commonly included as a feature. The prevalence of obesity is increasing globally, resulting in an increase in the number of people diagnosed with the metabolic syndrome.

7.2 FACTORS ASSOCIATED WITH METABOLIC SYNDROME

Evidence surrounding the risks of developing metabolic syndrome for survivors of childhood cancer is conflicting and based on observational, mainly retrospective, studies at high risk of bias and confounding by factors such as genetic predisposition and body mass index at diagnosis, as well as disease and lifestyle-related factors such as impaired mobility. The majority of studies investigating metabolic syndrome in childhood cancer survivors are in those treated for ALL and brain tumours. It is not possible to extrapolate these results to other survivors. Interpretation of findings is also limited by changes in treatment protocols over time as well as variation between treatment centres.

A cross-sectional study found greater prevalence of metabolic syndrome in individuals reporting themselves to be survivors of childhood cancer when compared with those reporting no cancer history. One follow-up study found the prevalence of obesity in teenage survivors of childhood cancer to be no different to a matched comparison group from the general population. Several studies report that survivors of ALL and brain tumours in childhood are at increased risk of developing metabolic syndrome. Those who have received bone marrow transplantation and cranial radiotherapy resulting in hypothalamic damage and growth hormone deficiency appear to be at greatest risk. However, one study reported no increased risk of obesity in adult survivors of childhood brain cancer when matched to a general population group. It may be that GHD itself is associated with the increased risk of metabolic syndrome, as growth hormone (GH) therapy in survivors of ALL has been shown to reduce the risk of cardiovascular disease. Insulin resistance and dyslipidaemia have been shown to be increased in childhood cancer survivors who have undergone bone marrow transplantation. This was not associated with an increased body mass index (BMI), but was associated with markers of central adiposity such as waist to height ratio, which is a strong predictor of increased abdominal fat in adults. It is unclear whether the increased risk is due to the transplant itself or the conditioning treatment involved, which may have included chemotherapy and total body irradiation, which can result in hypogonadism and growth hormone deficiency. Some of the studies involving bone marrow transplantation also included patients with non-malignant conditions and were not exclusive to childhood cancer survivors.

Survivors of childhood cancer (particularly those who have been treated for acute lymphoblastic leukaemia or brain tumours) should be advised that they may be at higher risk of developing metabolic syndrome than the general population.

Healthcare professionals should be aware that survivors of childhood cancer may exhibit features of metabolic syndrome even with a normal body mass index, particularly if their treatment involved bone marrow transplantation.
7.3 TREATMENT OF METABOLIC SYNDROME

No evidence was identified for the management of metabolic syndrome in survivors of childhood cancer. Consensus guidelines for follow up of cancer survivors recommend annual assessment of blood pressure and BMI. The metabolic profile, which includes fasting glucose, insulin and lipids should be performed every two years in overweight and obese individuals and every five years in individuals within a healthy weight range.137

✔ Management of metabolic syndrome in survivors of childhood cancer should follow evidence based guidelines for the general population.
8 Cognitive and psychosocial outcomes

8.1 BRAIN STRUCTURE AND NEUROLOGICAL FUNCTION

Observational studies and case series have highlighted the association between treatment for childhood cancers and structural abnormalities of the brain. Abnormalities have been shown by magnetic resonance imaging or computed tomography in a variable proportion of patients who have had cranial irradiation, but their significance in terms of function is difficult to assess. Disruption of frontal lobe/basal ganglia connections, temporal lobe calcification and cortical atrophy have also been reported. Results suggest functional impairment may be associated with structural abnormalities of calcification and vasculopathy and electroencephalography abnormalities. Cognitive impairment and structural abnormalities after treatment to the brain correlate with age and dose of radiation. There is insufficient evidence to predict outcome in individual patients.

In looking for evidence about the effect of treatment on neurological function, no high quality trials could be identified. Most of the evidence is based upon case series with various assessment methods. There is little attempt to control for the duration of follow up or for the inclusion of a comparison group.

Cranial irradiation is a risk factor for cognitive decline. The available evidence, however, does not support the view that a decline in cognitive function is a frequent or inevitable consequence of treatment for childhood cancer. Results are inconsistent but do indicate that total irradiation dosage, and younger age at diagnosis and treatment increase the risk for cognitive sequelae. Even when some effect is demonstrated, the effect size is small.

- Healthcare and education professionals should be aware that the treatment of childhood cancer may have an impact on neurological function in later life, particularly if irradiation of the brain occurs at a young age.
- Regular review of neurological function should be part of normal follow up.
- If a problem is suspected, the patient should be referred to a psychologist for a neuropsychological assessment.

Children with cancer who are due to receive cranial irradiation should undergo a neuropsychological assessment at the start of treatment. The assessment should be repeated annually, to monitor changes over time.

8.2 PSYCHOSOCIAL ISSUES

As childhood cancer survival rates improve, quality of life measures such as psychosocial adjustment become more important. The evidence for any effect of treatment on psychosocial function is derived from studies with a wide diversity of outcome measures that are not comparable. The outcome measures assessed range from formal psychiatric assessment measures to self completed questionnaires through to sociodemographic variables such as marriage or employment. Many studies lack comparison groups. Variation in the duration of follow up is another confounding factor. Conclusions must be cautious, but adverse outcomes with respect to adjustment, employment and marriage are common findings.

Evidence suggests that survivors are at an increased risk for a wide range of disabling psychological symptoms including low mood, anxiety, low self esteem and some symptoms of post-traumatic stress disorder. Lower rates of marriage and employment than in the general population are also common. Brain tumours and treatment with cranial irradiation are frequently reported risk factors for psychosocial dysfunction.
• Healthcare and education professionals should be aware that the treatment of childhood cancer may have an impact on educational and social function in later life.

• Regular review for possible educational and psychosocial dysfunction or morbidity should take place.

• If a problem is suspected, the patient should be referred appropriately.
9 Growth problems

9.1 GROWTH IMPAIRMENT

There is a large body of evidence showing that survivors of childhood cancer may have impaired growth before, during or after successful treatment for their cancer. A number of factors are responsible for this, including the disease process itself, complications of treatment (infection), direct effects during treatment (anorexia, vomiting) and direct and indirect late effects attributable to therapy.

Cranial radiotherapy can cause growth hormone deficiency and growth retardation, which in turn may be compounded by other pituitary hormone deficiencies, particularly adrenocorticotrophin (ACTH), follicle stimulating hormone (FSH), luteinising hormone (LH) and thyroid stimulating hormone (TSH).260-266

Localised tumour treatments may affect growth and function of individual organs. For example, spinal growth is adversely affected by spinal irradiation and may result in skeletal disproportion. Abdominal surgery and/or radiotherapy may cause sex hormone deficiencies and secondary effects on growth and pubertal development.

Chemotherapy alone may also have significant effects on growth.267

The particular risks of growth impairment for any individual survivor depend upon the cancer type, the treatment given and the age at presentation.

9.2 SPECIAL GROUPS AT RISK OF GROWTH IMPAIRMENT

9.2.1 CRANIOPHARYNGIOMA

The majority of children with craniopharyngioma have symptoms of abnormal pituitary function at presentation,268 most commonly growth impairment and/or pubertal delay. Treatment includes surgery and/or radiotherapy.

9.2.2 BRAIN TUMOURS REMOTE FROM THE PITUITARY-HYPOPHYSIAL REGION

Cranial or craniospinal radiotherapy following surgical excision of brain tumours leaves survivors at high risk of growth hormone deficiency.260-266 Radiation involving the spine will result in reduced spinal growth and disproportionate short stature which can be detected by sitting height measurements. Without growth hormone replacement, virtually all such patients will have a final height below the third centile. In a significant minority there will be additional pituitary hormone deficiencies, which contribute to reduced growth. In addition, both boys and girls may have an early onset of puberty, which may be precocious in girls. The younger the age at irradiation, the earlier the onset of puberty.265,269

9.2.3 ACUTE LYMPHOBLASTIC LEUKAEMIA TREATED WITH PROPHYLACTIC HIGH DOSE (18-25 GY) CRANIAL RADIOTHERAPY

There are multiple longitudinal and cross-sectional studies in this treatment group. These demonstrate consistently poor growth during chemo- and radiotherapy treatment, followed by catch-up growth after treatment cessation. Up to 50% may have growth hormone deficiency on testing.270,271 Overall, final height in the majority is less than predicted, but almost all fall within the normal adult range.272-283 Some studies show a dose dependent effect, with a higher frequency of growth problems at 24-25 Gy than at 18 Gy, but others do not.

Children who have received additional cranial or craniospinal radiotherapy tended to have more significant growth problems.271,284,285 Some survivors have additional pituitary hormone deficiencies, but the frequency is much less than with high dose radiotherapy. The effects on growth are age dependent, with a poorer outcome the younger the age at diagnosis.251,286,287 In survivors with normal growth before the onset of puberty there may be an attenuated growth spurt in puberty associated with growth hormone insufficiency.288 A significant minority of girls, but not boys, will have premature or precocious puberty.277,281,299
9.2.4 BONE MARROW TRANSPLANTATION

Conditioning for bone marrow transplants for patients with leukaemias has usually included total body irradiation, whereas that for severe aplastic anaemia has not. Comparison of these two groups has shown significant loss of height in the leukaemia group.\textsuperscript{278,285,290-294} Many of these children however attain adult height within the normal range.

Recipients of bone marrow transplants for neuroblastoma, who had received abdominal radiotherapy prior to transplant, had very poor growth.\textsuperscript{295} In contrast, survivors of acute myeloid leukaemia, who received no radiotherapy prior to bone marrow transplant, had no growth impairment.\textsuperscript{296}

9.2.5 OTHERS

More recently, prophylaxis in patients with acute lymphoblastic leukaemia has not included radiotherapy. Some of these children show impaired growth, but final height is usually normal, and GHD is much less common.\textsuperscript{270, 279, 282, 297} Similar results are seen with children with solid tumours.\textsuperscript{298,299}

9.3 MONITORING FOR GROWTH PROBLEMS

\begin{itemize}
  \item [B] All children who have survived childhood cancer should have their height measured regularly until they reach final adult height. Sitting height should also be measured in children who have received craniospinal irradiation.
  \item [C] Children with impaired growth velocity should be referred to a paediatric endocrinologist for growth hormone level measurement.
  \item [B] Causes of poor growth, other than growth hormone deficiency, including potential deficiencies of other pituitary hormones or problems related to early or delayed puberty, should be considered and treated as necessary.
  \item [B] Children with craniopharyngioma should be tested at presentation for growth and other pituitary hormone deficiencies, and at regular intervals thereafter.
  \item [B] Prepubertal girls receiving cranial radiotherapy should be closely monitored for clinical signs of precocious puberty.
  \item [✓] Growth assessment requires integration of information including height measurements, bone age and puberty staging, all of which should be plotted onto growth charts.
  \item [✓] Healthcare professionals should be aware that puberty growth can be mistaken for catch-up growth.
\end{itemize}

9.4 OBESITY

There is evidence that childhood cancer survivors, particularly those who have had leukaemia, are at increased risk of obesity with its associated morbidity, in adolescence and in adult life. This problem is worse in girls.\textsuperscript{275, 277,300,301} In a study of 1,765 adult survivors of childhood ALL, cranial radiotherapy ≥20 Gy was found to be associated with an increased prevalence of obesity, especially in females diagnosed at up to four years of age.\textsuperscript{188} The management of obesity in children and young people is discussed in detail in SIGN guideline number 115.\textsuperscript{302}

\begin{itemize}
  \item [C] Regular growth monitoring should include evaluation of body mass index and be related to growth charts.
  \item [✓] Advice on healthy eating and exercise should be given early and reinforced regularly.
  \item [✓] Healthcare professionals should be aware that obesity can result in normal growth at the expense of inappropriately rapid bone age advancement resulting in reduced height prognosis.
\end{itemize}
9.5 TREATMENT WITH GROWTH HORMONE

9.5.1 EFFECTIVENESS

GH replacement therapy has shown varying rates of success in growth impaired cancer survivors.\textsuperscript{274,284,303-314} In survivors of craniopharyngioma a growth response similar to that in children with idiopathic growth hormone deficiency is seen.\textsuperscript{315}

B On confirmation of growth hormone deficiency, growth hormone replacement therapy is indicated. For children with craniopharyngioma, the need for growth hormone replacement may be from presentation.

C If the cause of growth impairment is unclear, a trial of growth hormone treatment may be appropriate.

9.5.2 SAFETY

Doubts have been expressed about the safety of recombinant growth hormone replacement therapy for childhood cancer survivors, based on the theoretical possibility that it may cause unwanted effects on any remaining cancer cells after treatment. Patients on growth hormone therapy in the USA, Canada and Europe are registered and closely monitored, allowing large studies to address the rate of cancer recurrence. The evidence supports the view that there is no increased risk of cancer recurrence.\textsuperscript{303,315-319} Other adverse effects in survivors of craniopharyngioma are common and include headache, seizures and water retention. These effects are likely to be due to the tumour and/or surgery, rather than the growth hormone.\textsuperscript{315} No increase in melanocytic naevi was detected in children receiving growth hormone.\textsuperscript{320,321} A single large cohort study of growth hormone recipients with various diagnoses found double the population risk of leukaemia and lymphoma in growth hormone recipients, but this was only statistically significant at extended follow up, and the absolute risk remains very small.\textsuperscript{322}

B Survivors of childhood cancer should be informed that current evidence indicates that there is no increased risk of cancer recurrence from growth hormone replacement therapy.

✓ Growth hormone should be prescribed under the supervision of a paediatrician with an expertise in growth disorders. Detailed and comprehensive shared care protocols should be available, with prescribing normally done by the general practitioner.

In most circumstances, it is safe and appropriate to start growth hormone therapy when it is indicated. GH is important both to maximise growth potential and for bone mineralisation. Bone accretion is not complete until young adulthood.

9.6 DENTAL AND FACIAL PROBLEMS

With the increasing survival of children after treatment for cancer, the potential clinical impact on orofacial and dental development is considerable. Facial deformity and developmental defects of the crowns of teeth can affect appearance and require advanced restorative care. If there are arrested or short roots, the usefulness of orthodontic treatment to straighten teeth is limited and the consequence of periodontal disease will be greater. Whilst there are insufficient follow-up data to estimate effects into adulthood the implication is that specialist treatment may be required.
9.6.1 PROBLEMS WITH OROFACIAL AND DENTAL GROWTH

Studies have been carried out to investigate the effects of treatment for cancer in childhood on dental development and the findings consistently demonstrated disturbances in the mineralisation and development of crowns and roots of teeth. The younger the age of the child at treatment, the greater the chance of later dental problems. The magnitude of effect is difficult to estimate since the evidence base is from selected groups of patients with few studies extending beyond early adulthood.

Studies comparing levels of decay as an outcome consistently found no difference between case and control groups.

In survivors of head and neck cancer treated with radiotherapy both facial and dental problems were found. Facial asymmetry due to disturbance in the growth of the mandible and maxilla were more severe the younger the child at diagnosis and treatment. Orbital growth, cataracts and otological hearing loss have been reported for children receiving radiation of eyes and ears. Dental crown defects and root foreshortening are more prevalent the younger the child and more severe with increasing doses of radiation. For survivors of ALL the evidence suggests that more severe disturbances are evident in children treated with prophylactic cranial radiotherapy. Survivors who have received bone marrow transplants experience disturbances in dental development that are greater the younger the child and are more severe than in children receiving chemotherapy alone.

Evidence from studies of children treated for a range of cancers, and followed for between one to ten years, suggests that the growth of orofacial structures and teeth are affected. Results demonstrate disturbances in the mineralisation and development of crowns and roots of teeth. Facial growth and temporo-mandibular function can also be affected. Levels of decay were no different from control groups.

Children undergoing cancer treatment would benefit from being seen, as close to diagnosis as possible, by a specialist in paediatric dentistry who will carry out a full oral and dental examination and formulate a treatment plan in liaison with the paediatric oncologist. Restorable teeth should be filled and teeth of poor prognosis removed. A targeted preventative programme to include toothbrushing instruction, topical fluoride application in addition to the use of toothpaste, and antibacterial mouthwash to reduce the amount and adherence of plaque will help to reduce oral morbidity during treatment.

Children undergoing cancer treatment, and their parents/carers, should be advised about the possible effects on orofacial and dental development. Specialist paediatric dentists should have a role in the care of these children.

Children undergoing cancer treatment should see a specialist in paediatric dentistry and be advised to attend for routine dental monitoring as recommended for every child.
10 Thyroid dysfunction

Abnormalities of thyroid gland structure and function may occur following treatment for childhood cancer. This may be due to primary damage to the thyroid gland itself, particularly from neck irradiation, or may be secondary to damage to the hypothalamic-pituitary axis. Chemotherapy is an independent risk factor for thyroid dysfunction.

Thyroid cancer as a second primary cancer is a rare but highly significant potential long term problem following successful treatment for childhood cancer.

10.1 SPECIAL GROUPS AT RISK OF THYROID DYSFUNCTION

10.1.1 HIGH DOSE RADIATION TO THE NECK

This small subgroup of survivors includes children treated for thyroid cancer and survivors of neuroblastoma who have received treatment with $^{131}$I-MIBG (meta-iodo benzyl guanidine). These children will all require thyroid hormone replacement.

Children with Hodgkin's disease, treated with radiotherapy to the neck, have a significantly increased risk of thyroid function abnormalities, thyroid nodules and thyroid cancer, when compared with those treated with chemotherapy alone. Estimates of the prevalence of abnormal thyroid function in this group are very variable. Transient abnormalities of thyroid function tests are common in the first 1-2 years after treatment, and may resolve spontaneously. A significant minority, with persistently increased thyroid stimulating hormone levels, will require thyroid hormone replacement. Hypothyroidism may develop decades after treatment. Estimates of the prevalence of thyroid nodules in this group depend upon the methods used to detect them, and at present it is not possible to give an accurate figure, or to comment on their significance. The risk of second primary thyroid cancer is significant, about 1% over a lifetime.

10.1.2 CRANIOSPINAL IRRADIATION

Children with brain tumours, particularly medulloblastoma, treated with craniospinal radiotherapy, have a similar increased risk of thyroid function abnormalities. This risk may be less with hyperfractionated rather than conventional radiotherapy regimens. Cranial radiotherapy does not seem to confer additional risk of direct thyroid damage, but may increase risk of damage to the hypothalamic-pituitary axis.

10.1.3 LOW DOSE RADIOTHERAPY

Although there is no evidence from studies of cancer patients, in the past large numbers of children were treated with low dose radiotherapy for non-malignant conditions, including lymphoid hyperplasia and various skin conditions. These cohorts have been followed for up to 35 years, and have a significant risk of thyroid nodules (up to 27%) and of thyroid cancer (up to 10% over 35 years).

10.1.4 TOTAL BODY IRRADIATION PRIOR TO BONE MARROW TRANSPLANTATION

Estimates of the prevalence of abnormal thyroid function tests in this group range from 10-90%. These are more likely in the first 1-2 years, and may be transient. Long term data are not available. Effects on hypothalamic and pituitary function are also possible following treatment.

10.1.5 CRANIAL RADIOTHERAPY

This subgroup includes children with pituitary or hypothalamic tumours, other brain tumours and leukaemias. The effects depend on the dose of radiation used and other treatment factors, including surgery and chemotherapy.

Survivors of childhood cancer who received radiotherapy to the neck, spine or brain should have their thyroid function checked after completion of treatment and regularly thereafter. Survivors are likely to require lifetime surveillance.
10.2 SCREENING FOR THYROID NODULES OR SECOND PRIMARY THYROID CANCERS

There are no good quality clinical trials or cohort studies which address this question. There are preliminary studies comparing ultrasound scan with clinical examination, which suggest that the former will detect more abnormalities.\textsuperscript{356-358} The clinical significance of this is unclear.

At present there is insufficient evidence on which to base recommendations for screening.

✔ Survivors who are at risk of thyroid nodules or second primary thyroid cancers should be advised of the risk of thyroid cancer and to seek urgent medical attention if they notice palpable neck masses.

10.3 TREATMENT OPTIONS

Thyroid hormone replacement therapy is generally safe and effective. Thyroxine may need to be introduced gradually in people with potential cardiac dysfunction (eg in patients who have received anthracycline). There is no evidence to support or refute the use of thyroid hormone supplementation in cases of compensated hypothyroidism in this patient group.

✔ Annual thyroid function tests are recommended for survivors at risk of thyroid dysfunction.
11 Long term follow up

11.1 INTRODUCTION

Survey data demonstrate wide variation in the extent to which survivors of childhood cancer are discharged from hospital follow up and the degree to which follow up is conducted in specialist clinics. A systematic review of models of care for follow up of childhood cancer survivors was unable to identify any controlled studies comparing models of follow up such as physician-led versus nurse-led, primary care or secondary care follow up or the use of various communication methods compared with face-to-face clinic visits.

PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies is a consortium of 16 European institutions carrying out research studies into late effects of treatment for cancer, to establish guidelines for follow up. The project commenced in February 2011 (www.pancaresurfup.eu).

11.2 TIMESCALE

The evidence base to guide the establishment of a structure for long term clinical follow up is incomplete and current best practice is that all survivors of childhood cancer should be followed up for life. With increasing survival rates there is an urgent need for further research into therapy specific follow up and for the development of evidence based, long term follow up strategies.

All survivors of childhood cancer should be actively followed up for life.

11.3 SHARED CARE

There is no evidence for the optimum setting for following up long term survivors. It is likely that both primary and secondary care services will be involved to a different extent depending on the individual patient. It is therefore essential for the patients, their carers and all healthcare professionals who may come in contact with them to be aware of the diagnosis and what treatment they have received, in order to be vigilant for signs of potential problems.

At the end of a course of cancer treatment, patients, their parents or carers and general practitioners should be given a summary of the treatment and a list of signs of late effects to look out for.

11.4 PERSONNEL

It may not be appropriate for adult cancer specialists, who may lack the specific training required, to follow up childhood cancer survivors. Anticipation and monitoring of late adverse effects to optimise prevention and treatment outcomes requires multidisciplinary expertise (see Table 3 for a list of main team members). The multidisciplinary team will need access to other specialist expertise as required, for example, gynaecology, cardiology, allied healthcare professionals and others. There is an important role for a designated key worker for each patient to coordinate care. Depending upon the needs of the individual patient an appropriate key worker should be drawn from the multidisciplinary team. With appropriate training, specialist nurses can make a significant contribution to the care of these patients.

Table 3: Multidisciplinary follow up team (which should include one member as the key worker)

<table>
<thead>
<tr>
<th>The multidisciplinary team may include</th>
</tr>
</thead>
<tbody>
<tr>
<td>adult oncologist</td>
</tr>
<tr>
<td>clinical psychologist</td>
</tr>
<tr>
<td>general practitioner</td>
</tr>
<tr>
<td>paediatric endocrinologist</td>
</tr>
<tr>
<td>paediatric neurologist</td>
</tr>
<tr>
<td>dentist</td>
</tr>
</tbody>
</table>
Each survivor of childhood cancer should have access to an appropriate designated key worker to coordinate care.

A training programme and career structure for late effects nurse practitioners should be developed.

11.5 CONTINUITY OF CARE

This group of patients often has a large number and variety of health professionals looking after their care. A discussion involving all the main health professionals and patients, parents or carers, at an appropriate time in the patient journey, would offer an opportunity to decide on a follow up strategy and clarify who will be responsible for specific aftercare. It should be recognised that teenagers may not want to be seen by paediatric services and that adult services may not be appropriate to follow up survivors of childhood cancers. Individual solutions may need to be found for each specific circumstance.

In the long term, it is important that future medical encounters (including those with dentists and opticians) are informed by a full medical history. This is especially important as the child becomes an adult and if the patient moves to another health region or to another country. Some form of patient-held record may be worth considering for these patients, as they are often the best informed about their treatment history. For those that are not, a patient-held record will give them that information.

Some form of continuity of care is important and this may be one of the roles of the designated key worker (see section 11.4). A good working relationship with the key worker is an essential part of the long term care of survivors of childhood cancers as it allows the patients and families to remain informed about possible complications and the health professionals informed about the child’s progress.

11.6 FOLLOW UP STRATEGIES

The degree and nature of long term morbidity risk will depend on the site of the underlying malignancy, the type and intensity of treatment and age at treatment. An appropriate follow up strategy will depend on the nature of the patient group and treatment. Three levels of follow up are described, and are summarised in Table 4.

11.6.1 LEVEL 1 FOLLOW UP

At one end of the scale, there are survivors for whom the benefit of clinical follow up is not established and for whom annual or even two-yearly postal or telephone contact may be all that is necessary in order to determine whether there have been any adverse health consequences and to ask about quality of life issues.

11.6.2 LEVEL 2 FOLLOW UP

For the majority of patients on current protocols, the nature and intensity of follow up is less easily determined. Nurse- or primary care-led follow up on an annual basis may often be appropriate although this may miss some individual problems. For example level 2 contact may not detect a child who, as a consequence of low-dose cranial irradiation, develops an early puberty, becomes growth hormone deficient and has a reduced late pubertal growth spurt, in time to intervene.
11.6.2 LEVEL 3 FOLLOW UP

At the other end of the scale, there are patients who have received radiotherapy (other than lowdose cranial irradiation less than or equal to 24 Gy), bone marrow transplantation, or megatherapy. They should be seen in a medically supervised long term follow up clinic three to four times a year until final height is achieved and at least annually thereafter.

Table 4: Possible levels of follow up for patients five or more years from completion of treatment

<table>
<thead>
<tr>
<th>Level</th>
<th>Treatment</th>
<th>Method of follow up</th>
<th>Frequency</th>
<th>Examples of tumours</th>
</tr>
</thead>
</table>
| 1     | • surgery alone  
       • low risk chemotherapy | postal or telephone | 1-2 years | • Wilms’ stage I or II  
       • Langerhans cell histiocytosis (single system disease)  
       • germ cell tumours (surgery only) |
| 2     | • chemotherapy  
       • low dose cranial irradiation less than or equal to 24 Gy | nurse or primary care-led* | 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 bone marrow transplantation  
       • stage 4 patients (any tumour type) |

* with appropriate training protocols
12 Provision of information

12.1 PATIENT INFORMATION NEEDS

It is important to keep patients and their families fully informed of the diagnosis, different treatment options, likely short and long term consequences and of the necessity for vigilance over possible long term side effects of treatment. Patients and their families should be reassured that if signs are picked up early, many potential problems can be avoided and that it is essential for them to attend regular review appointments.

The information given should be relevant to the particular point in the journey for the child and the family and in an appropriate format, which may include written information. The child and their family must be able to comprehend treatment options in order to make informed decisions with the support of health professionals, whether in the community or in hospital.

12.2 CHECKLIST FOR PROVISION OF INFORMATION

This section gives examples of the information patients/carers may find helpful. The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive. Lifestyle advice is adapted from SIGN 115 Management of obesity. 302

FOLLOW UP

Healthcare professionals involved in care and treatment of patients with childhood cancer should inform patients and their families of the importance of participating in follow-up programmes and the benefits this may provide in accessing multidisciplinary care to address any problems which may develop.

Healthcare professionals should advise patients to ensure that they make all health professionals with whom they are in contact aware of their previous treatment for cancer so that care can be provided in the appropriate context.

Healthcare professionals should inform survivors of childhood cancer that treatments they have received may increase their risk of a number of health problems including:

- bone problems
- thyroid dysfunction
- cardiac problems
- metabolic syndrome (problems with weight gain, blood pressure and metabolism)
- neurological and psychosocial problems (eg low mood, anxiety or post-traumatic stress disorder or phobias associated with previous medical treatments)
- fertility issues
- subsequent primary cancers.

Patients should be advised that problems can occur at any age and that they should report any new symptoms or health concerns promptly so that assessment and treatment may be taken forward without delay.
**HEALTHY LIFESTYLE**

Healthcare professionals should encourage and support survivors to participate in national screening programmes for cancer detection and inform them of the benefits of adopting healthy lifestyle behaviours including maintaining a healthy weight, avoiding smoking and keeping alcohol intake within government recommended limits. Information on smoking cessation should be provided where appropriate.

Information should be provided on current healthy eating guidelines, as below:

- **Bread, rice, potatoes, pasta and other starchy foods**
  - Eat plenty, choose wholegrain varieties when you can.

- **Fruit and vegetables**
  - Eat plenty, at least five portions of a variety of fruit and vegetables a day.

- **Milk and dairy foods**
  - Eat some, choose lower fat alternatives whenever possible or eat higher fat versions infrequently or in smaller amounts.

- **Meat, fish, eggs, pulses and other non-dairy sources of protein**
  - Eat some, choose lower fat alternatives whenever possible or eat higher fat versions infrequently or in smaller amounts. The Food Standards Agency advises that if you eat more than 90 g of red and processed meat a day, you should cut down to 70 g.
  - Aim for at least two portions of fish a week, including a portion of oily fish.

- **Foods and drinks high in fat and/or sugar**
  - Consume just a small amount

- **Try to choose options that are lower in salt when you can. Adults should have no more than 6 g of salt a day.**

- **To aid weight management it is important to encourage limiting the intake of energy-dense foods including confectionery, sugary drinks, fast foods and alcohol.**

Healthcare professionals should discuss current UK advice on vitamin D supplementation which recommends that people aged 65 years and over and people who are not exposed to much sun should take a daily supplement containing 10 micrograms of vitamin D.361

Adults should be encouraged to do at least 30 minutes of moderate-intensity physical activity on five or more days a week. Advice to individuals about increasing their physical activity should focus on activities that can fit easily into their everyday life and are tailored to their individual preferences and circumstances.

- **The typical desirable activity patterns will comprise a mix of personal transport and job-related household and recreational activities.**

- **Encourage individuals to start by doing what they can, and then to look for ways to do more.**

- **If they have not been active for a while, they should start out slowly. After several weeks or months activities can be built up by doing them for longer and more often.**

- **Walking is one way to encourage building physical activity into everyday life. When first starting, advise walking 10 minutes a day on a few days during the first couple of weeks.**

- **Add more time and days. Encourage individuals to walk a little longer. Trying 15 minutes instead of 10 minutes and walking on more days a week.**

- **Pick up the pace. Once this is easy to do, encourage them to try walking faster. After regular brisk walking for a couple of months, try, for example, adding biking or swimming at weekends for variety.**

**SUPPORT**

Healthcare professionals should assist patients and their families in identifying information about support groups or peer support where this is likely to be of benefit.

Patients should be given the opportunity to discuss issues such as stress management, self esteem and confidence.

Healthcare professionals should discuss socioeconomic issues associated with late effects with patients and their families including access to work and education.
12.3 SOURCES OF FURTHER INFORMATION

**BT Buddies**  
Tel: 01688 400687  
Website: www.btbuddies.org.uk  
Aims to provides information, support and assistance directly or indirectly to people affected by a primary or secondary brain tumour.

**Cancer Research UK/CancerHelp UK**  
Tel: 0800 800 4040  
Email: cancerhelpuk@cancer.org.uk  
Website: www.cancerhelp.org.uk  
CancerHelp UK is a free information service about cancer and cancer care for people with cancer and their families. It is provided by Cancer Research UK. The site includes a comprehensive range of information including cancer prevention, diagnosis, treatment and follow up.

**Cancer Support Scotland**  
Flat 5, 30 Shelley Court, Gartnavel Complex  
Glasgow G12 0YN  
Tel: 0141 211 0122  
Email: info@cancersupportscotland.org  
Website: www.cancersupportscotland.org  
Cancer Support Scotland offers information, support, education and care for people with cancer, their families and friends and professionals. They have support groups throughout Scotland.

**Children’s Cancer and Leukaemia Group**  
Website: www.cclg.org.uk  
CCLG is an association of healthcare professionals involved in the care of children who develop cancer. It produces information for patients and parents, siblings, teachers and friends.

**CLAN Cancer Support**  
Tel: 01224 647 000  
Website: www.clanhouse.org  
CLAN provides support across Northern and North East Scotland for people of any age affected by any cancer.

**CLIC Sargent Scotland Office**  
5th Floor, Mercantile Chambers  
53 Bothwell Street  
Glasgow G2 6TS  
Tel: 0141 572 5700  
Website: www.clicsargent.org.uk  
CLIC Sargent provides clinical, practical and emotional support to children and young people with cancer, and their families.

**Leukaemia CARE Scotland**  
Suite 62, Mercantile Chambers  
53 Bothwell Street,  
Glasgow, G2 6TS  
Tel: 0141 222 9637  
24 hour free helpline Tel: 08088 010444  
Leukaemia CARE Scotland provides care and support for patients, carers and families that are affected by a diagnosis of a blood or lymphatic cancer.
Macmillan Cancer Support (Scotland)
132 Rose Street
Edinburgh EH2 3JD
Tel: 0131 260 3270
Email: southscotland@macmillan.org.uk
Website: www.macmillan.org.uk

The Scottish office of the UK charity, which supports people with cancer (and their families) with specialist information, treatment and care.

Macmillan Cancer Information and Support Centre
Westerhaven, 1 Hailesland Road
Edinburgh EH14 2QS
Tel: 0131 442 3126

Macmillan offers support and information to people affected by cancer. It also offers information and support to relatives, friends and carers of people with a cancer diagnosis.

Maggie’s Centres Scotland
www.maggiescentres.org
Email: enquiries@maggiescentres.org

Maggie’s provides practical, emotional and social support to people with cancer, their family and friends. Built alongside NHS cancer hospitals and staffed with professional experts, Maggie’s Centres are warm and welcoming, full of light and open space, with a big kitchen table at their heart.

Maggie’s Dundee
Tom McDonald Avenue, Ninewells Hospital
Dundee DD2 1NH
Tel: 01382 632999
Email: dundee@maggiescentres.org

Maggie’s Edinburgh
The Stables, Western General Hospital
Crewe Road South
Edinburgh EH4 2XU
Tel: 0131 537 3131
Email: edinburgh@maggiescentres.org

Maggie’s Fife
Victoria Hospital, Hayfield Road
Kirkcaldy KY2 5AH
Tel: 01592 647997
Email: fife@maggiescentres.org

Maggie’s Glasgow
The Gatehouse, Western Infirmary
10 Dumbarton Road
Glasgow G11 6PA
Tel: 0141 330 3311

Gartnavel General Hospital
1053 Great Western Road
Glasgow G12 0YN
Tel: 0141 357 2269
Email: glasgow@maggiescentres.org
Maggie's Highlands
Raigmore Hospital, Old Perth Road
Inverness IV2 3UJ
Tel: 01463 706306
Email: highlands@maggiescentres.org

Maggie’s Lanarkshire
Flat 78, Residential accommodation
Wishaw General Hospital
50 Netherton Road
Wishaw ML2 ODP
Tel: 01698 358392
Email: lanarkshire@maggiescentres.org

Marie Curie Cancer Care (Scotland)
14 Links Place
Edinburgh EH6 7EB
Tel: 0800 716 146
www.mariecurie.org.uk

Marie Curie Cancer Care, a care charity, provides practical nursing care at home and specialist care across its ten Marie Curie centres.

riprap
www.riprap.org.uk

The riprap website was developed to provide information and advice to 12-16 year olds who have a parent with cancer.

SurvivorNet
Website: www.survivornet.org

SurvivorNet offers international web based support and links to information for cancer survivors.

Teenage Cancer Trust
93 Newman Street
London W1T 3EZ
Website: www.teenagecancertrust.org

The Teenage Cancer Trust provides support to teenagers and young adults with cancer and their families.

Youth Cancer Trust
Tracy Ann House, 5 Studland Road
Alum Chine
Bournemouth BH4 8HZ
Website: www.youthcancertrust.org

The Youth Cancer Trust provides activity holidays for young people suffering with or in remission from cancer.
13 Implementing the guideline

This section provides advice on the resource implications associated with implementing the key clinical recommendations, and advice on audit as a tool to aid implementation.

13.1 IMPLEMENTATION STRATEGY

Implementation of national clinical guidelines is the responsibility of each NHS Board and is an essential part of clinical governance. The Managed Service Network for Children and Young People with Cancer in Scotland, which is committed to developing evidence based practice and risk-based long term follow up, will facilitate the implementation of this guideline across all Heath Boards.

13.2 RESOURCE IMPLICATIONS

Implementation of the guideline recommendations will require investment in nurse-led, medically supervised long term follow up.

13.3 AUDITING CURRENT PRACTICE

A first step in implementing a clinical practice guideline is to gain an understanding of current clinical practice. Audit tools designed around guideline recommendations can assist in this process. Audit tools should be comprehensive but not time consuming to use. Successful implementation and audit of guideline recommendations requires good communication between staff and multidisciplinary team working.

The guideline development group has identified the following as key points to audit to assist with the implementation of this guideline:

- regular height, weight, pubertal staging and BMI measurements, recorded on appropriate charts
- appropriate follow up of patients at risk of late effects
- dental advice being given
- at-risk patients receiving appropriate cardiac monitoring
- annual thyroid function test being performed for patients at risk of thyroid dysfunction
- review for educational and psychosocial dysfunction or morbidity being undertaken
- at-risk patients receiving appropriate assessment of gonadal function
- at-risk males being offered semen cryopreservation before treatment starts
- evaluation of BMD in survivors at risk of endocrine dysfunction
- appropriate assessment of cardiac muscle function.
14 The evidence base

14.1 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Evidence and Information Scientist. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. The year range covered was 2002-2011. Internet searches were carried out on various websites including the US National Guidelines Clearinghouse. The main searches were supplemented by material identified by individual members of the development group.

14.1.1 LITERATURE SEARCH FOR PATIENT ISSUES

At the start of the guideline development process, a SIGN Evidence and Information Scientist conducted a literature search for qualitative and quantitative studies that addressed patient issues of relevance to early management of patients who are survivors of childhood cancer. Databases searched include Medline, Embase, Cinahl and PsycINFO, and the results were summarised and presented to the guideline development group.

14.2 RECOMMENDATIONS FOR RESEARCH

The following areas for further research have been identified:

- studies examining the outcomes of lifestyle interventions in survivors of childhood cancers
- the effects of treatments for childhood cancer on renal outcomes
- comparisons of service models in the provision of care and treatment of survivors of childhood cancer and their effects on outcomes
- effects of advice to avoid radiation exposure on patient outcomes in survivors of childhood cancer
- studies on interventions to limit potential cardiac toxicity such as cardioprotective drugs
- long term studies on the role of sensitive cardiac measurements such as diastolic dysfunction and tissue Doppler as well as biomarkers and whether they can predict the development of later clinical cardiac dysfunction
- studies on whether treatments used for adult heart failure translate into improved clinical outcomes for childhood survivors of cancer who develop heart failure
- studies on the long term safety and efficacy of fertility preservation for young people with cancer
- evaluation of screening programmes for subsequent primary cancers in patients who have received radiotherapy to a field that includes the breast.

14.3 REVIEW AND UPDATING

This guideline was published in 2013 and will be considered for review in three years. Any updates to the guideline in the interim period will be noted on the SIGN website www.sign.ac.uk
15 Development of the guideline

15.1 INTRODUCTION
SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of Healthcare Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising clinicians using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in “SIGN 50: A Guideline Developer’s Handbook”, available at www.sign.ac.uk

15.2 THE GUIDELINE DEVELOPMENT GROUP

- Professor W Hamish Wallace (Chair) Consultant Paediatric Oncologist, Royal Hospital for Sick Children, Edinburgh
- Professor Richard Anderson (Vice-Chair) Professor of Clinical Reproductive Science, University of Edinburgh
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- Dr Guftar Shaikh Paediatric Endocrinologist, Royal Hospital for Sick Children, Glasgow
- Ms Ailsa Stein Programme Manager, SIGN
- Dr Lorna Thompson Programme Manager, SIGN

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest and further details of these are available on request from the SIGN Executive.
Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive. All members of the SIGN Executive make yearly declarations of interest and further details of these are available on request.

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Mrs Karen Graham  
Patient Involvement Officer
Mr Stuart Neville  
Publications Designer
Miss Gaynor Rattray  
Guideline Coordinator
Mr Campbell Reynolds  
Distribution and Office Coordinator

15.3 ACKNOWLEDGEMENTS

SIGN would like to acknowledge the guideline development group responsible for the development of SIGN 76: Long term follow up of survivors of childhood cancer, on which this guideline is based.

SIGN is grateful to the following former members of the guideline development group and others who have contributed to the development of the guideline.

Ms Vicky Campbell  
Paediatric Endocrine Specialist Nurse, Royal Hospital for Sick Children, Glasgow
Dr Christopher Driver  
Paediatric Surgeon and Urologist, Royal Aberdeen Children's Hospital
Dr Paul Lim  
General Practitioner, NHS Forth Valley
Dr Trevor Richens  
Consultant Paediatric Cardiologist, Royal Hospital for Sick Children, Glasgow

15.4 CONSULTATION AND PEER REVIEW

15.4.1 SPECIALIST REVIEW

This guideline was also reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. The guideline group addresses every comment made by an external reviewer, and must justify any disagreement with the reviewers' comments. All expert referees made declarations of interest and further details of these are available on request from the SIGN Executive.

SIGN is very grateful to all of these experts for their contribution to the guideline.

Professor Faisal Ahmed  
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The following expert referees commented collectively on behalf of the Royal College of Paediatrics and Child Health.

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Dr Anne Livesy  
Consultant Community Paediatrician, Brighton and Sussex University Hospitals NHS Trust

15.4.2 SIGN EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers’ comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. All members of the SIGN Editorial group make yearly declarations of interest and further details of these are available on request from the SIGN Executive.

The editorial group for this guideline was as follows.

Dr Keith Brown  
Chair of SIGN; Co-Editor

Dr Roberta James  
SIGN Programme Lead; Co-Editor

Dr Sara Twaddle  
Director of SIGN; Co-Editor
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>A-CHF</td>
<td>anthracycline-induced congestive heart failure</td>
</tr>
<tr>
<td>ACTH</td>
<td>adrenocorticotrophin</td>
</tr>
<tr>
<td>ALL</td>
<td>acute lymphoblastic leukaemia</td>
</tr>
<tr>
<td>AMH</td>
<td>anti-Mullerian hormone</td>
</tr>
<tr>
<td>AML</td>
<td>acute myeloid leukaemia</td>
</tr>
<tr>
<td>AOF</td>
<td>acute ovarian failure</td>
</tr>
<tr>
<td>BMC</td>
<td>bone mineral content</td>
</tr>
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</tr>
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</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>DXA</td>
<td>dual energy X-ray absorptiometry</td>
</tr>
<tr>
<td>EAR</td>
<td>excess absolute risk</td>
</tr>
<tr>
<td>EF</td>
<td>ejection fraction</td>
</tr>
<tr>
<td>ESD</td>
<td>effective sterilising dose</td>
</tr>
<tr>
<td>FS</td>
<td>fractional shortening</td>
</tr>
<tr>
<td>FSH</td>
<td>follicle stimulating hormone</td>
</tr>
<tr>
<td>GH</td>
<td>growth hormone</td>
</tr>
<tr>
<td>GHD</td>
<td>growth hormone deficiency</td>
</tr>
<tr>
<td>HRT</td>
<td>hormone replacement therapy</td>
</tr>
<tr>
<td>LH</td>
<td>luteinising hormone</td>
</tr>
<tr>
<td>LL</td>
<td>lymphoblastic leukaemia</td>
</tr>
<tr>
<td>LV</td>
<td>left ventricular</td>
</tr>
<tr>
<td>¹³¹I-MIBG</td>
<td>iodine-meta-iodo benzyl guanidine</td>
</tr>
<tr>
<td>MTA</td>
<td>multiple technology appraisal</td>
</tr>
<tr>
<td>MTX</td>
<td>methotrexate</td>
</tr>
<tr>
<td>NGF</td>
<td>non growing follicles</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>RR</td>
<td>relative risk</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SGA</td>
<td>small for gestational age</td>
</tr>
<tr>
<td>SIGN</td>
<td>Scottish Intercollegiate Guidelines Network</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>SIR</td>
<td>standardised incidence ratio</td>
</tr>
<tr>
<td>SMC</td>
<td>Scottish Medicines Consortium</td>
</tr>
<tr>
<td>SPC</td>
<td>subsequent primary cancer</td>
</tr>
<tr>
<td>TBI</td>
<td>total body irradiation</td>
</tr>
<tr>
<td>TSH</td>
<td>thyroid stimulating hormone</td>
</tr>
</tbody>
</table>
Annex 1

Key questions addressed in this update

The update of this guideline is based on a series of structured key questions that define the target population, the intervention, diagnostic test, or exposure under investigation, the comparison(s) used and the outcomes used to measure efficacy, effectiveness, or risk. These questions form the basis of the systematic literature search.

<table>
<thead>
<tr>
<th>Key question</th>
<th>See guideline section</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What are the risks of specific treatment modalities for primary cancers in the development of a subsequent primary cancer?</td>
<td>3.5</td>
</tr>
<tr>
<td>2. What surveillance strategies (frequency, modality and intervals) exist for monitoring or detecting secondary malignancies? Should certain monitoring strategies be avoided?</td>
<td>3.6</td>
</tr>
<tr>
<td>3. Are childhood cancer survivors at increased risk of developing metabolic syndrome? (Consider: type II diabetes, obesity, insulin resistance, hyperlipidaemia and hypertension)</td>
<td>7.2</td>
</tr>
<tr>
<td>4. What are the effects of treatment for childhood cancer on skeletal/bone development? (Consider: fracture, osteoporosis, avascular necrosis, bone mineral density, rickets)</td>
<td>6.2-6.4</td>
</tr>
<tr>
<td>5. What are the effects of treatment for childhood cancer on cardiac outcomes? (Consider: cardiac failure, mortality, cardiac transplantation, coronary heart disease, hyperlipidemia, iron overload, arrhythmias)</td>
<td>5.2</td>
</tr>
<tr>
<td>6. Are any cancer survivor subgroups at higher risk of developing cardiac problems following treatment?</td>
<td>5.2</td>
</tr>
<tr>
<td>7. Which diagnostic tests/interventions are appropriate for detecting cardiac failure, coronary heart disease and hyperlipidemia in survivors of childhood cancer?</td>
<td>5.3</td>
</tr>
<tr>
<td>8. What is the risk to fertility of treatment for childhood cancer? (Consider: infertility, pregnancy outcome (late and early), hormone deficiency, sexual dysfunction, early menopause)</td>
<td>4.2, 4.3</td>
</tr>
<tr>
<td>9. Can early menopause be predicted?</td>
<td>4.3</td>
</tr>
<tr>
<td>10. How can future fertility of males and females with childhood cancer be protected?</td>
<td>4.4</td>
</tr>
<tr>
<td>11. Do adult survivors of childhood cancer remain infertile and how often should fertility be assessed?</td>
<td>4.2,4.3</td>
</tr>
<tr>
<td>12. What is the risk of congenital abnormalities in offspring of survivors of childhood cancer?</td>
<td>4.5</td>
</tr>
</tbody>
</table>
References


Long term follow up of survivors of childhood cancer


References


Long term follow up of survivors of childhood cancer


The Healthcare Environment Inspectorate, the Scottish Health Council, the Scottish Health Technologies Group, the Scottish Intercollegiate Guidelines Network (SIGN) and the Scottish Medicines Consortium are key components of our organisation.