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SIGN 132 • Long term follow up of survivors of childhood cancer

A national clinical guideline

March 2013

Evidence

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE	
1^{++}	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2^{++}	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

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.	
A	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
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1^{++} or 1^{+}
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2^{++}
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2^{+}

GOOD PRACTICE POINTS	
✓	Recommended best practice based on the clinical experience of the guideline development group

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Scottish Intercollegiate Guidelines Network

Long term follow up of survivors of childhood cancer

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Scottish Intercollegiate Guidelines Network
Gyle Square, 1 South Gyle Crescent
Edinburgh EH12 9EBA

www.sign.ac.uk

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Contents

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

2	Key recommendations	New
3	Subsequent primary cancers	New
4	Fertility issues	Completely revised
5	Cardiac effects	Completely revised
6	Bone health	New
7	Metabolic syndrome	New
8	Cognitive and psychosocial outcomes	Minor changes. Interventions section removed. No new evidence examined.
12	Provision of information	Completely revised

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

D **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.[7]

- **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.

	Age at diagnosis (years)	Treatment Era	Entry point	n	Overall SIR
British Childhood Cancer Survivor Study[8-10]	≤15	1940- 1991	Survival of at least 5 years	17,981	3.9
Nordic Countries Registry[11]	≤19	1943-2005 (some variation)	Diagnosis of initial malignancy	47,697	3.3
British Columbia Registry[12]	≤19	1970-1995	Survival of at least 5 years	2,322	5.0
German Cancer Registry[13]	≤15	1980-2008	Diagnosis of original malignancy	37,291	(odds ratio 2.1)
North American Childhood Cancer Survivor Study Cohort[14]	<21	1970-1986	Survival of at least 5 years	13,581	6.4
Dutch Single Centre Study[15]	≤18	1966-1996	Survival of at least 5 years	1,368	11.2

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] **3**

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. **3**

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] **3**

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] **3**

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 excluded.[14,17,18] **3**

A Dutch single centre study found an overall SIR for SPC of 11.2 (95% CI 8.5 to 14.4).[15] | 3

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)*.

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.**

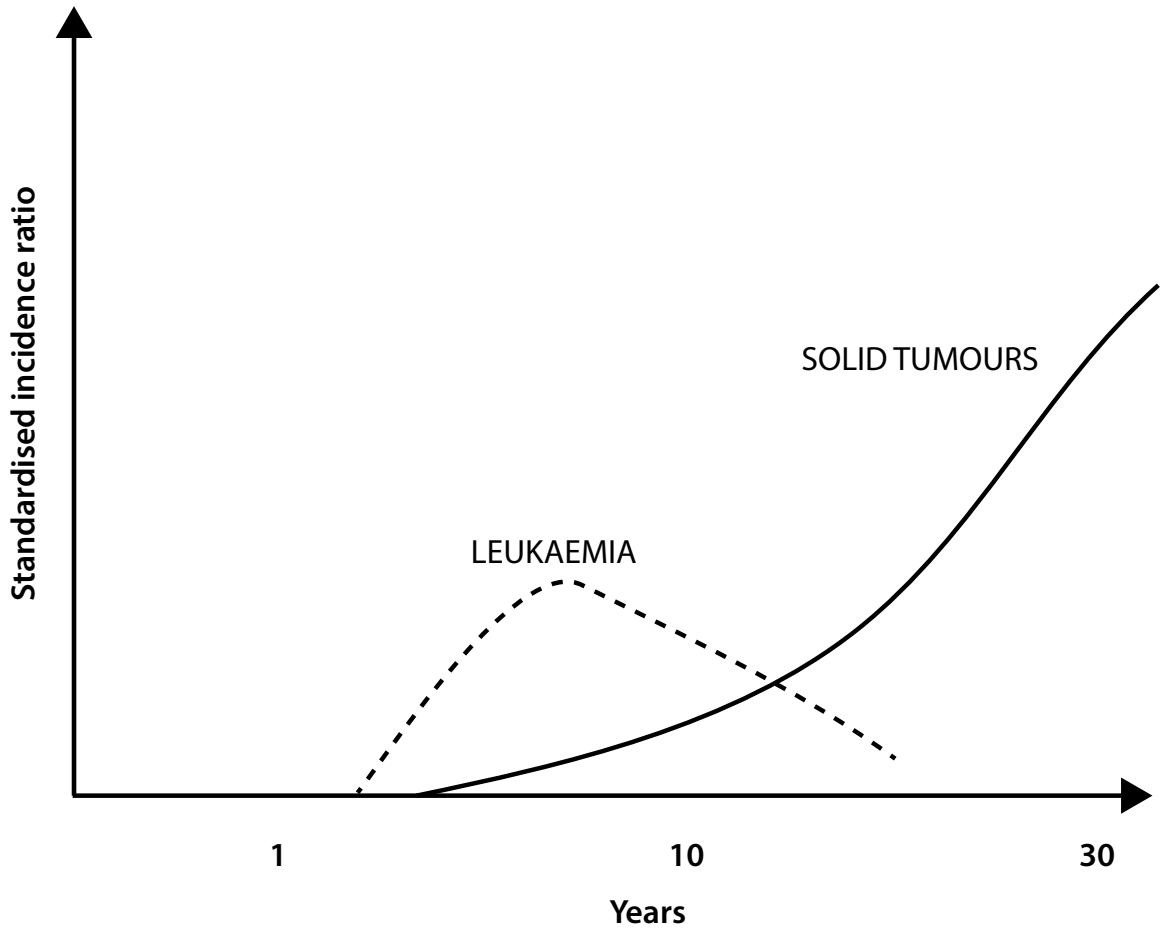
3.4 ONSET AND DURATION OF INCREASED RISK

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.[16] This means that studies which take three or five year survival as the entry point may not include such cases. | 3

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.[11] | 3

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**

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 dose,[13,19-23] 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] **3**

Studies looking specifically at breast cancer as an SPC have reported increased risk following radiotherapy to the breast region in childhood.[10,20,25] **3**

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] **2+**

Whilst most SPC occur within the radiotherapy field, there is no demonstrated link between the volume of the body irradiated and development of SPC.[27] **2+**

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] **2+**

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] **3**

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] **3**

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] **2+**

C **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] **3**

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] **3**

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.[14] **3**

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.[32] **3**

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.[34] **3**

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.[35] **2+**

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).[24] **2+**

C **Healthcare professionals should be aware that chemotherapy exposure is associated with increased risk of subsequent primary cancers in patients treated for childhood cancer. The effect is most consistently seen with alkylating agents and epipodophyllotoxins.**

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).[36] **3**

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.[27] **3**

One study found an increased risk of SPC of any type with combined modality treatment in childhood Hodgkin's lymphoma patients (p= 0.047).[37] **3**

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.[23] **2+**

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).[15] **3**

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.[27] 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.[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.[38] 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.[39]

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.[40] Age is also a factor; adolescent girls have a higher risk of ovarian failure after abdominopelvic radiotherapy than younger girls.[41]

The UK Royal Colleges have produced a guideline on the management of the effects of cancer treatment on reproductive function in adults.[42] **4**

✓ 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).[43] 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.[44] **3**

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.[45, 46] **2⁺** **3**

Both pre- and post-pubertal testes are susceptible to cytotoxic treatment by alkylating agents or radiotherapy to the gonads.[45-63] 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.[64-67] **2⁺⁺** **2⁺** **3**

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.[68] **3**

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, ifosphamide 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] **3**

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] **2+ 3**

Recovery of spermatogenesis has been documented after anthracycline-based treatment alone.[76] **3**

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] **3**

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] **3**

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] **3**

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] **3**

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. **3**

In a cohort of eleven pre-pubertal boys treated with high dose alkylating agent for osteosarcoma, all progressed through puberty normally.[70] 3

D **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.[83] 3

Treatment of some genitourinary childhood cancers (eg pelvic rhabdomyosarcoma) involves extensive local therapy which can adversely affect sexual function.[84] 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.[85]

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.[86]

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.[87]

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.[41] 3

Radiotherapy to the pelvis/abdomen is associated with ovarian failure. This is related to age at treatment.[41,88] 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 to1,840 cGy, at 20 years to 1,650 cGy and at 30 years to 1,430 cGy.[89] 3

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.[90] 3

AMH concentration in blood may reflect gonadal damage in pre-pubertal and pubertal girls, with absent recovery in girls treated with high-risk regimens.[91] In adults, pre-treatment AMH is predictive of post-chemotherapy ovarian function but this has not been demonstrated in girls or adolescents.[92] 3

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.[93] 3

✓ 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.[94] 3

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

D **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.[95] 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.[96-98] 3

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.[99] 3

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.[100] The increased obstetric risks related to chemotherapy reported in this study are novel findings that need to be confirmed in larger well controlled studies. 3

C **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.[101] This is likely to be relevant to the treatment of girls and adolescents, but no direct evidence was identified. **4**

4.4 PROTECTING FERTILITY

4.4.1 PRINCIPLES

Pre-treatment assessment requires individualised evaluation of the risk of treatment to fertility.[40, 102] See Table 2 for a system of risk assessment.

Table 2: Risk assessment for fertility preservation[102]

Intrinsic factors
Health status of patient
Consent (patient/parent)
Assessment of pubertal stage in boys/young men (including testicular volume)
Assessment of ovarian reserve in girls/young women
Extrinsic factors
Nature of predicted treatment (high/medium/low/uncertain risk)
Time available
Expertise available

✓ 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.[103] Successful storage has been reported in a high proportion (67%) of post-pubertal boys.[104] In young teenage patients semen collection may be restricted by willingness or ability to masturbate. **4**

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

D **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.[105] Data from surveys demonstrate that this may be acceptable to patients and their parents.[106] At present there is no technique sufficiently established to offer to pre-pubertal boys outwith a clinical trial. **4 3**

4.4.3 PROTECTING FERTILITY IN GIRLS UNDERGOING TREATMENT FOR CHILDHOOD CANCER

Oocyte cryopreservation is increasingly used for fertility preservation in adult women.[107] This may also be an option in post-pubertal girls. **4**

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[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.[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.[110,111] **1+**

Ovarian transposition has also been used in adults to move the ovaries out of a proposed radiation field.[40] There are no data on the efficacy of this approach in girls and adolescents. **4**

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.[112] **2+**

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.[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. **2+**

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).[114] **2+**

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.[115-117] 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.[115] Efforts to limit this potential cardiotoxicity with cardioprotective agents, liposomal preparations and prolonged anthracycline infusions have yielded mixed results.[118,119] **3**

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.[120] **4**

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/m^2 was 10% at 20 years. In patients treated with doses <300 mg/m^2 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.[116] **3**

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/m^2 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.[121] **3**

An anthracycline dose >250 mg/m^2 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.[122] **3**

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/m^2 with uncertain clinical significance. [123] **3**

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.[124] **3**

✓ 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] **3**

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. **3**

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] **4**

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] **3**

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] **4**

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] **4**

No studies were identified which assessed the effectiveness of screening programmes on outcomes for survivors of childhood cancers.

D **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.**

✓ Patients with asymptomatic left ventricular dysfunction after cancer therapy require long term echocardiographic monitoring since prognosis is uncertain.

✓ The frequency of echocardiographic surveillance should be individualised to the risk of anthracycline induced cardiotoxicity with a maximum interval of five years for those at low risk who received cumulative anthracycline doses less than 250 mg/m^2.

✓ Patients at high risk of anthracycline induced cardiotoxicity (cumulative anthracycline doses greater than 250 mg/m^2) or who have also received radiotherapy to a field that includes the heart should be screened every two to three years.

5.4 TREATMENT OF CARDIAC PROBLEMS

There is limited evidence on the efficacy of angiotensin converting enzyme inhibitors such as enalapril and beta-blockers such as carvedilol for the treatment of anthracycline induced cardiomyopathy in childhood cancer survivors. A study of adult cancer survivors suggested that those receiving early treatment of subclinical cardiac dysfunction with enalapril and carvedilol showed better improvement in cardiac function than a group who received late treatment or no treatment.[139] **3**

A study in childhood cancer survivors concluded that whilst enalapril treatment produces a six to ten year benefit in patients with asymptomatic left ventricular (LV) dysfunction, this only temporarily delays the natural history before return to baseline. In those with congestive heart failure there was a two to six year benefit before medical management failed. This is a generally poorer prognosis than in adult studies and suggests that enalapril does not address the primary defect in wall thickness but rather reduces afterload by reducing blood pressure and LV dilatation.[118] **3**

✓ Patients who develop heart failure should be treated according to evidence based guidelines for heart failure therapy.

✓ Patients should be informed about the importance of a healthy lifestyle, paying particular attention to smoking behaviour, exercise and avoidance of overweight or obesity.

✓ Healthcare professionals should monitor risk factors associated with coronary heart disease such as hypertension and hyperlipidaemia as these may modulate the heart's susceptibility to the development of heart failure.

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 <-1SD 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 ≤-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.[151] 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.[152] **3**

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.[150,153-156] 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.[157,158] **3**

Hodgkin's lymphoma

Observational studies of survivors of Hodgkin's lymphoma have conflicting results with three studies reporting a decreased BMD[159-161] and one study reporting only negligible BMD deficits.[162] **3**

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.[163] 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.[164] One study suggests that bone deficit may be due to other factors such as inadequate vitamin D and calcium intake.[165] **3**

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.[166] It is unclear if this is related to the transplantation itself or associated with disease factors or treatment interventions such as steroid use.[167,168] **3**

6.3.2 CHEMOTHERAPY/GLUCOCORTICOIDS

In ALL survivors, lower BMD was associated with treatment with higher cumulative doses of glucocorticoids (GCs) (>9,080 mg/m^2 prednisone equivalent) methotrexate (MTX) (>25,000 mg/m^2) and 6-mercaptopurine.[149,150,154,157] 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.[169] Femoral neck BMD is affected in those children who received high dose of MTX and GCs compared with age matched healthy controls.[157] **3**

6.3.3. CRANIAL IRRADIATION

Cranial irradiation is reported to have a detrimental effect on BMD and bone growth in ALL survivors.[157] 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).[156] This effect is dose dependent.[150] 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.[169] **3**

6.3.4 ENDOCRINE DYSFUNCTION

Childhood cancer survivors with hypogonadism and hypothyroidism[151] together with GHD[170] are more likely to have low BMD. **3**

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] **3**

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 age14 years, male sex was a risk factor for reduced BMD.[160] **3**

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] **3**

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] **3**

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] **4**

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.

✓ 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 LIFSTYLE 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] **3**

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] **3**

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 characterised 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.[181]The prevalence of obesity is increasing globally,[182] 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.[183,184] 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.[185] **3**

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.[186] **3**

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.[187-191,192] However, one study reported no increased risk of obesity in adult survivors of childhood brain cancer when matched to a general population group.[193] 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.[180,194] 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.[195,196] 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.[197] Some of the studies involving bone marrow transplantation also included patients with non-malignant conditions and were not exclusive to childhood cancer survivors.[192,198,199] **3**

D **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]

4

✓ 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.[200-213] Results suggest functional impairment may be associated with structural abnormalities of calcification and vasculopathy and electroencephalography abnormalities.[202, 206, 209, 210, 212] 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. **2+ 3**

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.[214-232] **3**

D

- **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.[233-259] **3**

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.[244,259] Lower rates of marriage and employment than in the general population are also common.[253, 259] Brain tumours and treatment with cranial irradiation are frequently reported risk factors for psychosocial dysfunction.[244, 253]

D

- **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. **2⁺**

9.2.2 BRAIN TUMOURS REMOTE FROM THE PITUITARY-HYPOPHYSEAL 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] **2⁺**

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. **2⁺⁺** **2⁺**

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.[261,286, 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, 281,289] **2⁺⁺** **2⁺**

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.[278,285,290-294] Many of these children however attain adult height within the normal range. **2++** **2+**

Recipients of bone marrow transplants for neuroblastoma, who had received abdominal radiotherapy prior to transplant, had very poor growth.[295] In contrast, survivors of acute myeloid leukaemia, who received no radiotherapy prior to bone marrow transplant, had no growth impairment.[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.[270, 279, 282, 297] Similar results are seen with children with solid tumours.[298,299] **2++** **2+**

9.3 MONITORING FOR GROWTH PROBLEMS

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.**

C **Children with impaired growth velocity should be referred to a paediatric endocrinologist for growth hormone level measurement.**

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.**

B **Children with craniopharyngioma should be tested at presentation for growth and other pituitary hormone deficiencies, and at regular intervals thereafter.**

B **Prepubertal girls receiving cranial radiotherapy should be closely monitored for clinical signs of precocious puberty.**

✓ Growth assessment requires integration of information including height measurements, bone age and puberty staging, all of which should be plotted onto growth charts.

✓ Healthcare professionals should be aware that puberty growth can be mistaken for catch-up growth.

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.[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.[188] The management of obesity in children and young people is discussed in detail in SIGN guideline number 115.[302] **2+**

C **Regular growth monitoring should include evaluation of body mass index and be related to growth charts.**

✓ Advice on healthy eating and exercise should be given early and reinforced regularly.

✓ 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.

9.5 TREATMENT WITH GROWTH HORMONE

9.5.1 EFFECTIVENESS

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

2++
2+

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.[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.[315] No increase in melanocytic naevi was detected in children receiving growth hormone.[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.[322]

2++
2+

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.[323-329] The younger the age of the child at treatment, the greater the chance of later dentalproblems.[324-326, 328, 330-332] 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. **2+**

Studies comparing levels of decay as an outcome consistently found no difference between case and control groups.[323,330-339]

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.[327,338] Orbital growth, cataracts and otological hearing loss have been reported for children receiving radiation of eyes and ears.[323, 331] Dental crown defects and root foreshortening are more prevalent the younger the child and more severe with increasing doses of radiation.[323-325] For survivors of ALL the evidence suggests that more severe disturbances are evident in children treated with prophylactic cranial radiotherapy.[326,328,329] 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.[327,330,332,333] **2+**

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.[340] **4**

D **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.[341] 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).[342] 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.[287,343-345] 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.[343] A significant minority, with persistently increased thyroid stimulating hormone levels, will require thyroid hormone replacement.[287,344] Hypothyroidism may develop decades after treatment.[287] 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.[287,344,346,347] **2^{++}** **2^{+}**

10.1.2 CRANIOSPINAL IRRADIATION

Children with brain tumours, particularly medulloblastoma, treated with craniospinal radiotherapy, have a similar increased risk of thyroid function abnormalities.[348,349] This risk may be less with hyperfractionated rather than conventional radiotherapy regimens.[348] Cranial radiotherapy does not seem to confer additional risk of direct thyroid damage, but may increase risk of damage to the hypothalamic-pituitary axis. **2^{++}** **2^{+}**

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).[350,351] **2^{++}**

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%.[352-354] 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. **2^{+}**

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.[285,349,355] **2^{+}**

B **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.[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.[359]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.[360]

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)

The multidisciplinary team may include	
adult oncologist	paediatric neurosurgeon
clinical psychologist	paediatric oncologist
general practitioner	radiation oncologist
paediatric endocrinologist	social worker
paediatric neurologist	specialist nurse/nurse practitioner
dentist	optician

✓ 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

Level	Treatment	Method of follow up	Frequency	Examples of tumours
1	• surgery alone • low risk chemotherapy	postal or telephone	1-2 years	• Wilms' stage I or II • Langerhans cell histiocytosis (single system disease) • germ cell tumours (surgery only)
2	• chemotherapy • low dose cranial irradiation lessthan or equal to 24 Gy	nurse or primary care-led*	1-2 years	• majority of patients (eg 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*
Ms Juliet Brown	*Evidence and Information Scientist, SIGN*
Dr Susan Buck	*General Practitioner, Edinburgh*
Dr Janet Burns	*Consultant Cardiologist, Royal Hospital for Sick Children, Edinburgh*
Dr Fiona Cowie	*Consultant Oncologist, Beatson West of Scotland Cancer Centre, Glasgow*
Dr Ian Craigie	*Associate Specialist Paediatrician, Greater Glasgow and Clyde Children's Diabetes Service, Glasgow*
Dr Angela Edgar	*Consultant Paediatric Oncologist, Royal Hospital for Sick Children, Edinburgh*
Mr Musab Elmantaser	*PhD Student, Royal Hospital for Sick Children, Glasgow*
Dr Brenda Gibson	*Consultant Paediatric Haematologist, Royal Hospital for Sick Children, Glasgow*
Dr Nicholas Heaney	*Consultant in Adolescent Haematology, Royal Hospital for Sick Children, Glasgow*
Miss Jen Layden	*Programme Manager, SIGN*
Mrs Caroline McManus	*Childhood cancer survivor, Edinburgh*
Dr John Murphy	*Consultant Haematologist, Monklands Hospital, Airdrie*
Dr Dzung Nguyen	*Consultant Paediatrician, St John's Hospital, Livingston*
Dr Stephen Rogers	*Consultant Haematologist, Victoria Hospital, Kirkcaldy*
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.

Mrs Lesley Forsyth	*Events Coordinator*
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	*Professor of Developmental Endocrinology, Royal Hospital for Sick Children, Glasgow*
Professor Annie Anderson	*Professor of Public Health Nutrition, University of Dundee*
Dr Patrick Cadigan	*Registrar, Royal College of Physicians, London*
Ms Diana Greenfield	*Macmillan Consultant Nurse, Survivorship and Late Effects, Weston Park Hospital, Sheffield*
Dr Mark Hamilton	*Consultant Gynaecologist, Aberdeen Maternity Hospital*
Professor Mike Hawkins	*Director of Centre for Childhood Cancer Survivor Studies, Birmingham University*
Dr Cathryn Hughes	*Survivorship Integration Manager, Macmillan Cancer Support, London*
Dr Gill Levitt	*Consultant in Paediatric Oncology and Late Effects, Great Ormond St Hospital NHS Trust*
Dr Jenny Limond	*Consultant Clinical Neuropsychologist, Coral Psychology Limited, Glasgow*

Dr David Linden	*Specialist in Cancer Care Prevention, Scottish Government, Edinburgh*
Ms Susan Mehta	*Lead Clinical Nurse Specialist, Late Effects of Cancer, University College London*
Dr Rod Skinner	*Consultant Paediatric Oncologist, Royal Victoria Infirmary, Newcastle upon Tyne*
Dr Allistair Stark	*Lead Cancer Clinician, Dumfries and Galloway Royal Infirmary*
Mr David Tolley	*President, Royal College of Surgeons, Edinburgh*
Ms Bernadine Wilkie	*National Clinical Nurse Specialist for Late Effects, Scotland, Royal Hospital for Sick Children, Edinburgh*

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

Dr Helen Jenkinson	*Consultant Paediatric Oncologist, Birmingham Children's Hospital*
Dr John Gibbs	*Consultant Paediatrician, Countess of Chester Hospital NHS Foundation Trust*
Dr Paul Arundel	*Consultant in Paediatric Metabolic Bone Disease, Sheffield Children's Hospital*
Dr Justin Warner	*Consultant in Paediatric Endocrinology and Diabetes, University Hospital of Wales, Cardiff*
Dr Richa Kulshrestha	*SpR, Paediatric Neurodisability, Robert Jones and Agnes Hunt Orthopaedic Hospital NHS Foundation Trust, Oswestry*
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

A-CHF	anthracycline-induced congestive heart failure
ACTH	adrenocorticotrophin
ALL	acute lymphoblastic leukaemia
AMH	anti-Mullerian hormone
AML	acute myeloid leukaemia
AOF	acute ovarian failure
BMC	bone mineral content
BMD	bone mineral density
BMI	body mass index
BNF	British National Formulary
CCSS	childhood cancer survivor study
cGy	centigray
CI	confidence interval
CNS	central nervous system
DXA	dual energy X-ray absorptiometry
EAR	excess absolute risk
EF	ejection fraction
ESD	effective sterilising dose
FS	fractional shortening
FSH	follicle stimulating hormone
GH	growth hormone
GHD	growth hormone deficiency
HRT	hormone replacement therapy
LH	luteinising hormone
LL	lymphoblastic leukaemia
LV	left ventricular
^{131}I-MIBG	Iodine-meta-iodo benzyl guanidine
MTA	multiple technology appraisal
MTX	methotrexate
NGF	non growing follicles
NICE	National Institute for Health and Clinical Excellence
OR	odds ratio
RR	relative risk
SD	standard deviation
SGA	small for gestational age
SIGN	Scottish Intercollegiate Guidelines Network

SIR	standardised incidence ratio
SMC	Scottish Medicines Consortium
SPC	subsequent primary cancer
TBI	total body irradiation
TSH	thyroid stimulating hormone

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.

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

References

1. Stiller C. Aetiology and epidemiology. In: Pinkerton CR and Plowman PN, editor. Paediatric Oncology: Clinical practice and controversies. London: Chapman and Hall Medical; 1997. p.3-21. (2nd ed)

2. UK Cancer Research. Cancer Stats - Childhood Cancer - Great Britain & UK [cited 01/12/2012]. Available from url: http://info.cancerresearchuk.org/cancerstats/childhoodcancer/survival/#source1

3. Reulen RC, Winter DL, Frobisher C, Lancashire ER, Stiller CA, Jenney ME, et al. Long-term cause-specific mortality among survivors of childhood cancer. Jama 2010;304(2):172-9.

4. Managed Service Network for Children and Young People with Cancer. Cancer Plan for Children and Young People in Scotland 2012-15 [cited 02/12/2012]. Available from url: http://www.scotland.gov.uk/Publications/2012/03/5105/downloads

5. The British National Formulary No. 64. London: British Medical Association and Royal Pharmaceutical Society of Great Britain;2012.

6. Medicines and Healthcare products Regulatory Agency. Off-label use or unlicensed medicines: prescribers' responsibilities. Drug Safety Update 2009;2(9):6-7.

7. A Dictionary of Epidemiology 5th Edition. [cited 02/12/2012]. Available from url: http://jpkc.fudan.edu.cn/picture/article/189/c4/24/81c086374fd8a31d9be7208bbb80/eb7e72b0-3b41-4b6b-8b23-168950e0e794.pdf

8. Reulen RC, Frobisher C, Winter DL, Kelly J, Lancashire ER, Stiller CA, et al. Long-term risks of subsequent primary neoplasms among survivors of childhood cancer. Jama 2011;305(22):2311-9.

9. Reulen RC, Taylor AJ, Winter DL, Stiller CA, Frobisher C, Lancashire ER, et al. Long-term population-based risks of breast cancer after childhood cancer. Int J Cancer 2008;123(9):2156-63.

10. Taylor AJ, Winter DL, Stiller CA, Murphy M, Hawkins MM. Risk of breast cancer in female survivors of childhood Hodgkin's disease in Britain: a population-based study. Int J Cancer 2007;120(2):384-91.

11. Olsen J, Moller T, Anderson H, Langmark F, Sankila R, Tryggvadottir L, et al. Lifelong cancer incidence in 47,697 patients treated for childhood cancer in the Nordic countries. J Natl Cancer Inst 2009;101(11):806-13.

12. MacArthur AC, Spinelli JJ, Rogers PC, Goddard KJ, Phillips N, McBride ML. Risk of a second malignant neoplasm among 5-year survivors of cancer in childhood and adolescence in British Columbia, Canada. Pediatr Blood Cancer 2007;48(4):453-9.

13. Kaatsch P, Reinisch I, Spix C, Berthold F, Janka-Schaub G, Mergenthaler A, et al. Case-control study on the therapy of childhood cancer and the occurrence of second malignant neoplasms in Germany. Cancer Causes Control 2009;20(6):965-80.

14. Neglia JP, Friedman DL, Yasui Y, Mertens AC, Hammond S, Stovall M, et al. Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study. J Natl Cancer Inst 2001;93(8):618-29.

15. Cardous-Ubbink MC, Heinen RC, Bakker PJM, van den Berg H, Oldenburger F, Caron HN, et al. Risk of second malignancies in long-term survivors of childhood cancer. Eur J Cancer 2007;43(2):351-62.

16. Kaatsch P, Debling D, Blettner M, Spix C. Second malignant neoplasms after childhood cancer in Germany--results from the long-term follow-up of the German Childhood Cancer Registry. Strahlenther Onkol 2009;185 Suppl 2:8-10.

17. Friedman DL, Whitton J, Leisenring W, Mertens AC, Hammond S, Stovall M, et al. Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. J Natl Cancer Inst 2010;102(14):1083-95.

18. Inskip PD, Curtis RE. New malignancies following childhood cancer in the United States, 1973-2002. Int J Cancer 2007;121(10):2233-40.

19. Neglia JP, Robison LL, Stovall M, Liu Y, Packer RJ, Hammond S, et al. New primary neoplasms of the central nervous system in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Natl Cancer Inst 2006;98(21):1528-37.

20. Inskip PD, Robison LL, Stovall M, Smith SA, Hammond S, Mertens AC, et al. Radiation dose and breast cancer risk in the childhood cancer survivor study. J Clin Oncol 2009;27(24):3901-7.

21. Guibout C, Adjadj E, Rubino C, Shamsaldin A, Grimaud E, Hawkins M, et al. Malignant breast tumors after radiotherapy for a first cancer during childhood. J Clin Oncol 2005;23(1):197-204.

22. Menu-Branthomme A, Rubino C, Shamsaldin A, Hawkins MM, Grimaud E, Dondon MG, et al. Radiation dose, chemotherapy and risk of soft tissue sarcoma after solid tumours during childhood. Int J Cancer 2004;110(1):87-93.

23. Svahn-Tapper G, Garwicz S, Anderson H, Shamsaldin A, De Vathaire F, Olsen J, et al. Radiation dose and relapse are predictors for development of second malignant solid tumors after cancer in childhood and adolescence: a population-based case-control study in the five Nordic countries. Acta Oncol 2006;45(4):438-48.

24. Nguyen F, Rubino C, Guerin S, Diallo I, Samand A, Hawkins M, et al. Risk of a second malignant neoplasm after cancer in childhood treated with radiotherapy: correlation with the integral dose restricted to the irradiated fields. Int J Radiat Oncol Biol Phys 2008;70(3):908-15.

25. Travis LB, Hill DA, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, et al. Breast Cancer Following Radiotherapy and Chemotherapy Among Young Women With Hodgkin Disease. JAMA 2003;290(4):465-75.

26. Sigurdson AJ, Ronckers CM, Mertens AC, Stovall M, Smith SA, Liu Y, et al. Primary thyroid cancer after a first tumour in childhood (the Childhood Cancer Survivor Study): a nested case-control study. Lancet 2005;365(9476):2014-23.

27. Franklin J, Pluetschow A, Paus M, Specht L, Anselmo AP, Aviles A, et al. Second malignancy risk associated with treatment of Hodgkin's lymphoma: meta-analysis of the randomised trials. Ann Oncol 2006;17(12):1749-60.

28. Constine LS, Tarbell N, Hudson MM, Schwartz C, Fisher SG, Muhs AG, et al. Subsequent Malignancies in Children Treated for Hodgkin's Disease: Associations With Gender and Radiation Dose. Int J Radiat Oncol Biol Phys 2008;72(1):24-33.

29. Henderson TO, Whitton J, Stovall M, Mertens AC, Mitby P, Friedman D, et al. Secondary sarcomas in childhood cancer survivors: a report from the Childhood Cancer Survivor Study. J Natl Cancer Inst 2007;99(4):300-8.

30. Taylor AJ, Little MP, Winter DL, Sugden E, Ellison DW, Stiller CA, et al. Population-based risks of CNS tumors in survivors of childhood cancer: the British Childhood Cancer Survivor Study. J Clin Oncol 2010;28(36):5287-93.

31. Armstrong GT, Liu Q, Yasui Y, Neglia JP, Leisenring W, Robison LL, et al. Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study. J Clin Oncol 2009;27(14):2328-38.

32. Bacci G, Ferrari C, Longhi A, Ferrari S, Forni C, Bacchini P, et al. Second malignant neoplasm in patients with osteosarcoma of the extremities treated with adjuvant and neoadjuvant chemotherapy. J Pediatr Hematol Oncol 2006;28(12):774-80.

33. Breslow NE, Lange JM, Friedman DL, Green DM, Hawkins MM, Murphy MFG, et al. Secondary malignant neoplasms after Wilms tumor: an international collaborative study. Int J Cancer 2010;127(3):657-66.

34. Borgmann A, Zinn C, Hartmann R, Herold R, Kaatsch P, Escherich G, et al. Secondary malignant neoplasms after intensive treatment of relapsed acute lymphoblastic leukaemia in childhood. Eur J Cancer 2008;44(2):257-68.

35. Haddy N, Le Deley MC, Samand A, Diallo I, Guerin S, Guibout C, et al. Role of radiotherapy and chemotherapy in the risk of secondary leukaemia after a solid tumour in childhood. Eur J Cancer 2006;42(16):2757-64.

36. Cohen RJ, Curtis RE, Inskip PD, Fraumeni JF, Jr. The risk of developing second cancers among survivors of childhood soft tissue sarcoma. Cancer 2005;103(11):2391-6.

37. Bhatia S, Yasui Y, Robison LL, Birch JM, Bogue MK, Diller L, et al. High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: report from the Late Effects Study Group. J Clin Oncol 4386;21(23):4386-94.

38. Greenfield DM, Wright J, Brown JE, Hancock BW, Davies HA, O'Toole L, et al. High incidence of late effects found in Hodgkin's lymphoma survivors, following recall for breast cancer screening. Br J Cancer 2006;94(4):469-72.

39. Howell SJ, Searle C, Goode V, Gardener T, Linton K, Cowan RA, et al. The UK national breast cancer screening programme for survivors of Hodgkin lymphoma detects breast cancer at an early stage. Br J Cancer 2009;101(4):582-8.

40. Lee SJ, Schover LR, Partridge AH, Patrizio P, Wallace WH, Hagerty K, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol 2006;24(18):2917-31.

41. Chemaitilly W, Mertens AC, Mitby P, Whitton J, Stovall M, Yasui Y, et al. Acute ovarian failure in the childhood cancer survivor study. J Clin Endocrinol Metab 2006;91(5):1723-8.

42. The Royal College of Physicians The Royal College of Radiologists The Royal College of Obstetricians and Gynaecologists. The effects of cancer treatment on reproductive functions: Guidance on management. Report of a Working Party. London: RCP 2007;

43. Nielsen CT, Skakkebaek NE, Richardson DW, Darling JA, Hunter WM, Jorgensen M, et al. Onset of the release of spermatozoa (spermarche) in boys in relation to age, testicular growth, pubic hair, and height. J Clin Endocrinol Metab 1986;62(3):532-5.

44. Lahteenmaki PM, Arola M, Suominen J, Salmi TT, Andersson AM, Toppari J. Male reproductive health after childhood cancer. Acta Paediatr 2008;97(7):935-42.

45. Lahteenmaki PM, Toppari J, Ruokonen A, Laitinen P, Salmi TT. Low serum inhibin B concentrations in male survivors of childhood malignancy. Eur J Cancer 1999;35(4):612-9.

46. Muller HL, Klinkhammer-Schalke M, Seelbach-Gobel B, Hartmann AA, Kuhl J. Gonadal function of young adults after therapy of malignancies during childhood or adolescence. Eur J Pediatr 1996;155(9):763-9.

47. Siimes MA, Rautonen J. Small testicles with impaired production of sperm in adult male survivors of childhood malignancies. Cancer 1990;65(6):1303-6.

48. Papadakis V, Vlachopapadopoulou E, Van Syckle K, Ganshaw L, Kalmanti M, Tan C, et al. Gonadal function in young patients successfully treated for Hodgkin disease. Med Pediatr Oncol 1999;32(5):366-72.

49. Ahmed SR, Shalet SM, Campbell RH, Deakin DP. Primary gonadal damage following treatment of brain tumors in childhood. J Pediatr 1983;103(4):562-5.

50. Blatt J, Poplack DG, Sherins RJ. Testicular function in boys after chemotherapy for acute lymphoblastic leukemia. N Engl J Med 1981;304(19):1121-4.

51. Mayer EI, Dopfer RE, Klingebiel T, Scheel-Walter H, Ranke MB, Niethammer D. Longitudinal gonadal function after bone marrow transplantation for acute lymphoblastic leukemia during childhood. Pediatr Transplant 1999;3(1):38-44.

52. Kobayashi H, Urashima M, Hoshi Y, Uchiyama H, Fujisawa K, Akatsuka J, et al. Testicular morphological changes in children with acute lymphoblastic leukemia following chemotherapy. Acta Paediatr Jpn 1996;38(6):640-3.

53. Ogilvy-Stuart AL, Clark DJ, Wallace WH, Gibson BE, Stevens RF, Shalet SM, et al. Endocrine deficit after fractionated total body irradiation. Arch Dis Child 1992;67(9):1107-10.

54. Wallace WH, Shalet SM, Lendon M, Morris-Jones PH. Male fertility in long-term survivors of childhood acute lymphoblastic leukaemia. Int J Androl 1991;14(5):312-9.

55. Ortin TT, Shostak CA, Donaldson SS. Gonadal status and reproductive function following treatment for Hodgkin's disease in childhood: the Stanford experience. Int J Radiat Oncol Biol Phys 1990;19(4):873-80.

56. Lannering B, Jansson C, Rosberg S, Albertsson-Wikland K. Increased LH and FSH secretion after cranial irradiation in boys. Med Pediatr Oncol 1997;29(4):280-7.

57. Green DM, Brecher ML, Lindsay AN, Yakar D, Voorhess ML, MacGillivray MH, et al. Gonadal function in pediatric patients following treatment for Hodgkin disease. Med Pediatr Oncol 1981;9(3):235-44.

58. Sanders JE, Buckner CD, Leonard JM, Sullivan KM, Witherspoon RP, Deeg HJ, et al. Late effects on gonadal function of cyclophosphamide, total-body irradiation, and marrow transplantation. Transplantation 1983;36(3):252-5.

59. Whitehead E, Shalet SM, Jones PH, Beardwell CG, Deakin DP. Gonadal function after combination chemotherapy for Hodgkin's disease in childhood. Arch Dis Child 1982;57(4):287-91.

60. Shalet SM, Hann IM, Lendon M, Morris Jones PH, Beardwell CG. Testicular function after combination chemotherapy in childhood for acute lymphoblastic leukaemia. Arch Dis Child 1981;56(4):275-8.

61. Grundy RG, Leiper AD, Stanhope R, Chessells JM. Survival and endocrine outcome after testicular relapse in acute lymphoblastic leukaemia. Arch Dis Child 1997;76(3):190-6.

62. Aubier F, Flamant F, Brauner R, Caillaud JM, Chaussain JM, Lemerle J. Male gonadal function after chemotherapy for solid tumors in childhood. J Clin Oncol 1989;7(3):304-9.

63. Heikens J, Behrendt H, Adriaanse R, Berghout A. Irreversible gonadal damage in male survivors of pediatric Hodgkin's disease. Cancer 1996;78(9):2020-4.

64. Siimes MA, Rautonen J, Makipernaa A, Sipila I. Testicular function in adult males surviving childhood malignancy. Pediatr Hematol Oncol 1995;12(3):231-41.

65. Shalet SM, Horner A, Ahmed SR, Morris-Jones PH. Leydig cell damage after testicular irradiation for lymphoblastic leukaemia. Med Pediatr Oncol 1985;13(2):65-8.

66. Sklar CA, Robison LL, Nesbit ME, Sather HN, Meadows AT, Ortega JA, et al. Effects of radiation on testicular function in long-term survivors of childhood acute lymphoblastic leukemia: a report from the Children Cancer Study Group. J Clin Oncol 1990;8(12):1981-7.

67. Leiper AD, Grant DB, Chessells JM. Gonadal function after testicular radiation for acute lymphoblastic leukaemia. Arch Dis Child 1986;61(1):53-6.

68. Anserini P, Chiodi S, Spinelli S, Costa M, Conte N, Copello F, et al. Semen analysis following allogeneic bone marrow transplantation. Additional data for evidence-based counselling. Bone Marrow Transplant 2002;30(7):447-51.

69. van Casteren NJ, van der Linden GH, Hakvoort-Cammel FG, Hahlen K, Dohle GR, van den Heuvel-Eibrink MM, et al. Effect of childhood cancer treatment on fertility markers in adult male long-term survivors. Pediatr Blood Cancer 2009;52(1):108-12.

70. Longhi A, Macchiagodena M, Vitali G, Bacci G, Longhi A, Macchiagodena M, et al. Fertility in male patients treated with neoadjuvant chemotherapy for osteosarcoma. J Pediatr Hematol Oncol 2003;25(4):292-6.

71. Thomson AB, Campbell AJ, Irvine DC, Anderson RA, Kelnar CJ, Wallace WH. Semen quality and spermatozoal DNA integrity in survivors of childhood cancer: a case-control study. Lancet 2002;360(9330):361-7.

72. Dhabhar BN, Malhotra H, Joseph R, Garde S, Bhasin S, Sheth A, et al. Gonadal function in prepubertal boys following treatment for Hodgkin's disease. Am J Pediatr Hematol Oncol 1993;15(3):306-10.

73. Mackie EJ, Radford M, Shalet SM. Gonadal function following chemotherapy for childhood Hodgkin's disease. Med Pediatr Oncol 1996;27(2):74-8.

74. Bramswig JH, Heimes U, Heiermann E, Schlegel W, Nieschlag E, Schellong G. The effects of different cumulative doses of chemotherapy on testicular function. Results in 75 patients treated for Hodgkin's disease during childhood or adolescence. Cancer 1990;65(6):1298-302.

75. Livesey EA, Brook CG. Gonadal dysfunction after treatment of intracranial tumours. Arch Dis Child 1988;63(5):495-500.

76. Viviani S, Santoro A, Ragni G, Bonfante V, Bestetti O, Bonadonna G. Gonadal toxicity after combination chemotherapy for Hodgkin's disease. Comparative results of MOPP vs ABVD. Eur J Cancer Clin Oncol 1985;21(5):601-5.

77. Byrne J, Fears TR, Mills JL, Zeltzer LK, Sklar C, Meadows AT, et al. Fertility of long-term male survivors of acute lymphoblastic leukemia diagnosed during childhood. Pediatr Blood Cancer 2004;42(4):364-72.

78. Jahnukainen K, Ehmcke J, Hou M, Schlatt S. Testicular function and fertility preservation in male cancer patients. Best Pract Res Clin Endocrinol Metabol 2011;25(2):287-302.

79. Chow EJ, Kamineni A, Daling JR, Fraser A, Wiggins CL, Mineau GP, et al. Reproductive outcomes in male childhood cancer survivors: a linked cancer-birth registry analysis. Arch Pediatr Adolesc Med 2009;163(10):887-94.

80. Green DM, Whitton JA, Stovall M, Mertens AC, Donaldson SS, Ruymann FB, et al. Pregnancy outcome of partners of male survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Clin Oncol 2003;21(4):716-21.

81. Frisk P, Arvidson J, Gustafsson J, Lonnerholm G. Pubertal development and final height after autologous bone marrow transplantation for acute lymphoblastic leukemia. Bone Marrow Transplant 2004;33(2):205-10.

82. Ishiguro H, Yasuda Y, Tomita Y, Shinagawa T, Shimizu T, Morimoto T, et al. Gonadal shielding to irradiation is effective in protecting testicular growth and function in long-term survivors of bone marrow transplantation during childhood or adolescence. Bone Marrow Transplant 2007;39(8):483-90.

83. Arden-Close E, Eiser C, Pacey A, Arden-Close E, Eiser C, Pacey A. Sexual functioning in male survivors of lymphoma: a systematic review (CME). J Sex Med 2011;8(7):1833-41.

84. Macedo A, Jr., Ferreira PV, Barroso U, Jr., Demarchi GT, Garrone G, Liguori R, et al. Sexual function in teenagers after multimodal treatment of pelvic rhabdomyosarcoma: A preliminary report. J Pediatr Urol 2010;6(6):605-8.

85. Wallace WH, Kelsey TW. Human ovarian reserve from conception to the menopause. PLoS ONE 2010; 5: e8772.

86. Kelsey TW, Wright P, Nelson SM, Anderson RA, Wallace WH. A validated model of serum anti-mullerian hormone from conception to menopause. PLoS ONE 2011; 6: e22024.

87. Palmert MR, Dunkel L. Delayed Puberty. N Engl J Med 2012;366(5):443-53.

88. Green DM, Whitton JA, Stovall M, Mertens AC, Donaldson SS, Ruymann FB, et al. Pregnancy outcome of female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Am J Obstet Gynecol 2002;187(4):1070-80.

89. Wallace WH, Thomson AB, Saran F, Kelsey TW. Predicting age of ovarian failure after radiation to a field that includes the ovaries. Int J Radiat Oncol Biol Phys 2005;62(3):738-44.

90. Hagen CP, Aksglaede L, Sorensen K, Mouritsen A, Andersson AM, Petersen JH, et al. Individual serum levels of anti-Mullerian hormone in healthy girls persist through childhood and adolescence: a longitudinal cohort study. Hum Reprod 2012;27(3):861-6.

91. Brougham MF, Crofton PM, Johnson EJ, Evans N, Anderson RA, Wallace WH. Anti-Mullerian Hormone Is a Marker of Gonadotoxicity in Pre- and Postpubertal Girls Treated for Cancer: A Prospective Study. J Clin Endocrinol Metab 2012;97(6):2059-67.

92. Anderson RA, Cameron DA. Pretreatment serum anti-mullerian hormone predicts long-term ovarian function and bone mass after chemotherapy for early breast cancer. J Clin Endocrinol Metab 2011;96(5):1336-43.

93. Langrish JP, Mills NL, Bath LE, Warner P, Webb DJ, Kelnar CJ, et al. Cardiovascular Effects of Physiological and Standard Sex Steroid Replacement Regimens in Premature Ovarian Failure. Hypertension 2009;53(5):805-11.

94. Green DM, Kawashima T, Stovall M, Leisenring W, Sklar CA, Mertens AC, et al. Fertility of female survivors of childhood cancer: a report from the childhood cancer survivor study. J Clin Oncol 2009;27(16):2677-85.

95. Arnon J, Meirow D, Lewis-Roness H, Ornoy A. Genetic and teratogenic effects of cancer treatments on gametes and embryos. Hum Reprod Update 2001;7(4):394-403.

96. Bath LE, Critchley HO, Chambers SE, Anderson RA, Kelnar CJ, Wallace WH. Ovarian and uterine characteristics after total body irradiation in childhood and adolescence: response to sex steroid replacement. Br J Obstet Gynaecol 1999;106(12):1265-72.

97. Larsen EC, Schmiegelow K, Rechnitzer C, Loft A, Muller J, Andersen AN. Radiotherapy at a young age reduces uterine volume of childhood cancer survivors. Acta Obstet Gynecol Scand 2004;83(1):96-102.

98. Signorello LB, Mulvihill JJ, Green DM, Munro HM, Stovall M, Weathers RE, et al. Stillbirth and neonatal death in relation to radiation exposure before conception: a retrospective cohort study. Lancet 2010;376(9741):624-30.

99. Signorello LB, Cohen SS, Bosetti C, Stovall M, Kasper CE, Weathers RE, et al. Female survivors of childhood cancer: preterm birth and low birth weight among their children. J Natl Cancer Inst 2006;98(20):1453-61.

100. Mueller BA, Chow EJ, Kamineni A, Daling JR, Fraser A, Wiggins CL, et al. Pregnancy outcomes in female childhood and adolescent cancer survivors: a linked cancer-birth registry analysis. Arch Pediatr Adolesc Med 2009;163(10):879-86.

101. Brotto LA, Yule M, Breckon E. Psychological interventions for the sexual sequelae of cancer: a review of the literature. J Cancer Surviv 2010;4(4):346-60.

102. Wallace WH, Critchley HO, Anderson RA. Optimizing reproductive outcome in children and young people with cancer. J Clin Oncol 2012;30(1):3-5.

103. Pacey AA. Fertility issues in survivors from adolescent cancers. Cancer Treat Rev 2007;33(7):646-55.

104. Edge B. Sperm banking in adolescent cancer patients. Arch Dis Child 2006;91(2):149-52.

105. Wyns C, Curaba M, Vanabelle B, Van Langendonckt A, Donnez J. Options for fertility preservation in prepubertal boys. Hum Reprod Update 2010;16(3):312-28.

106. Anderson RA, Weddell A, Spoudeas HA, Douglas C, Shalet SM, Levitt G, et al. Do doctors discuss fertility issues before they treat young patients with cancer? Hum Reprod 2008;23(10):2246-51.

107. The Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology. Mature oocyte cryopreservation: a guideline. Fertil Steril 2012; 99: 37-43.

108. Jadoul P, Dolmans MM, Donnez J. Fertility preservation in girls during childhood: is it feasible, efficient and safe and to whom should it be proposed? Hum Reprod Update 2010;16(6):617-30.

109. Anderson RA, Wallace WH, Baird DT. Ovarian cryopreservation for fertility preservation: indications and outcomes. Reproduction 2008;136(6):681-9.

110. Del Mastro L, Boni L, Michelotti A, Gamucci T, Olmeo N, Gori S, et al. Effect of the gonadotropin-releasing hormone analogue triptorelin on the occurrence of chemotherapy-induced early menopause in premenopausal women with breast cancer: a randomized trial. Jama 2011;306(3):269-76.

111. Gerber B, von Minckwitz G, Stehle H, Reimer T, Felberbaum R, Maass N, et al. Effect of luteinizing hormone-releasing hormone agonist on ovarian function after modern adjuvant breast cancer chemotherapy: the GBG 37 ZORO study. J Clin Oncol 2011;29(17):2334-41.

112. Winther JF, Boice JD, Jr., Frederiksen K, Bautz A, Mulvihill JJ, Stovall M, et al. Radiotherapy for childhood cancer and risk for congenital malformations in offspring: a population-based cohort study. Clin Genet 2009;75(1):50-6.

113. Signorello LB, Mulvihill JJ, Green DM, Munro HM, Stovall M, Weathers RE, et al. Congenital anomalies in the children of cancer survivors: a report from the childhood cancer survivor study. J Clin Oncol 2012;30(3):239-45.

114. Winther JF, Olsen JH, Wu H, Shyr Y, Mulvihill JJ, Stovall M, et al. Genetic disease in the children of Danish survivors of childhood and adolescent cancer. J Clin Oncol 2012;30(1):27-33.

115. Appel JM, Nielsen D, Zerahn B, Jensen BV, Skagen K. Anthracycline-induced chronic cardiotoxicity and heart failure. Acta Oncol 2007;46(5):576-80.

116. van Dalen EC, van der Pal HJ, Kok WE, Caron HN, Kremer LC, van Dalen EC, et al. Clinical heart failure in a cohort of children treated with anthracyclines: a long-term follow-up study. Eur J Cancer 2006;42(18):3191-8.

117. Shankar SM, Marina N, Hudson MM, Hodgson DC, Adams MJ, Landier W, et al. Monitoring for Cardiovascular Disease in Survivors of Childhood Cancer: Report From the Cardiovascular Disease Task Force of the Children's Oncology Group. Pediatrics 2008;121(2):e387-e96.

118. Lipshultz SE, Lipsitz SR, Sallan SE, Simbre IVC, Shaikh SL, Mone SM, et al. Long-term enalapril therapy for left ventricular dysfunction in doxorubicin-treated survivors of childhood cancer. J Clin Oncol 2002;20 (23):4517-22.

119. Wexler LH, Andrich MP, Venzon D, Berg SL, Weaver-McClure L, Chen CC, et al. Randomized trial of the cardioprotective agent ICRF-187 in pediatric sarcoma patients treated with doxorubicin. J Clin Oncol 1996;14(2):362-72.

120. Eschenhagen T, Force T, Ewer MS, De Keulenaer GW, Suter TM, Anker SD, et al. Cardiovascular side effects of cancer therapies: A position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2011;13 (1):1-10.

121. Creutzig U, Diekamp S, Zimmermann M, Reinhardt D. Longitudinal evaluation of early and late anthracycline cardiotoxicity in children with AML. Pediatr Blood Cancer 2007;48 (7):651-62.

122. Mulrooney DA, Yeazel MW, Kawashima T, Mertens AC, Mitby P, Stovall M, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. BMJ 2009;339:b4606.

123. Hudson MM, Rai SN, Nunez C, Merchant TE, Marina NM, Zalamea N, et al. Noninvasive evaluation of late anthracycline cardiac toxicity in childhood cancer survivors. J Clin Oncol 2007;25(24):3635-43.

124. Bar J, Davidi O, Goshen Y, Hod M, Yaniv I, Hirsch R. Pregnancy outcome in women treated with doxorubicin for childhood cancer. Am J Obstet Gynecol 2003;189 (3):853-7.

125. van der Pal HJ, van Dalen EC, Kremer LC, Bakker PJ, van Leeuwen FE. Risk of morbidity and mortality from cardiovascular disease following radiotherapy for childhood cancer: a systematic review. Cancer Treat Rev 2005;31(3):173-85.

126. Boivin JF, Hutchison GB, Lubin JH, Mauch P. Coronary artery disease mortality in patients treated for Hodgkin's disease. Cancer 1992;69(5):1241-7.

127. Hancock SL, Donaldson SS, Hoppe RT. Cardiac disease following treatment of Hodgkin's disease in children and adolescents. J Clin Oncol 1993;11(7):1208-15.

128. Hancock SL, Tucker MA, Hoppe RT. Factors affecting late mortality from heart disease after treatment of Hodgkin's disease. Jama 1993;270(16):1949-55.

129. Green DM, Gingell RL, Pearce J, Panahon AM, Ghoorah J. The effect of mediastinal irradiation on cardiac function of patients treated during childhood and adolescence for Hodgkin's disease. J Clin Oncol 1987;5(2):239-45.

130. Heikens J, Ubbink MC, van der Pal HP, Bakker PJ, Fliers E, Smilde TJ, et al. Long term survivors of childhood brain cancer have an increased risk for cardiovascular disease. Cancer 2000;88(9):2116-21.

131. Ilhan I, Sarialioglu F, Ozbarlas N, Buyukpamukcu M, Akyuz C, Kutluk T. Late cardiac effects after treatment for childhood Hodgkin's disease with chemotherapy and low-dose radiotherapy. Postgrad Med J 1995;71(833):164-7.

132. Johnson GL, Moffett CB, Geil JD, Greenwood MF, Noonan JA. Late echocardiographic findings following childhood chemotherapy with normal serial cardiac monitoring. J Pediatr Hematol Oncol 1996;18(1):72-5.

133. King V, Constine LS, Clark D, Schwartz RG, Muhs AG, Henzler M, et al. Symptomatic coronary artery disease after mantle irradiation for Hodgkin's disease. Int J Radiat Oncol Biol Phys 1996;36(4):881-9.

134. Reinders JG, Heijmen BJ, Olofsen-van Acht MJ, van Putten WL, Levendag PC. Ischemic heart disease after mantlefield irradiation for Hodgkin's disease in long-term follow-up. Radioth Oncol 1999;51(1):35-42.

135. Pihkala J, Saarinen UM, Lundstrom U, Virtanen K, Virkola K, Siimes MA, et al. Myocardial function in children and adolescents after therapy with anthracyclines and chest irradiation. Eur J Cancer 1996;32A(1):97-103.

136. Dorup I, Levitt G, Sullivan I, Sorensen K. Prospective longitudinal assessment of late anthracycline cardiotoxicity after childhood cancer: the role of diastolic function. Heart 2004;90(10):1214-6.

137. Childrens Oncology Group. Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers. [cited 1/12/2012]. Available from url: http://www.survivorshipguidelines.org/pdf/HeartHealth.pdf

138. Sieswerda E, Postma A, van Dalen EC, van der Pal HJ, Tissing WJ, Rammeloo LA, et al. The Dutch Childhood Oncology Group guideline for follow-up of asymptomatic cardiac dysfunction in childhood cancer survivors. Ann Oncol 2012;23(8):2191-8.

139. Cardinale D, Colombo A, Lamantia G, Colombo N, Civelli M, De Giacomi G, et al. Anthracycline-Induced Cardiomyopathy. Clinical Relevance and Response to Pharmacologic Therapy. J Am Coll Cardiol 2010;55 (3):213-20.

140. Boot AM, van den Heuvel-Eibrink MM, Hahlen K, Krenning EP, de Muinck Keizer-Schrama SM. Bone mineral density in children with acute lymphoblastic leukaemia. Eur J Cancer 1999;35(12):1693-7.

141. Hadjidakis DJ Al. Bone remodelling. Ann N Y Acad Sci 2006;1092 (Women's Health and Disease: Gynecologic, Endocrine, and Reproductive Issues):385- 96.

142. Kaste SC, Tong X, Hendrick JM, Karimova EJ, Srivastava DK, Tylavsky FA, et al. QCT versus DXA in 320 survivors of childhood cancer: association of BMD with fracture history. Pediatr Blood Cancer 2006;47(7):936-43.

143. Baim S, Binkley N, Bilezikian JP, Kendler DL, Hans DB, Lewiecki EM, et al. Official Positions of the International Society for Clinical Densitometry and executive summary of the 2007 ISCD Position Development Conference. J Clin Densitom 2008;11(1):75-91.

144. Ahmed SF, Elmantaser M. Secondary osteoporosis. Endocr Dev 2009;16 170-90.

145. Barr RD, Sala A. Osteonecrosis in children and adolescents with cancer. Pediatr Blood Cancer 2008;50(2 Suppl):483-5; discussion 6.

146. Arico M, Boccalatte MF, Silvestri D, Barisone E, Messina C, Chiesa R, et al. Osteonecrosis: An emerging complication of intensive chemotherapy for childhood acute lymphoblastic leukemia. Haematologica 2003;88(7):747-53.

147. Mattano LA, Jr., Sather HN, Trigg ME, Nachman JB. Osteonecrosis as a complication of treating acute lymphoblastic leukemia in children: a report from the Children's Cancer Group. J Clin Oncol 2000;18(18):3262-72.

148. Crofton PM, Ahmed SF, Wade JC, Elmlinger MW, Ranke MB, Kelnar CJ, et al. Bone turnover and growth during and after continuing chemotherapy in children with acute lymphoblastic leukemia. Pediatr Res 2000;48(4):490-6.

149. Crofton PM, Ahmed SF, Wade JC, Stephen R, Elmlinger MW, Ranke MB, et al. Effects of intensive chemotherapy on bone and collagen turnover and the growth hormone axis in children with acute lymphoblastic leukemia. J Clin Endocrinol Metab 1998;83(9):3121-9.

150. Kaste SC, Jones-Wallace D, Rose SR, Boyett JM, Lustig RH, Rivera GK, et al. Bone mineral decrements in survivors of childhood acute lymphoblastic leukemia: frequency of occurrence and risk factors for their development. Leukemia 2001;15(5):728-34.

151. Polgreen LE, Petryk A, Dietz AC, Sinaiko AR, Leisenring W, Goodman P, et al. Modifiable risk factors associated with bone deficits in childhood cancer survivors. BMC Pediatr 2012;12:40.

152. Wilson CL, Dilley K, Ness KK, Leisenring WL, Sklar CA, Kaste SC, et al. Fractures among long-term survivors of childhood cancer. Cancer 2012:n/a-n/a.

153. Kaste SC, Rai SN, Fleming K, McCammon EA, Tylavsky FA, Danish RK, et al. Changes in bone mineral density in survivors of childhood acute lymphoblastic leukemia. Pediatr Blood Cancer 2006;46(1):77-87.

154. Tillmann V, Darlington AS, Eiser C, Bishop NJ, Davies HA. Male sex and low physical activity are associated with reduced spine bone mineral density in survivors of childhood acute lymphoblastic leukemia. J Bone Miner Res 2002;17(6):1073-80.

155. Rai SN, Hudson MM, McCammon E, Carbone L, Tylavsky F, Smith K, et al. Implementing an intervention to improve bone mineral density in survivors of childhood acute lymphoblastic leukemia: BONEII, a prospective placebo-controlled double-blind randomized interventional longitudinal study design. Contemp Clin Trials 2008;29(5):711-9.

156. Thomas IH, Donohue JE, Ness KK, Dengel DR, Baker KS, Gurney JG. Bone mineral density in young adult survivors of acute lymphoblastic leukemia. Cancer 2008;113(11):3248-56.

157. Mandel K, Atkinson S, Barr RD, Pencharz P. Skeletal morbidity in childhood acute lymphoblastic leukemia. J Clin Oncol 2004;22(7):1215-21.

158. Muszynska-Roslan K, Panasiuk A, Latoch E, Krawczuk-Rybak M, Konstantynowicz J. Little Evidence of Low Bone Mass in Acute Lymphoblastic Leukemia Survivors. J Clin Densitom 2012;15(1):108-15.

159. Nysom K, Holm K, Michaelsen KF, Hertz H, Muller J, Molgaard C. Bone mass after treatment of malignant lymphoma in childhood. Med Pediatr Oncol 2001;37(6):518-24.

160. Sala A, Talsma D, Webber C, Posgate S, Atkinson S, Barr R. Bone mineral status after treatment of malignant lymphoma in childhood and adolescence. Eur J Cancer Care (Engl) 2007;16(4):373-9.

161. Van Beek RD, Van Den Heuvel-Eibrink MM, Hakvoort-Cammel FG, Van Den Bos C, Van Der Pal HJH, Krenning EP, et al. Bone mineral density, growth, and thyroid function in long-term survivors of pediatric Hodgkin's lymphoma treated with chemotherapy only. J Clin Endocrinol Metab 2009;94 (6):1904-9.

162. Kaste SC, Metzger ML, Minhas A, Xiong Z, Rai SN, Ness KK, et al. Pediatric Hodgkin lymphoma survivors at negligible risk for significant bone mineral density deficits. Pediatr Blood Cancer 2009;52(4):516-21.

163. Kelly J, Damron T, Grant W, Anker C, Holdridge S, Shaw S, et al. Cross-sectional study of bone mineral density in adult survivors of solid pediatric cancers. J Pediatr Hematol Oncol 2005;27(5):248-53.

164. Odame I, Duckworth J, Talsma D, Beaumont L, Furlong W, Webber C, et al. Osteopenia, physical activity and health-related quality of life in survivors of brain tumors treated in childhood. Pediatr Blood Cancer 2006;46(3):357-62.

165. Bilariki. Low bone mineral density and high incidences of fractures and vitamin D deficiency in 52 pediatric cancer survivors. Horm Res Paediatr 2010;74(5):319-27.

166. Kaste S. Bone-mineral density deficits from childhood cancer and its therapy. A review of at-risk patient cohorts and available imaging methods. Pediatr Radiol 2004;34(5):373-8.

167. Ruble K, Hayat MJ, Stewart KJ, Chen AR. Bone mineral density after bone marrow transplantation in childhood: measurement and associations. Biol Blood Marrow Transplant 2010;16(10):1451-7.

168. Sharma S, Yang S, Rochester R, Britton L, Leung WH, Yang J, et al. Prevalence of osteonecrosis and associated risk factors in children before allogeneic BMT. Bone Marrow Transplant 2011;46(6):813-9.

169. Le Meignen M, Auquier P, Barlogis V, Sirvent N, Contet A, Simeoni MC, et al. Bone mineral density in adult survivors of childhood acute leukemia: impact of hematopoietic stem cell transplantation and other treatment modalities. Blood 2011;118(6):1481-9.

170. van den Heijkant S, Hoorweg-Nijman G, Huisman J, Drent M, van der Pal H, Kaspers GJ, et al. Effects of growth hormone therapy on bone mass, metabolic balance, and well-being in young adult survivors of childhood acute lymphoblastic leukemia. J Pediatr Hematol Oncol 2011;33(6):e231-8.

171. Jones TS, Kaste SC, Liu W, Cheng C, Yang W, Tantisira KG, et al. CRHR1 polymorphisms predict bone density in survivors of acute lymphoblastic leukemia. J Clin Oncol 2008;26(18):3031-7.

172. te Winkel ML, van Beek RD, de Muinck Keizer-Schrama SM, Uitterlinden AG, Hop WC, Pieters R, et al. Pharmacogenetic risk factors for altered bone mineral density and body composition in pediatric acute lymphoblastic leukemia. Haematologica 2010;95(5):752-9.

173. Wasilewski-Masker K, Kaste SC, Hudson MM, Esiashvili N, Mattano LA, Meacham LR. Bone mineral density deficits in survivors of childhood cancer: long-term follow-up guidelines and review of the literature. Pediatrics 2008;121(3):e705-13.

174. Heath JA, Ramzy JM, Donath SM. Physical activity in survivors of childhood acute lymphoblastic leukaemia. J Paediatr Child Health 2010;46(4):149-53.

175. Joyce ED, Nolan VG, Ness KK, Ferry RJ, Jr., Robison LL, Pui CH, et al. Association of muscle strength and bone mineral density in adult survivors of childhood acute lymphoblastic leukemia. Arch Phys Med Rehabil 2011;92(6):873-9.

176. Tylavsky FA, Smith K, Surprise H, Garland S, Yan X, McCammon E, et al. Nutritional intake of long-term survivors of childhood acute lymphoblastic leukemia: Evidence for bone health interventional opportunities. Pediatr Blood Cancer 2010;55 (7):1362-9.

177. Kumar J, Muntner P, Kaskel FJ, Hailpern SM, Melamed ML. Prevalence and associations of 25-hydroxyvitamin D deficiency in US children: NHANES 2001-2004. Pediatrics 2009;124(3):e362-70.

178. Simmons JH, Chow EJ, Koehler E, Esbenshade A, Smith LA, Sanders J, et al. Significant 25-hydroxyvitamin D deficiency in child and adolescent survivors of acute lymphoblastic leukemia: treatment with chemotherapy compared with allogeneic stem cell transplant. Pediatr Blood Cancer 2011;56(7):1114-9.

179. Crofton PM, Evans N, Bath LE, Warner P, Whitehead TJ, Critchley HO, et al. Physiological versus standard sex steroid replacement in young women with premature ovarian failure: effects on bone mass acquisition and turnover. Clin Endocrinol (Oxf) 2010;73(6):707-14.

180. Follin C, Thilen U, Osterberg K, Bjork J, Erfurth EM. Cardiovascular risk, cardiac function, physical activity, and quality of life with and without long-term growth hormone therapy in adult survivors of childhood acute lymphoblastic leukemia. J Clin Endocrinol Metab 2010;95(8):3726-35.

181. Alberti KGMM, Zimmet P, Shaw J. The metabolic syndrome—a new worldwide definition. Lancet 2005;366(9491):1059-62.

182. Swinburn BA, Sacks G, Hall KD, McPherson K, Finegood DT, Moodie ML, et al. The global obesity pandemic: shaped by global drivers and local environments. Lancet 2011;378(9793):804-14.

183. Shaw MP, Bath LE, Duff J, Kelnar CJ, Wallace WHB. Obesity in leukemia survivors: The familial contribution. Pediatr Hematol Oncol 2000;17(3):231-7.

184. Razzouk BI, Rose SR, Hongeng S, Wallace D, Smeltzer MP, Zacher M, et al. Obesity in survivors of childhood acute lymphoblastic leukemia and lymphoma. J Clin Oncol 2007;25(10):1183-9.

185. Ness KK, Oakes JM, Punyko JA, Baker KS, Gurney JG. Prevalence of the Metabolic Syndrome in Relation to Self-reported Cancer History. Ann Epidemiol 2005;15(3):202-6.

186. Nathan PC, Jovcevska V, Ness KK, Mammone D'Agostino N, Staneland P, Urbach SL, et al. The prevalence of overweight and obesity in pediatric survivors of cancer. J Pediatr 2006;149 (4):518-25.e2.

187. Pietila S, Makipernaa A, Sievanen H, Koivisto AM, Wigren T, Lenko HL. Obesity and metabolic changes are common in young childhood brain tumor survivors. Pediatr Blood Cancer 2009;52 (7):853-9.

188. Oeffinger KC, Mertens AC, Sklar CA, Yasui Y, Fears T, Stovall M, et al. Obesity in adult survivors of childhood acute lymphoblastic leukemia: A report from the childhood cancer survivor study. J Clin Oncol 2003;21(7):1359-65.

189. Nysom K, Holm K, Michaelsen KF, Hertz H, Jacobsen N, Muller J, et al. Degree of fatness after allogeneic BMT for childhood leukaemia or lymphoma. Bone Marrow Transplant 2001;27(8):817-20.

190. Van Waas M, Neggers SJ, Van Der Lelij AJ, Pieters R, Van Den Heuvel-Eibrink MM. The metabolic syndrome in adult survivors of childhood cancer, a review. J Pediatr Hematol Oncol 2010;32 (3):171-9.

191. Trimis G, Moschovi M, Papassotiriou I, Chrousos G, Tzortzatou-Stathopoulou F. Early indicators of dysmetabolic syndrome in young survivors of acute lymphoblastic leukemia in childhood as a target for preventing disease. J Pediatr Hematol Oncol 2007;29(5):309-14.

192. Annaloro C, Usardi P, Airaghi L, Giunta V, Forti S, Orsatti A, et al. Prevalence of metabolic syndrome in long-term survivors of hematopoietic stem cell transplantation. Bone Marrow Transplant 2008;41(9):797-804.

193. Gurney JG, Ness KK, Stovall M, Wolden S, Punyko JA, Neglia JP, et al. Final Height and Body Mass Index among Adult Survivors of Childhood Brain Cancer: Childhood Cancer Survivor Study. J Clin Endocrinol Metab 2003;88 (10):4731-9.

194. Gurney JG, Ness KK, Sibley SD, O'Leary M, Dengel DR, Lee JM, et al. Metabolic syndrome and growth hormone deficiency in adult survivors of childhood acute lymphoblastic leukemia. Cancer 2006;107(6):1303-12.

195. Steffens M, Beauloye V, Brichard B, Robert A, Alexopoulou O, Vermylen C, et al. Endocrine and metabolic disorders in young adult survivors of childhood acute lymphoblastic leukaemia (ALL) or non-Hodgkin lymphoma (NHL). Clin Endocrinol (Oxf) 2008;69(5):819-27.

196. Ashwell M, Cole TJ, Dixon AK. Ratio of waist circumference to height is strong predictor of intra-abdominal fat. BMJ 1996;313(7056):559-60.

197. Baker KS, Chow E, Steinberger J. Metabolic syndrome and cardiovascular risk in survivors after hematopoietic cell transplantation. Bone Marrow Transplant 2012;47(5):619-25.

198. Taskinen M, Saarinen-Pihkala UM, Hovi L, Lipsanen-Nyman M. Impaired glucose tolerance and dyslipidaemia as late effects after bone-marrow transplantation in childhood. Lancet 2000;356(9234):993-7.

199. Shalitin S, Phillip M, Stein J, Goshen Y, Carmi D, Yaniv I. Endocrine dysfunction and parameters of the metabolic syndrome after bone marrow transplantation during childhood and adolescence. Bone Marrow Transplant 2006;37(12):1109-17.

200. Abayomi O, Chun MS, Kelly K. Cerebral calcification and learning disabilities following cranial irradiation for medulloblastoma. J Natl Med Assoc 1990;82(12):833-6.

201. Bakke SJ, Fossen A, Storm-Mathiesen I, Lie SO. Long-term cerebral effects of CNS chemotherapy in children with acute lymphoblastic leukemia. Pediatr Hematol Oncol 1993;10(3):267-70.

202. Brouwers P, Riccardi R, Poplack D, Fedio P. Attentional deficits in long-term survivors of childhood acute lymphoblastic leukemia (ALL). J Clin Neuropsychol 1984;6(3):325-36.

203. Catsman-Berrevoets CE, Van Dongen HR, Mulder PG, Paz y Geuze D, Paquier PF, Lequin MH. Tumour type and size are high risk factors for the syndrome of "cerebellar" mutism and subsequent dysarthria. J Neurol Neurosurg Psychiatry 1999;67(6):755-7.

204. Ciesielski KT, Yanofsky R, Ludwig RN, Hill DE, Hart BL, Astur RS, et al. Hypoplasia of the cerebellar vermis and cognitive deficits in survivors of childhood leukemia. Arch Neurol 1994;51(10):985-93.

205. Harila-Saari AH, Paakko EL, Vainionpaa LK, Pyhtinen J, Lanning BM. A longitudinal magnetic resonance imaging study of the brain in survivors in childhood acute lymphoblastic leukemia. Cancer 1998;83(12):2608-17.

206. Heukrodt C, Powazek M, Brown WS, Kennelly D, Imbus C, Robinson H, et al. Electrophysiological signs of neurocognitive deficits in long-term leukemia survivors. J Pediatr Psychol 1988;13(2):223-36.

207. Laitt RD, Chambers EJ, Goddard PR, Wakeley CJ, Duncan AW, Foreman NK. Magnetic resonance imaging and magnetic resonance angiography in long term survivors of acute lymphoblastic leukemia treated with cranial irradiation. Cancer 1995;76(10):1846-52.

208. Lamothe I RP, Precourt S, Kabene S, Moghrabi A. Psychophysiological evaluation of treatments on visual attention processes in young girls who survived to acute lymphoblastic leukemia. Brain Cogn 1998;;37((1):):152-5.

209. Moore BD, 3rd, Ater JL, Copeland DR. Improved neuropsychological outcome in children with brain tumors diagnosed during infancy and treated without cranial irradiation. J Child Neurol 1992;7(3):281-90.

210. Mulhern RK, Reddick WE, Palmer SL, Glass JO, Elkin TD, Kun LE, et al. Neurocognitive deficits in medulloblastoma survivors and white matter loss. Ann Neurol 1999;46(6):834-41.

211. Paakko E, Talvensaari K, Pyhtinen J, Lanning M. Late cranial MRI after cranial irradiation in survivors of childhood cancer. Neuroradiology 1994;36(8):652-5.

212. Russo A, Schiliro G. Some aspects of neurotoxicity associated with central nervous system prophylaxis in childhood leukemia. Acta Haematol 1987;78 Suppl 1:139-41.

213. Siffert J, Poussaint TY, Goumnerova LC, Scott RM, LaValley B, Tarbell NJ, et al. Neurological dysfunction associated with postoperative cerebellar mutism. J Neurooncol 2000;48(1):75-81.

214. Ch'ien LT, Aur RJ, Stagner S, Cavallo K, Wood A, Goff J, et al. Long-term neurological implications of somnolence syndrome in children with acute lymphocytic leukemia. Ann Neurol 1980;8(3):273-7.

215. Davidson A, Childs J, Hopewell JW, Tait D. Functional neurological outcome in leukaemic children receiving repeated cranial irradiation. Radiother Oncol 1994;31(2):101-9.

216. Dennis M, Spiegler BJ, Hetherington CR, Greenberg ML. Neuropsychological sequelae of the treatment of children with medulloblastoma. J Neurooncol 1996;29(1):91-101.

217. Eiser C. Psychological sequelae of brain tumours in childhood: a retrospective study. Br J Clin Psychol 1981;20(Pt 1):35-8.

218. Garcia-Perez A, Sierrasesumaga L, Narbona-Garcia J, Calvo-Manuel F, Aguirre-Ventallo M. Neuropsychological evaluation of children with intracranial tumors: impact of treatment modalities. Med Pediatr Oncol 1994;23(2):116-23.

219. Halberg FE, Kramer JH, Moore IM, Wara WM, Matthay KK, Ablin AR. Prophylactic cranial irradiation dose effects on late cognitive function in children treated for acute lymphoblastic leukemia. Int J Radiat Oncol Biol Phys 1992;22(1):13-6.

220. Hill JM, Kornblith AB, Jones D, Freeman A, Holland JF, Glicksman AS, et al. A comparative study of the long term psychosocial functioning of childhood acute lymphoblastic leukemia survivors treated by intrathecal methotrexate with or without cranial radiation. Cancer 1998;82(1):208-18.

221. Ilveskoski I, Pihko H, Wiklund T, Lamminranta S, Perkkio M, Makipernaa A, et al. Neuropsychologic late effects in children with malignant brain tumors treated with surgery, radiotherapy and "8 in 1" chemotherapy. Neuropediatrics 1996;27(3):124-9.

222. Jankovic M, Brouwers P, Valsecchi MG, Van Veldhuizen A, Huisman J, Kamphuis R, et al. Association of 1800 cGy cranial irradiation with intellectual function in children with acute lymphoblastic leukaemia. ISPACC. International Study Group on Psychosocial Aspects of Childhood Cancer. Lancet 1994;344(8917):224-7.

223. Kingma A, Rammeloo LA, van Der Does-van den Berg A, Rekers-Mombarg L, Postma A. Academic career after treatment for acute lymphoblastic leukaemia. Arch Dis Child 2000;82(5):353-7.

224. MacLean WE, Jr., Noll RB, Stehbens JA, Kaleita TA, Schwartz E, Whitt JK, et al. Neuropsychological effects of cranial irradiation in young children with acute lymphoblastic leukemia 9 months after diagnosis. The Children's Cancer Group. Arch Neurol 1995;52(2):156-60.

225. Mulhern RK, Kovnar EH, Kun LE, Crisco JJ, Williams JM. Psychologic and neurologic function following treatment for childhood temporal lobe astrocytoma. J Child Neurol 1988;3(1):47-52.

226. Mulhern RK, Ochs J, Fairclough D. Deterioration of intellect among children surviving leukemia: IQ test changes modify estimates of treatment toxicity. J Consult Clin Psychol 1992;60(3):477-80.

227. Mulhern RK, Wasserman AL, Friedman AG, Fairclough D. Social competence and behavioral adjustment of children who are long-term survivors of cancer. Pediatrics 1989;83(1):18-25.

228. Said JA, Waters BG, Cousens P, Stevens MM. Neuropsychological sequelae of central nervous system prophylaxis in survivors of childhood acute lymphoblastic leukemia. J Consult Clin Psychol 1989;57(2):251-6.

229. Syndikus I, Tait D, Ashley S, Jannoun L. Long-term follow-up of young children with brain tumors after irradiation. Int J Radiat Oncol Biol Phys 1994;30(4):781-7.

230. Tamaroff M, Miller DR, Murphy ML, Salwen R, Ghavimi F, Nir Y. Immediate and long-term posttherapy neuropsychologic performance in children with acute lymphoblastic leukemia treated without central nervous system radiation. J Pediatr 1982;101(4):524-9.

231. Waber DP, Tarbell NJ, Fairclough D, Atmore K, Castro R, Isquith P, et al. Cognitive sequelae of treatment in childhood acute lymphoblastic leukemia: cranial radiation requires an accomplice. J Clin Oncol 1995;13(10):2490-6.

232. Waber DP, Tarbell NJ, Kahn CM, Gelber RD, Sallan SE. The relationship of sex and treatment modality to neuropsychologic outcome in childhood acute lymphoblastic leukemia. J Clin Oncol 1992;10(5):810-7.

233. Anderson SI, Taylor R, Whittle IR. Mood disorders in patients after treatment for primary intracranial tumours. Br J Neurosurg 1999;13(5):480-5.

234. Anholt UV FG, Keener M. Self-concept in survivors of childhood and adolescent cancer. J Psychosoc Oncol 1993;;11:1-16.

235. Arvidson J, Kihlgren M, Hall C, Lonnerholm G. Neuropsychological functioning after treatment for hematological malignancies in childhood, including autologous bone marrow transplantation. Pediatr Hematol Oncol 1999;16(1):9-21.

236. Barakat LP, Kazak AE, Meadows AT, Casey R, Meeske K, Stuber ML. Families surviving childhood cancer: a comparison of posttraumatic stress symptoms with families of healthy children. J Pediatr Psychol 1997;22(6):843-59.

237. Boman K, Bodegard G. Psychological long-term coping with experience of disease and treatment in childhood cancer survivors. Acta Paediatr 1995;84(12):1395-402.

238. Elkin TD, Phipps S, Mulhern RK, Fairclough D. Psychological functioning of adolescent and young adult survivors of pediatric malignancy. Med Pediatr Oncol 1997;29(6):582-8.

239. Fobair P, Hoppe RT, Bloom J, Cox R, Varghese A, Spiegel D. Psychosocial problems among survivors of Hodgkin's disease. J Clin Oncol 1986;4(5):805-14.

240. Glaser AW, Abdul Rashid NF, U CL, Walker DA. School behaviour and health status after central nervous system tumours in childhood. Br J Cancer 1997;76(5):643-50.

241. Gogan JL, Koocher GP, Fine WE, Foster DJ, O'Malley JE. Pediatric cancer survival and marriage: issues affecting adult adjustment. Am J Orthopsychiatry 1979;49(3):423-30.

242. Gray RE, Doan BD, Shermer P, FitzGerald AV, Berry MP, Jenkin D, et al. Psychologic adaptation of survivors of childhood cancer. Cancer 1992;70(11):2713-21.

243. Hays DM, Landsverk J, Sallan SE, Hewett KD, Patenaude AF, Schoonover D, et al. Educational, occupational, and insurance status of childhood cancer survivors in their fourth and fifth decades of life. J Clin Oncol 1992;10(9):1397-406.

244. Jenkin D, Danjoux C, Greenberg M. Subsequent quality of life for children irradiated for a brain tumor before age four years. Med Pediatr Oncol 1998;31(6):506-11.

245. Kaleita TA, Reaman GH, MacLean WE, Sather HN, Whitt JK. Neurodevelopmental outcome of infants with acute lymphoblastic leukemia: a Children's Cancer Group report. Cancer 1999;85(8):1859-65.

246. Kazak AE. Posttraumatic distress in childhood cancer survivors and their parents. Med Pediatr Oncol 1998;Suppl 1:60-8.

247. Kazak AE, Meadows AT. Families of young adolescents who have survived cancer: social-emotional adjustment, adaptability, and social support. J Pediatr Psychol 1989;14(2):175-91.

248. Madan-Swain A, Brown RT, Foster MA, Vega R, Byars K, Rodenberger W, et al. Identity in adolescent survivors of childhood cancer. J Pediatr Psychol 2000;25(2):105-15.

249. Olson AL, Boyle WE, Evans MW, Zug LA. Overall function in rural childhood cancer survivors. The role of social competence and emotional health. Clin Pediatr (Phila) 1993;32(6):334-42.

250. Pelcovitz D, Libov BG, Mandel F, Kaplan S, Weinblatt M, Septimus A. Posttraumatic stress disorder and family functioning in adolescent cancer. J Trauma Stress 1998;11(2):205-21.

251. Pendley JS, Dahlquist LM, Dreyer Z. Body image and psychosocial adjustment in adolescent cancer survivors. J Pediatr Psychol 1997;22(1):29-43.

252. Peper M, Steinvorth S, Schraube P, Fruehauf S, Haas R, Kimmig BN, et al. Neurobehavioral toxicity of total body irradiation: a follow-up in long-term survivors. Int J Radiat Oncol Biol Phys 2000;46(2):303-11.

253. Rauck AM, Green DM, Yasui Y, Mertens A, Robison LL. Marriage in the survivors of childhood cancer: a preliminary description from the Childhood Cancer Survivor Study. Med Pediatr Oncol 1999;33(1):60-3.

254. Sawyer M, Antoniou G, Toogood I, Rice M. Childhood cancer: a two-year prospective study of the psychological adjustment of children and parents. J Am Acad Child Adolesc Psychiatry 1997;36(12):1736-43.

255. Sloper T, Larcombe IJ, Charlton A. Psychosocial adjustment of five-year survivors of childhood cancer. J Cancer Educ 1994;9(3):163-9.

256. Teta MJ, Del Po MC, Kasl SV, Meigs JW, Myers MH, Mulvihill JJ. Psychosocial consequences of childhood and adolescent cancer survival. J Chronic Dis 1986;39(9):751-9.

257. Wasserman AL, Thompson EI, Wilimas JA, Fairclough DL. The psychological status of survivors of childhood/adolescent Hodgkin's disease. Am J Dis Child 1987;141(6):626-31.

258. Williams KS, Ochs J, Williams JM, Mulhern RK. Parental report of everyday cognitive abilities among children treated for acute lymphoblastic leukemia. J Pediatr Psychol 1991;16(1):13-26.

259. Zeltzer LK, Chen E, Weiss R, Guo MD, Robison LL, Meadows AT, et al. Comparison of psychologic outcome in adult survivors of childhood acute lymphoblastic leukemia versus sibling controls: a cooperative Children's Cancer Group and National Institutes of Health study. J Clin Oncol 1997;15(2):547-56.

260. Abayomi OK, Sadeghi-Nejad A. The incidence of late endocrine dysfunction following irradiation for childhood medulloblastoma. Int J Radiat Oncol Biol Phys 1986;12(6):945-8.

261. Albertsson-Wikland K, Lannering B, Marky I, Mellander L, Wannholt U. A longitudinal study on growth and spontaneous growth hormone (GH) secretion in children with irradiated brain tumors. Acta Paediatr Scand 1987;76(6):966-73.

262. Chin HW, Maruyama Y. Age at treatment and long-term performance results in medulloblastoma. Cancer 1984;53(9):1952-8.

263. Clayton PE, Shalet SM. The evolution of spinal growth after irradiation. Clin Oncol (R Coll Radiol) 1991;3(4):220-2.

264. Clayton PE, Shalet SM. Dose dependency of time of onset of radiation-induced growth hormone deficiency. J Pediatr 1991;118(2):226-8.

265. Oberfield SE, Soranno D, Nirenberg A, Heller G, Allen JC, David R, et al. Age at onset of puberty following high-dose central nervous system radiation therapy. Arch Pediatr Adolesc Med 1996;150(6):589-92.

266. Ogilvy-Stuart AL, Wallace WH, Shalet SM. Radiation and neuroregulatory control of growth hormone secretion. Clin Endocrinol (Oxf) 1994;41(2):163-8.

267. Clayton PE, Shalet SM, Morris-Jones PH, Price DA. Growth in children treated for acute lymphoblastic leukaemia. Lancet 1988;1(8583):460-2.

268. DeVile CJ, Grant DB, Hayward RD, Stanhope R. Growth and endocrine sequelae of craniopharyngioma. Arch Dis Child 1996;75(2):108-14.

269. Ogilvy-Stuart AL, Clayton PE, Shalet SM. Cranial irradiation and early puberty. J Clin Endocrinol Metab 1994;78(6):1282-6.

270. Birkebaek NH, Fisker S, Clausen N, Tuovinen V, Sindet-Pedersen S, Christiansen JS. Growth and endocrinological disorders up to 21 years after treatment for acute lymphoblastic leukemia in childhood. Med Pediatr Oncol 1998;30(6):351-6.

271. Shalet SM, Beardwell CG, Pearson D, Jones PH. The effect of varying doses of cerebral irradiation on growth hormone production in childhood. Clin Endocrinol (Oxf) 1976;5(3):287-90.

272. Berglund G, Karlberg J, Marky I, Mellander L. A longitudinal study of growth in children with acute lymphoblastic leukemia. Acta Paediatr Scand 1985;74(4):530-3.

273. Bramswig JH, Wegele M, von Lengerke HJ, Muller RP, Schellong G. The effect of the number of fractions of cranial irradiation on growth in children with acute lymphoblastic leukaemia. Acta Paediatr Scand 1989;78(2):296-302.

274. Clayton PE, Shalet SM, Price DA. Growth response to growth hormone therapy following cranial irradiation. Eur J Pediatr 1988;147(6):593-6.

275. Dacou-Voutetakis C, Kitra V, Grafakos S, Polychronopoulou S, Drakopoulou M, Haidas S. Auxologic data and hormonal profile in long-term survivors of childhood acute lymphoid leukemia. Am J Pediatr Hematol Oncol 1993;15(3):277-83.

276. Davies HA, Didcock E, Didi M, Ogilvy-Stuart A, Wales JK, Shalet SM. Disproportionate short stature after cranial irradiation and combination chemotherapy for leukaemia. Arch Dis Child 1994;70(6):472-5.

277. Davies HA, Didcock E, Didi M, Ogilvy-Stuart A, Wales JK, Shalet SM. Growth, puberty and obesity after treatment for leukaemia. Acta Paediatr Suppl 1995;411:45-50; discussion 1.

278. Holm K, Nysom K, Rasmussen MH, Hertz H, Jacobsen N, Skakkebaek NE, et al. Growth, growth hormone and final height after BMT. Possible recovery of irradiation-induced growth hormone insufficiency. Bone Marrow Transplant 1996;18(1):163-70.

279. Katz JA, Pollock BH, Jacaruso D, Morad A. Final attained height in patients successfully treated for childhood acute lymphoblastic leukemia. J Pediatr 1993;123(4):546-52.

280. Logghe KA, Bourguignon JP, Craen M, Benoit Y. Factors contributing to the impairment of growth in children with acute lymphoblastic leukemia. Horm Res 1988;30(2-3):62-7.

281. Melin AE, Adan L, Leverger G, Souberbielle JC, Schaison G, Brauner R. Growth hormone secretion, puberty and adult height after cranial irradiation with 18 Gy for leukaemia. Eur J Pediatr 1998;157(9):703-7.

282. Moell C, Marky I, Hovi L, Kristinsson J, Rix M, Moe PJ, et al. Cerebral irradiation causes blunted pubertal growth in girls treated for acute leukemia. Med Pediatr Oncol 1994;22(6):375-9.

283. Robison LL, Nesbit ME, Jr., Sather HN, Meadows AT, Ortega JA, Hammond GD. Height of children successfully treated for acute lymphoblastic leukemia: a report from the Late Effects Study Committee of Childrens Cancer Study Group. Med Pediatr Oncol 1985;13(1):14-21.

284. Herber SM, Dunsmore IR, Milner RD. Final stature in brain tumours other than craniopharyngioma: effect of growth hormone. Horm Res 1985;22(1-2):63-7.

285. Leiper AD, Stanhope R, Lau T, Grant DB, Blacklock H, Chessells JM, et al. The effect of total body irradiation and bone marrow transplantation during childhood and adolescence on growth and endocrine function. Br J Haematol 1987;67(4):419-26.

286. Leiper AD, Stanhope R, Kitching P, Chessells JM. Precocious and premature puberty associated with treatment of acute lymphoblastic leukaemia. Arch Dis Child 1987;62(11):1107-12.

287. Sklar CA, Mertens AC, Walter A, Mitchell D, Nesbit ME, O'Leary M, et al. Changes in body mass index and prevalence of overweight in survivors of childhood acute lymphoblastic leukemia: role of cranial irradiation. Med Pediatr Oncol 2000;35(2):91-5.

288. Crowne EC, Moore C, Wallace WH, Ogilvy-Stuart AL, Addison GM, Morris-Jones PH, et al. A novel variant of growth hormone (GH) insufficiency following low dose cranial irradiation. Clin Endocrinol (Oxf) 1992;36(1):59-68.

289. Didcock E, Davies HA, Didi M, Ogilvy Stuart AL, Wales JK, Shalet SM. Pubertal growth in young adult survivors of childhood leukemia. J Clin Oncol 1995;13(10):2503-7.

290. Clement-De Boers A, Oostdijk W, Van Weel-Sipman MH, Van den Broeck J, Wit JM, Vossen JM. Final height and hormonal function after bone marrow transplantation in children. J Pediatr 1996;129(4):544-50.

291. Cohen A, Duell T, Socie G, van Lint MT, Weiss M, Tichelli A, et al. Nutritional status and growth after bone marrow transplantation (BMT) during childhood: EBMT Late-Effects Working Party retrospective data. European Group for Blood and Marrow Transplantation. Bone Marrow Transplant 1999;23(10):1043-7.

292. Cohen A, Rovelli A, Bakker B, Uderzo C, van Lint MT, Esperou H, et al. Final height of patients who underwent bone marrow transplantation for hematological disorders during childhood: a study by the Working Party for Late Effects-EBMT. Blood 1999;93(12):4109-15.

293. Cohen A, Rovelli A, Van-Lint MT, Uderzo C, Morchio A, Pezzini C, et al. Final height of patients who underwent bone marrow transplantation during childhood. Arch Dis Child 1996;74(5):437-40.

294. Cohen A, van Lint MT, Uderzo C, Rovelli A, Lavagetto A, Vitale V, et al. Growth in patients after allogeneic bone marrow transplant for hematological diseases in childhood. Bone Marrow Transplant 1995;15(3):343-8.

295. Willi SM, Cooke K, Goldwein J, August CS, Olshan JS, Moshang T, Jr. Growth in children after bone marrow transplantation for advanced neuroblastoma compared with growth after transplantation for leukemia or aplastic anemia. J Pediatr 1992;120(5):726-32.

296. Afify Z, Shaw PJ, Clavano-Harding A, Cowell CT. Growth and endocrine function in children with acute myeloid leukaemia after bone marrow transplantation using busulfan/cyclophosphamide. Bone Marrow Transplant 2000;25(10):1087-92.

297. Katz JA, Chambers B, Everhart C, Marks JF, Buchanan GR. Linear growth in children with acute lymphoblastic leukemia treated without cranial irradiation. J Pediatr 1991;118(4 Pt 1):575-8.

298. Makipernaa A, Dunkel L, Siimes MA. Growth after treatment of solid tumours in childhood. Acta Paediatr Scand 1990;79(8-9):817-22.

299. Roman J, Villaizan CJ, Garcia-Foncillas J, Salvador J, Sierrasesumaga L. Growth and growth hormone secretion in children with cancer treated with chemotherapy. J Pediatr 1997;131(1 Pt 1):105-12.

300. Odame I, Reilly JJ, Gibson BE, Donaldson MD. Patterns of obesity in boys and girls after treatment for acute lymphoblastic leukaemia. Arch Dis Child 1994;71(2):147-9.

301. Craig F, Leiper AD, Stanhope R, Brain C, Meller ST, Nussey SS. Sexually dimorphic and radiation dose dependent effect of cranial irradiation on body mass index. Arch Dis Child 1999;81(6):500-4.

302. (SIGN). SIGN. Mangement of obesity . Edinburgh;SIGN:2010.(SIGN publication no.115). 2003.

303. Clayton PE, Shalet SM, Price DA. Growth response to growth hormone therapy following craniospinal irradiation. Eur J Pediatr 1988;147(6):597-601.

304. Burns EC, Tanner JM, Preece MA, Cameron N. Growth hormone treatment in children with craniopharyngioma: final growth status. Clin Endocrinol (Oxf) 1981;14(6):587-95.

305. Butenandt O, Jocham A, Schwarz HP, Sperlich M, Tschop M. Childhood onset of GH deficiency: reassessment of GH status and effects of substitution. Growth Horm IGF Res 1998;8 Suppl A:9-13.

306. Hogeveen M, Noordam C, Otten B, Wit JM, Massa G. Growth before and during growth hormone treatment in children operated for craniopharyngioma. Horm Res 1997;48(6):258-62.

307. Hovi L, Saarinen-Pihkala UM, Vettenranta K, Lipsanen M, Tapanainen P. Growth in children with poor-risk neuroblastoma after regimens with or without total body irradiation in preparation for autologous bone marrow transplantation. Bone Marrow Transplant 1999;24(10):1131-6.

308. Ogilvy-Stuart AL, Shalet SM. Growth and puberty after growth hormone treatment after irradiation for brain tumours. Arch Dis Child 1995;73(2):141-6.

309. Ogilvy-Stuart AL, Stirling HF, Kelnar CJ, Savage MO, Dunger DB, Buckler JM, et al. Treatment of radiation-induced growth hormone deficiency with growth hormone-releasing hormone. Clin Endocrinol (Oxf) 1997;46(5):571-8.

310. Papadimitriou A, Urena M, Hamill G, Stanhope R, Leiper AD. Growth hormone treatment of growth failure secondary to total body irradiation and bone marrow transplantation. Arch Dis Child 1991;66(6):689-92.

311. Price DA, Ranke MB, Guilbaud O. Growth response in the first year of growth hormone treatment in prepubertal children with organic growth hormone deficiency: a comparison with idiopathic growth hormone deficiency. The Executive Scientific Committee of the Kabi International Growth Study. Acta Paediatr Scand Suppl 1990;370:131-7; discussion 8.

312. Sulmont V, Brauner R, Fontoura M, Rappaport R. Response to growth hormone treatment and final height after cranial or craniospinal irradiation. Acta Paediatr Scand 1990;79(5):542-9.

313. Vassilopoulou S, Klein MJ, Moore BD, 3rd, Reid HL, Ater J, Zietz HA. Efficacy of growth hormone replacement therapy in children with organic growth hormone deficiency after cranial irradiation. Horm Res 1995;43(5):188-93.

314. Winter RJ, Green OC. Irradiation-induced growth hormone deficiency: blunted growth response and accelerated skeletal maturation to growth hormone therapy. J Pediatr 1985;106(4):609-12.

315. Price DA, Wilton P, Jonsson P, Albertsson-Wikland K, Chatelain P, Cutfield W, et al. Efficacy and safety of growth hormone treatment in children with prior craniopharyngioma: an analysis of the Pharmacia and Upjohn International Growth Database (KIGS) from 1988 to 1996. Horm Res 1998;49(2):91-7.

316. Arslanian SA, Becker DJ, Lee PA, Drash AL, Foley TP, Jr. Growth hormone therapy and tumor recurrence. Findings in children with brain neoplasms and hypopituitarism. Am J Dis Child 1985;139(4):347-50.

317. Buchanan CR, Preece MA, Milner RD. Mortality, neoplasia, and Creutzfeldt-Jakob disease in patients treated with human pituitary growth hormone in the United Kingdom. Bmj 1991;302(6780):824-8.

318. Clayton PE, Shalet SM, Gattamaneni HR, Price DA. Does growth hormone cause relapse of brain tumours? Lancet 1987;1(8535):711-3.

319. Sklar CA, Mertens AC, Mitby P, Occhiogrosso G, Qin J, Heller G, et al. Risk of disease recurrence and second neoplasms in survivors of childhood cancer treated with growth hormone: a report from the Childhood Cancer Survivor Study. J Clin Endocrinol Metab 2002;87(7):3136-41.

320. Wyatt D. Melanocytic nevi in children treated with growth hormone. Pediatrics 1999;104(4 Pt 2):1045-50.

321. Zvulunov A, Wyatt DT, Laud PW, Esterly NB. Lack of effect of growth hormone therapy on the count and density of melanocytic naevi in children. Br J Dermatol 1997;137(4):545-8.

322. Fradkin JE, Mills JL, Schonberger LB, Wysowski DK, Thomson R, Durako SJ, et al. Risk of leukemia after treatment with pituitary growth hormone. Jama 1993;270(23):2829-32.

323. Fromm M, Littman P, Raney RB, Nelson L, Handler S, Diamond G, et al. Late effects after treatment of twenty children with soft tissue sarcomas of the head and neck. Experience at a single institution with a review of the literature. Cancer 1986;57(10):2070-6.

324. Jaffe N, Toth BB, Hoar RE, Ried HL, Sullivan MP, McNeese MD. Dental and maxillofacial abnormalities in long-term survivors of childhood cancer: effects of treatment with chemotherapy and radiation to the head and neck. Pediatrics 1984;73(6):816-23.

325. Kaste SC, Hopkins KP, Bowman LC. Dental abnormalities in long-term survivors of head and neck rhabdomyosarcoma. Med Pediatr Oncol 1995;25(2):96-101.

326. Kaste SC, Hopkins KP, Jones D, Crom D, Greenwald CA, Santana VM. Dental abnormalities in children treated for acute lymphoblastic leukemia. Leukemia 1997;11(6):792-6.

327. Nasman M, Forsberg CM, Dahllof G. Long-term dental development in children after treatment for malignant disease. Eur J Orthod 1997;19(2):151-9.

328. Pajari U, Lanning M. Developmental defects of teeth in survivors of childhood ALL are related to the therapy and age at diagnosis. Med Pediatr Oncol 1995;24(5):310-4.

329. Purdell-Lewis DJ, Stalman MS, Leeuw JA, Humphrey GB, Kalsbeek H. Long term results of chemotherapy on the developing dentition: caries risk and developmental aspects. Community Dent Oral Epidemiol 1988;16(2):68-71.

330. Dahllof G, Forsberg CM, Ringden O, Bolme P, Borgstrom B, Nasman M, et al. Facial growth and morphology in long-term survivors after bone marrow transplantation. Eur J Orthod 1989;11(4):332-40.

331. Imhof SM, Mourits MP, Hofman P, Zonneveld FW, Schipper J, Moll AC, et al. Quantification of orbital and mid-facial growth retardation after megavoltage external beam irradiation in children with retinoblastoma. Ophthalmology 1996;103(2):263-8.

332. Nasman M, Bjork O, Soderhall S, Ringden O, Dahllof G. Disturbances in the oral cavity in pediatric long-term survivors after different forms of antineoplastic therapy. Pediatr Dent 1994;16(3):217-23.

333. Dahllof G, Krekmanova L, Kopp S, Borgstrom B, Forsberg CM, Ringden O. Craniomandibular dysfunction in children treated with total-body irradiation and bone marrow transplantation. Acta Odontol Scand 1994;52(2):99-105.

334. Dens F, Boogaerts M, Boute P, Declerck D, Demuynck H, Vinckier F, et al. Caries-related salivary microorganisms and salivary flow rate in bone marrow recipients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996;81(1):38-43.

335. Dens F, Boute P, Otten J, Vinckier F, Declerck D. Dental caries, gingival health, and oral hygiene of long term survivors of paediatric malignant diseases. Arch Dis Child 1995;72(2):129-32.

336. Duggal MS, Curzon ME, Bailey CC, Lewis IJ, Prendergast M. Dental parameters in the long-term survivors of childhood cancer compared with siblings. Oral Oncol 1997;33(5):348-53.

337. Fleming P, Kinirons MJ. Study of the dental health of children in remission from acute lymphoblastic leukaemia in Northern Ireland. Community Dent Oral Epidemiol 1993;21(5):309-12.

338. Guyuron B, Dagys AP, Munro IR, Ross RB. Effect of irradiation on facial growth: a 7- to 25-year follow-up. Ann Plast Surg 1983;11(5):423-7.

339. Sonis AL, Waber DP, Sallan S, Tarbell NJ. The oral health of long-term survivors of acute lymphoblastic leukaemia: a comparison of three treatment modalities. Eur J Cancer B Oral Oncol 1995;31B(4):250-2.

340. Clinical guideline on dental management of pediatric patients receiving chemotherapy, hematopoietic cell transplantation, and/or radiation. Pediatr Dent 2004;26(7 Suppl):144-9.

341. Sklar C, Whitton J, Mertens A, Stovall M, Green D, Marina N, et al. Abnormalities of the thyroid in survivors of Hodgkin's disease: data from the Childhood Cancer Survivor Study. J Clin Endocrinol Metab 2000;85(9):3227-32.

342. Picco P, Garaventa A, Claudiani F, Gattorno M, De Bernardi B, Borrone C. Primary hypothyroidism as a consequence of 131-I-metaiodobenzylguanidine treatment for children with neuroblastoma. Cancer 1995;76(9):1662-4.

343. Devney RB, Sklar CA, Nesbit ME, Jr., Kim TH, Williamson JF, Robison LL, et al. Serial thyroid function measurements in children with Hodgkin disease. J Pediatr 1984;105(2):223-7.

344. Fleming ID, Black TL, Thompson EI, Pratt C, Rao B, Hustu O. Thyroid dysfunction and neoplasia in children receiving neck irradiation for cancer. Cancer 1985;55(6):1190-4.

345. Green DM, Brecher ML, Yakar D, Blumenson LE, Lindsay AN, Voorhess ML, et al. Thyroid function in pediatric patients after neck irradiation for Hodgkin disease. Med Pediatr Oncol 1980;8(2):127-36.

346. Black P, Straaten A, Gutjahr P. Secondary thyroid carcinoma after treatment for childhood cancer. Med Pediatr Oncol 1998;31(2):91-5.

347. Tucker MA, Jones PH, Boice JD, Jr., Robison LL, Stone BJ, Stovall M, et al. Therapeutic radiation at a young age is linked to secondary thyroid cancer. The Late Effects Study Group. Cancer Res 1991;51(11):2885-8.

348. Chin D, Sklar C, Donahue B, Uli N, Geneiser N, Allen J, et al. Thyroid dysfunction as a late effect in survivors of pediatric medulloblastoma/primitive neuroectodermal tumors: a comparison of hyperfractionated versus conventional radiotherapy. Cancer 1997;80(4):798-804.

349. Oberfield SE, Allen JC, Pollack J, New MI, Levine LS. Long-term endocrine sequelae after treatment of medulloblastoma: prospective study of growth and thyroid function. J Pediatr 1986;108(2):219-23.

350. Pottern LM, Kaplan MM, Larsen PR, Silva JE, Koenig RJ, Lubin JH, et al. Thyroid nodularity after childhood irradiation for lymphoid hyperplasia: a comparison of questionnaire and clinical findings. J Clin Epidemiol 1990;43(5):449-60.

351. Favus MJ, Schneider AB, Stachura ME, Arnold JE, Ryo UY, Pinsky SM, et al. Thyroid cancer occurring as a late consequence of head-and-neck irradiation. Evaluation of 1056 patients. N Engl J Med 1976;294(19):1019-25.

352. Borgstrom B, Bolme P. Thyroid function in children after allogeneic bone marrow transplantation. Bone Marrow Transplant 1994;13(1):59-64.

353. Katsanis E, Shapiro RS, Robison LL, Haake RJ, Kim T, Pescovitz OH, et al. Thyroid dysfunction following bone marrow transplantation: long-term follow-up of 80 pediatric patients. Bone Marrow Transplant 1990;5(5):335-40.

354. Thomas BC, Stanhope R, Plowman PN, Leiper AD. Endocrine function following single fraction and fractionated total body irradiation for bone marrow transplantation in childhood. Acta Endocrinol (Copenh) 1993;128(6):508-12.

355. Livesey EA, Brook CG. Thyroid dysfunction after radiotherapy and chemotherapy of brain tumours. Arch Dis Child 1989;64(4):593-5.

356. Shafford EA, Kingston JE, Healy JC, Webb JA, Plowman PN, Reznek RH. Thyroid nodular disease after radiotherapy to the neck for childhood Hodgkin's disease. Br J Cancer 1999;80(5-6):808-14.

357. Soberman N, Leonidas JC, Cherrick I, Schiff R, Karayalcin G. Sonographic abnormalities of the thyroid gland in longterm survivors of Hodgkin disease. Pediatr Radiol 1991;21(4):250-3.

358. Solt I, Gaitini D, Pery M, Hochberg Z, Stein M, Arush MW. Comparing thyroid ultrasonography to thyroid function in long-term survivors of childhood lymphoma. Med Pediatr Oncol 2000;35(1):35-40.

359. Aslett H, Levitt G, Richardson A, Gibson F. A review of long-term follow-up for survivors of childhood cancer. Eur J Cancer 2007;43(12):1781-90.

360. Heirs M, Suekarran S, Slack R, Light K, Gibson F, Glaser A, et al. A systematic review of models of care for the follow up of childhood cancer survivors. Pediatr Blood Cancer 2012.

361. Chief Medical Officers for the United Kingdom. VITAMIN D - Advice on supplements for at risk groups. [cited 01/12/2012]. Available from url: http://www.scotland.gov.uk/Resource/0038/00386921.pdf

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Edinburgh Office | Gyle Square |1 South Gyle Crescent | Edinburgh | EH12 9EB
Telephone 0131 623 4300 Fax 0131 623 4299

Glasgow Office | Delta House | 50 West Nile Street | Glasgow | G1 2NP
Telephone 0141 225 6999 Fax 0141 248 3776

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