



Long term follow up of survivors of childhood cancer

A national clinical guideline



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January 2004

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE

1 ⁺⁺	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1 ⁺	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1 ⁻	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
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 of RCTs, or RCT rated as 1 ⁺⁺ and directly applicable to the target population; <i>or</i> 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; <i>or</i> 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; <i>or</i> Extrapolated evidence from studies rated as 2 ⁺⁺
D	Evidence level 3 or 4; <i>or</i> Extrapolated evidence from studies rated as 2 ⁺

GOOD PRACTICE POINTS

<input checked="" type="checkbox"/>	Recommended best practice based on the clinical experience of the guideline development group
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1 Introduction

1.1 POPULATION COVERED BY THE GUIDELINE

This guideline is applicable to all young people who have survived cancer, and who may experience expected and unexpected late effects that are related to the treatment received, rather than the specific cancer. The guideline is aimed at primary care staff who have cancer survivors as their patients, as well as secondary care and long term follow up (late effects) clinic staff who usually manage the long term care of this group.

1.2 DEFINITIONS

Childhood cancers exhibit greater diversity in terms of anatomical site and histological type than adult cancers, where carcinomas of the breast, lung and gut predominate.

Of all childhood cancers, approximately:

- one third are leukaemias and 80% of these 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; NHL*)

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

1.3 REMIT OF THE GUIDELINE

Childhood cancer may be treated with surgery, chemotherapy, radiotherapy and/or bone marrow transplantation. Long term morbidity risks in childhood cancer survivors largely relate to treatment modality and the challenge remains to further improve survival rates whilst reducing the incidence and severity of such treatment-induced late effects. A major challenge faced by paediatric oncologists is to sustain the excellent survival rates whilst striving to achieve optimal quality of life. With follow up and early detection and treatment, many potential problems may be ameliorated, allowing cancer survivors to enjoy full and active lives.

This guideline covers five key areas:

- assessment and achievement of normal growth (*see section 3*)
- achievement of normal progression through puberty and factors affecting fertility (*see section 4*)
- early identification, assessment and treatment of cardiac abnormalities (*see section 5*)
- assessment of thyroid function (*see section 6*)
- assessment and achievement of optimum neurodevelopment and psychological health (*see section 7*).

The guideline does not systematically address other important areas, including second malignancy, or renal, respiratory and liver dysfunction. Late effects involving vision and hearing have also not been addressed.

1.4 THE NEED FOR A GUIDELINE

Continuing therapeutic advances for the management of childhood malignancies mean that the majority of children can realistically expect long term survival.^{1,2} Cancer in childhood is rare, with about 125 new cases per year in Scotland, and a cumulative risk of around one in 500 by the age of 15 years. With long term survival rates of around 70%, it has been estimated that by the year 2010, about one in 715 of the adult population will be a long term survivor of childhood cancer (NHSScotland Information and Statistics Division, unpublished data).

*Table 1: 5-year survival rates (%) in childhood cancers from 1962-1996.
(Source - National Registry of Childhood Tumours)*

	1962-66	1967-71	1972-76	1977-81	1982-86	1987-91	1992-96
ALL	4	17	44	56	70	75	81
Acute non-lymphoblastic leukaemia	2	2	7	17	30	47	54
CNS	37	37	43	48	54	57	68
Ewing's	25	23	40	34	45	68	61
Gonadal germ-cell	55	52	56	74	90	94	96
Hodgkin's	39	68	81	89	89	93	94
NHL	17	21	26	45	67	76	78
Neuroblastoma	18	17	19	31	43	41	53
Osteosarcoma	17	18	22	25	47	51	57
Retinoblastoma	88	86	86	88	90	95	96
Rhabdomyo-sarcoma	25	23	33	44	58	59	66
Wilms'	29	43	62	76	80	82	80
ALL CANCERS	24	29	42	51	62	67	73

Data up to 1999 show that these survival rates have been sustained (NHSScotland Information and Statistics Division, unpublished data). Large epidemiological studies have analysed the subsequent mortality and its causes in children and adolescents who survived five years from the diagnosis of cancer. Two studies^{3,4} found that 5-year survivors of childhood cancer have a standardised mortality ratio of 11 (ie an 11 fold increased risk of death in subsequent years when compared with age and sex specific expected rates for the general population). A North American study³ described a cohort of 20,227 5-year survivors of cancer diagnosed between 1970 and 1986 before the age of 21, which included 208,947 person years of follow up. The risk of death in this cohort was significantly higher in females (standardised mortality ratio, SMR = 18.2), individuals diagnosed with cancer before the age of 5 years (SMR = 14.0) and those with an initial diagnosis of leukaemia (SMR = 15.5) or central nervous system tumour (SMR = 15.7). The leading cause of death among 5-year survivors was recurrence of the original cancer with a statistically significant excess mortality rate seen due to subsequent malignancies (SMR = 19.4) as well as cardiac (SMR = 8.2), pulmonary (SMR = 9.2) and other causes (SMR = 3.3). Of the cohort, 90% were alive at the time of the study with death due to recurrent cancer accounting for 67% of all deaths. There was no excess mortality from external causes, for example, road traffic accidents. These studies may provide a resource for understanding how mortality may be reduced further, and how modifications of current therapy may reduce treatment related mortality in the future.

An important challenge for this guideline is to make evidence based recommendations for the long term follow up of survivors that address their needs. In areas where there is no evidence, the guideline highlights research opportunities to study and evaluate the long term effects of treatment so that promising interventions can be assessed through collaborative multicentre studies.⁵

1.5 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of medical 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. These parameters of practice should be considered guidelines only. Adherence to them 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 regarding a particular clinical procedure or treatment plan must be made by the doctor, following discussion of the options with the patient, in light of the diagnostic and treatment choices available. However, it is advised 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.

1.6 REVIEW AND UPDATING

This guideline was issued in 2004 and will be considered for review as new evidence becomes available. Any updates to the guideline in the interim period will be noted on the SIGN website: www.sign.ac.uk

2 Long term follow up

2.1 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. The British Childhood Cancer Survivor Study will investigate the risks of particular adverse health outcomes occurring amongst survivors and their offspring and relate outcomes to treatment modalities. This study may answer some of these questions when it reports.

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

2.2 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.

2.3 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 2 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 2: 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.

2.4 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 3.

2.4.1 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.

2.4.2 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.

2.4.3 LEVEL 3 FOLLOW UP

At the other end of the scale, there are patients who have received radiotherapy (other than low-dose 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 3: 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	<ul style="list-style-type: none"> ▪ surgery alone ▪ low risk chemotherapy 	postal or telephone	1-2 years	<ul style="list-style-type: none"> ▪ Wilms' stage I or II ▪ Langerhans cell histiocytosis (single system disease) ▪ germ cell tumours (surgery only)
2	<ul style="list-style-type: none"> ▪ chemotherapy ▪ low-dose cranial irradiation less than or equal to 24 Gy 	nurse or primary care-led*	1-2 years	<ul style="list-style-type: none"> ▪ majority of patients (eg ALL in first remission)
3	<ul style="list-style-type: none"> ▪ radiotherapy, except low-dose cranial irradiation ▪ megatherapy 	medically supervised long term follow up clinic	annual	<ul style="list-style-type: none"> ▪ brain tumours ▪ post bone marrow transplantation ▪ stage 4 patients (any tumour type)

* with appropriate training protocols

2.5 SECOND CANCERS IN HODGKIN'S DISEASE

Second cancer is the leading cause of death in long term survivors of Hodgkin's disease, with exceptionally high risks of breast cancer among women treated at a young age.¹⁴⁵ Breast cancer risk increases with increasing radiation dose up to at least 40 Gy. A radiation dose of 4 Gy or more delivered to the breast was associated in one study with a 3.2-fold (95% CI 1.4-8.2) excess risk. The risk increased to eight fold (95% CI 2.6-26.4) with a dose of more than 40 Gy.¹⁴⁶ Young age at treatment has a major effect on risk of second malignancy after Hodgkin's disease.¹⁴⁷ Although absolute excess risks are greater for older patients, relative risks of several important malignancies are much greater for patients who are treated when young.

2+

Following advice from the National Cancer Research Institute (NCRI), a UK-wide patient notification exercise is being planned and co-ordinated across the four UK Departments of Health to inform individual patients of their increased risk of breast cancer following supradiaphragmatic radiotherapy for Hodgkin's Disease. These women will be contacted to inform them of their increased risk and to invite them to attend a consultation session to discuss follow up arrangements.

2.6 CONCLUSIONS

There is an increasing evidence base of mainly retrospective studies that underpins decisions concerning the clinical follow up of the long term survivor. There is a need for prospective evaluation of new treatments. Information to guide and inform the follow up of the survivors of childhood cancer will come from national, population-based cohort studies, large multicentre clinical studies, and randomised clinical trials which are designed to evaluate both survival and long term toxicities of alternative treatment strategies. As knowledge accumulates the level of clinical surveillance should more appropriately match clinical need.

3 Growth problems

3.1 GROWTH IMPAIRMENT FOLLOWING THERAPY FOR CHILDHOOD CANCER

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).⁶⁻¹²

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.¹³

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

3.2 SPECIAL GROUPS AT RISK OF GROWTH IMPAIRMENT

3.2.1 SURVIVORS OF CRANIOPHARYNGIOMA

The majority of children with craniopharyngioma have symptoms of abnormal pituitary function at presentation,¹⁴ most commonly growth impairment and/or pubertal delay. Treatment includes surgery and/or radiotherapy.

2+

3.2.2 SURVIVORS OF 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.⁶⁻¹² 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.^{11,15}

2+

3.2.3 SURVIVORS OF ACUTE LYMPHOBLASTIC LEUKAEMIA TREATED WITH PROPHYLACTIC LOW-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.^{16,17} Overall, final height in the majority is less than predicted, but almost all fall within the normal adult range.¹⁸⁻²⁹ 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.^{17,30,31}

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.^{7,32,33}

In survivors with normal growth before the onset of puberty there may be an attenuated growth spurt in puberty associated with growth hormone insufficiency.³⁴

A significant minority of girls, but not boys, will have premature or precocious puberty.^{23,27,35}

2⁺⁺
2⁺

3.2.4 SURVIVORS WHO HAVE RECEIVED BONE MARROW TRANSPLANTS

Conditioning for bone marrow transplants for 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.^{24,31,36-40} Many of these children however attain adult height within the normal range.

Recipients of bone marrow transplants for neuroblastoma, who had received abdominal radiotherapy prior to transplant, had very poor growth.⁴¹ In contrast, survivors of acute myeloid leukaemia, who received no radiotherapy prior to bone marrow transplant, had no growth impairment.⁴²

2⁺⁺
2⁺

3.2.5 OTHERS

More recently, prophylaxis in acute lymphoblastic leukaemia has not included radiotherapy. Some of these children show impaired growth, but final height is usually normal, and growth hormone deficiency is much less common.^{16,25,28,43} Similar results are seen with children with solid tumours.^{44,45}

2⁺⁺
2⁺

3.3 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 (see section 4).
- 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.

3.4 OBESITY

There is accumulating 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.⁴⁶ This problem is worse in girls.^{21,23,47,48} 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 4 years of age.⁴⁹ The management of obesity in children and young people is discussed in detail in SIGN guideline number 69.

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.

3.5 TREATMENT WITH GROWTH HORMONE

3.5.1 EFFECTIVENESS

Growth hormone replacement therapy has shown varying rates of success in growth impaired cancer survivors.^{13,20,30,50-61} In survivors of craniopharyngioma a growth response similar to that in children with idiopathic growth hormone deficiency is seen.⁶²

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.

3.5.2 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.^{52,62-66} 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.⁶² No increase in melanocytic naevi was detected in children receiving growth hormone.^{67,68} 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.⁶⁹

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. Growth hormone is important both to maximise growth potential and for bone mineralisation. Bone accretion is not complete until young adulthood.

3.6 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.

3.6.1 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.⁷⁰⁻⁷⁶ The younger the age of the child at treatment, the greater the chance of later dental problems.^{70-73,77-79} 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.^{75,77-86}

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.^{75,81} Orbital growth, cataracts and otological hearing loss have been reported for children receiving radiation of eyes and ears.^{75,78} Dental crown defects and root foreshortening are more prevalent the younger the child and more severe with increasing doses of radiation.^{72,73,75} For survivors of acute lymphoblastic leukaemia the evidence suggests that more severe disturbances are evident in children treated with prophylactic cranial radiotherapy.^{70,71,74} 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.^{76,77,79,80}

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.⁸⁷

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.

4 Problems with puberty and reproduction

One of the most important issues for the 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.⁸⁸

4.1 MALE PUBERTY AND FERTILITY

4.1.1 NORMAL PHYSIOLOGY

The seminiferous epithelium of normal 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 4 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).⁸⁹

The prepubertal 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 volumes and maximal at approximately 12 ml. The normal adult testis is 15-25 ml. Azoospermia is likely if the volume of each adult testis is 10 ml or less.

4.1.2 DAMAGE TO TESTES AND FERTILITY PROBLEMS

Both prepubertal and postpubertal testes are susceptible to cytotoxic treatment by alkylating agents or radiotherapy to the gonads.⁹⁰⁻¹⁰⁸ Sertoli cells and germ cells are more susceptible than Leydig cells to chemotherapeutic or radiotherapeutic damage.^{92,109} 2++
2+
3

Decreased testicular volume (≤ 10 ml) is associated with impaired spermatogenesis in the postpubertal male. Testicular damage is also associated with elevated follicle stimulating hormone (FSH) and reduced serum inhibin B.^{90,91} 2++
2+
3

Direct irradiation to the testes causes permanently impaired spermatogenesis.¹¹⁰⁻¹¹³ Leydig cell failure is unlikely below a threshold dose of 20 Gy.^{112,114} Doses to the testes in excess of 20 Gy may result in delayed puberty.^{111,112,114} 3

Total body irradiation causes permanently impaired spermatogenesis but has variable effects on Leydig cell function.^{96,98,114} Most prepubertal boys undergoing bone marrow transplantation with chemotherapy and hyperfractionated total body irradiation can expect to progress normally through puberty.¹¹⁴ 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.¹¹⁵ 2+

Most studies suggest that fertility outcomes are good for young people treated for leukaemia, and solid tumours except Hodgkin's disease. Treatment for Hodgkin's disease with multiple courses of alkylating agent based chemotherapy, irrespective of stage of puberty at treatment, is likely to be sterilising.^{94,109,116-118} 2+

Sequential treatment regimens (alkylating agent based, alternating with anthracycline based), still carry a significant risk of infertility.¹¹⁹ Recovery of spermatogenesis has been documented after anthracycline based treatment alone.¹²⁰ 2+

It is not possible to protect prepubertal testes from potentially toxic treatment nor is it currently appropriate to obtain germ cells for later use. It is also not currently possible to predict fertility outcome in individual male patients who are prepubertal at time of treatment.

Spontaneous progression through puberty is not a guarantee of future fertility.

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

- 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, inhibin B (if available)
 - semen analysis.
- Men who have evidence of impaired fertility should be referred for specialist assessment as they could benefit from ART.
- Fertility counselling should be provided to survivors of childhood cancer.

4.1.3 FERTILITY PRESERVATION

Cryopreservation of semen from young patients (14-17 years of age) is as effective as that of semen from young adults (18-20 years).¹²¹⁻¹²³ Cryopreservation of semen is dependent on the ability of the young patient to produce a specimen, and in the UK, consent for storage requires him to be “Gillick” competent.

2+
3

- Cryopreservation of semen should be offered to young male patients whose cancer therapy will include potentially gonadotoxic treatments.

4.1.4 PROGENY

The offspring of male Wilms’ tumour survivors have no apparent excess risk for birth defects.¹²⁴ Spontaneously conceived offspring of patients treated for cancer in childhood have no excess of congenital anomalies or other diseases.^{100,125}

2+
3

4.2 FEMALE PUBERTY AND FERTILITY

4.2.1 NORMAL PHYSIOLOGY

Oogonia arising from primordial germ cells in the yolk sac reach a complement of 6-7 million by the sixth month of gestation; these represent the total fixed number of germ cells available.¹²⁶ Primordial follicles consist of a primary oocyte surrounded by a single layer of spindle-shaped cells. By the time of birth, the pool of primordial follicles has already been reduced to 2-4 million by ongoing apoptosis and further attrition leaves approximately 400,000 by the time of menarche.

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.¹²⁷ 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.

During childhood, increased amplitude, frequency and duration of gonadotrophin secretion, will result in consonant pubertal progression, taking an average two years to menarche (at B3 or B4),¹²⁷ at mean age 12.4 years (range 10-14.5).

For the first year after menarche, menstrual cycles are often anovulatory. Ovulatory cycles, and thus the potential for fertility, can occasionally occur in girls whose sexual development is not quite complete.

4.2.2 PUBERTY

Radiotherapy to the hypothalamus/pituitary may result in delayed puberty; the risk increasing with higher doses (greater than 30–40 Gy). Lower doses (less than 30 Gy) are more commonly associated with precocious puberty especially in young girls.^{11,23,27,33,35,128} 2+

C Girls treated with cranial irradiation should have their pubertal status assessed three to four times a year from the end of treatment as part of a routine clinical assessment.

4.2.3 REPRODUCTIVE DYSFUNCTION

In the female, chemotherapy and radiotherapy may affect uterine growth, damage the ovary and hasten oocyte depletion, resulting in loss of hormone production, uterine dysfunction and a premature menopause.¹²⁹

Treatment of Hodgkin's disease with chemotherapy alone is less likely to be damaging to reproductive function in girls than it is in boys.^{91,100,116} 2+
3

Cyclophosphamide when used alone as conditioning treatment for bone marrow transplantation, is not associated with long term gonadal function impairment.¹⁰³ High dose busulfan is a major cause of ovarian failure.¹³⁰ 3

Whole abdominal, pelvic or total body irradiation is likely to result in impairment of ovarian function.^{98,103,114,124,131-133} 2+
3

Uterine distensibility and blood flow are irreversibly affected by high dose pelvic or abdominal irradiation in childhood.¹³⁴ Non-invasive assessment may predict potential for pregnancy following ovum donation and embryo transfer. 3

Physiological sex steroid replacement improves uterine function. Women who have had total body irradiation may benefit from assisted reproductive technology.¹³⁵ 3

Most studies are reassuring about female reproductive outcome after chemotherapy alone for childhood cancer although these young women may be at risk of a premature menopause due to reduced ovarian reserve, and may benefit from hormone replacement therapy (HRT).^{104,116,136-139} 2+
2+
3

C Women who have evidence of impaired fertility should be referred for specialist assessment as they could benefit from assisted reproductive technology.

4.2.4 PROGENY

Female survivors of Wilms' tumours who have been treated with abdominal radiation, are at an increased risk for a variety of reproductive problems including fetal loss, early delivery, and birth defects in offspring.^{124,140} 3

Flank irradiation is associated with low birth weight in subsequent offspring.^{102,141,142} 3

Females successfully treated for childhood acute lymphoblastic leukaemia have a nearly normal reproductive pattern during young adulthood,¹³⁸ without increased risk of congenital anomalies in the offspring.¹⁴³ Spontaneously conceived offspring of patients treated for cancer in childhood have no excess of congenital anomalies or other diseases.^{100,125,142} 2+
3

4.2.5 BREAST HYPOPLASIA

A field of radiation that includes prepubertal breast tissue may result in significant breast hypoplasia and asymmetry.¹⁴⁴ 3

5 Cardiac problems

5.1 CARDIAC PROBLEMS

Evidence on the cardiotoxic effects of chemotherapy and/or radiation therapy in the treatment of children with cancer comes from retrospective cohort studies, which cover a range of ages and regimens and which include differing drugs and radiation.¹⁴⁸⁻¹⁶⁰ Most of these studies are historical and employ different schedules and doses from those currently in use. Given these limitations, the studies suggest that there is no evidence of an increased risk of coronary artery disease if chemotherapy alone is used.

2⁺⁺

There is robust evidence that anthracyclines can cause congestive cardiac failure.¹⁶¹⁻¹⁸² The main anthracyclines reported in the literature are daunorubicin and doxorubicin, with some studies addressing the cardiotoxicity of other anthracyclines, namely mitoxantrone, epirubicin, idarubicin^{183,184} and amsacrine.¹⁸⁵ There is probably no safe dose,¹⁸² but the higher the accumulated dose, the greater the risk.^{171,174} Adverse cardiac effects increase over time. Higher doses of anthracyclines are associated with an increased incidence of abnormal echocardiograms. Younger age at treatment and female gender are independent risk factors in several studies.^{165,171,172}

2⁺

3

C Healthcare professionals should be aware that effective doses of anthracyclines for the treatment of childhood cancer may cause congestive cardiac failure later in life. These problems should be assessed during regular review.

A single preliminary study reported that the cardioprotective agent ICRF-187 reduced the risk of developing short term subclinical cardiotoxicity in paediatric sarcoma patients who received up to 410 mg/m² of doxorubicin. Further clinical trials with larger numbers of patients are required to determine if the short term cardioprotection afforded by ICRF-187 will reduce the incidence of late cardiac complications in long term survivors of childhood cancer.¹⁸⁶

1⁻

Liposomal daunorubicin*, daunoxome, is currently under evaluation for both efficacy and reduced cardiotoxicity. There is insufficient evidence at this time to make recommendations.

Although there is some evidence to support prolonged anthracycline infusions in adults,¹⁶⁵ a recent RCT has shown no cardioprotective effect from 48-hour infusions in children. Continuous doxorubicin infusion over 48 hours for childhood leukaemia did not appear to offer a cardioprotective advantage over bolus infusion although differences may emerge with longer follow up.¹⁸⁷

1⁻

5.1.1 RADIATION THERAPY AND CARDIAC PROBLEMS

Mediastinal irradiation as treatment for Hodgkin's disease increases the incidence of coronary artery disease and myocardial infarction.¹⁴⁸ The risk increases with high mediastinal doses (30 Gy or greater), minimal protective cardiac blocking and young age at irradiation.^{149,152} These observations support the use of combined modality, low-dose irradiation regimens in children and adolescents and suggest the need for cardiac screening of treated patients.

2⁺

Whilst there is evidence that irradiation at levels over 30 to 35 Gy is a risk factor for cardiac disease in later life, there is insufficient evidence to comment on the lower dose range of 20 to 25 Gy. 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.^{148,149,151-156,160,174}

C Healthcare professionals should be aware that mediastinal irradiation over 30 Gy is a risk factor for cardiac disease in later life and monitoring is necessary.

Exposure to anthracyclines and obesity⁴⁶ are independent risk factors for congestive cardiac failure.

* Liposomal daunorubicin has been withdrawn from the market

5.2 ASSESSMENT FOR CARDIAC PROBLEMS

The literature has concentrated on the use of echocardiography in the assessment of cardiac dysfunction as this is non-invasive and widely available. The measurement of fractional shortening is least affected by mathematical error compared with other measures. The sensitivity of echocardiography is increased by introducing more invasive tests such as a dopamine stress test. Such tests are unlikely to be routine but may be reserved for patients in whom there may be difficulties discriminating normal from mildly abnormal fractional shortening measurements, and in particular, those taking part in competitive sports.^{163,164,171,172}

2+

Deterioration of cardiac function during treatment for childhood cancer correlates with increasing anthracycline dose, with evidence of cardiac dysfunction at relatively low doses.

The literature supports the use of echocardiography at diagnosis of the malignancy and at regular intervals during treatment in order to assess cardiac function.¹⁸⁸ Involvement of a paediatric cardiologist may be appropriate.

Although not based on evidence, in the opinion of the guideline development group a recommendation for echocardiograms at regular intervals (which may be dose determined) during treatment and every three years thereafter is practical and widely achievable. More frequent assessment should be instituted should clinical evidence of cardiac dysfunction develop.

Children with satisfactory left ventricular function on simple echocardiographic measures, who have received modest cumulative anthracycline doses (< 250 mg/m²) may benefit from three-yearly echocardiogram surveillance.

Detailed cardiological assessment is appropriate for survivors of childhood cancer:

- who are pregnant or planning a pregnancy
- who wish to take part in competitive sports.

5.3 TREATMENT FOR CARDIAC PROBLEMS

There is relatively little literature on the effective treatment of anthracycline-induced cardiac dysfunction.

The angiotensin converting enzyme inhibitors, captopril and enalapril, are currently used in the treatment of patients with reduced cardiac function secondary to anthracycline therapy. Initial benefit has been demonstrated, but it is not yet apparent whether early treatment benefit translates into improved long term outcome.^{189,190} Research is currently underway to address these issues.¹⁹¹

2+
3

Survivors of childhood cancer with demonstrably impaired cardiac function may benefit symptomatically from treatment with angiotensin converting enzyme inhibitors, their left ventricular function may deteriorate with time despite continuing treatment. Cardiac function in some patients will deteriorate to a level requiring cardiac transplantation.¹⁹²

2+

There is no evidence in the literature to recommend limiting employment and activity in these patients. The knowledge that exercise reduces systemic vascular resistance (and also cardiovascular risk) suggests that moderate physical activity should be encouraged.

Survivors of childhood cancer should be advised from a young age to:

- follow a healthy diet
- take regular exercise
- avoid taking up smoking or to aim towards smoking cessation.

6 Thyroid dysfunction

Abnormalities of thyroid gland structure and function may occur following treatment for childhood cancer.¹⁹³ 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.

6.1 SPECIAL GROUPS AT RISK OF THYROID DYSFUNCTION

6.1.1 SURVIVORS WHO RECEIVED 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 ¹³¹I-MIBG (meta-iodo benzyl guanidine).¹⁹⁴ 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.^{32,195-197} 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.¹⁹⁵ A significant minority, with persistently increased thyroid stimulating hormone levels, will require thyroid hormone replacement.^{32,196} Hypothyroidism may develop decades after treatment.³² 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.^{32,196,198,199}

2++
2+

6.1.2 SURVIVORS WHO RECEIVED CRANIOSPINAL RADIATION

Children with brain tumours, particularly medulloblastoma, treated with craniospinal radiotherapy, have a similar increased risk of thyroid function abnormalities.^{200,201} This risk may be less with hyperfractionated rather than conventional radiotherapy regimens.²⁰⁰ 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+

6.1.3 ADULTS WHO WERE TREATED WITH LOW-DOSE RADIOTHERAPY IN CHILDHOOD

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).^{202,203}

2++

6.1.4 SURVIVORS WHO HAVE BEEN TREATED WITH TOTAL BODY IRRADIATION PRIOR TO BONE MARROW TRANSPLANTATION

Estimates of the prevalence of abnormal thyroid function tests in this group range from 10-90%.²⁰⁴⁻²⁰⁶ 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+

6.1.5 SURVIVORS WHO HAVE BEEN TREATED WITH 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.^{31,201,207}

2+

B Survivors of childhood cancer who received radiotherapy to the neck, spine or brain should have thyroid function checked after completion of treatment and regularly thereafter. Survivors are likely to require lifetime surveillance.

6.2 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.²⁰⁸⁻²¹⁰ 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.

6.3 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.

7 Cognitive and psychosocial outcomes

7.1 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. Magnetic resonance imaging or computed tomography abnormalities have been shown in a variable proportion of cases after 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.²¹¹⁻²²⁴ Results suggest functional impairment may be associated with structural abnormalities of calcification and vasculopathy and electroencephalography (EEG) abnormalities.^{211,218-221} Cognitive impairment and structural abnormalities after treatment to the brain correlate with age and dose of radiation. There is not enough 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.

The available evidence does not support the view that a decline in cognitive function is a frequent or inevitable consequence of treatment for childhood cancer. Cranial irradiation is a risk factor for cognitive decline. 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.²²⁵⁻²⁴³

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 cognitive assessment.**

- Children with cancer who are due to receive cranial irradiation should undergo a cognitive assessment with a standard measure (for instance an abbreviated version of the Wechsler Intelligence Scale for Children) at the start of treatment. The assessment should be repeated annually, to monitor changes over time.

7.2 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.²⁴⁴⁻²⁷⁰

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.^{249,250} Lower rates of marriage and employment than in the general population are also common.^{250,254} Brain tumours and treatment with cranial irradiation are frequently reported risk factors for psychosocial dysfunction.^{249,254}

- 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.**

7.3 TREATMENT INTERVENTIONS

There are no available studies assessing the effectiveness of intervention programmes for cognitive impairment or psychosocial dysfunction. Some descriptive studies have been published but these cannot be used to make specific recommendations.

One study described the benefits of providing more information about follow up and health care for survivors.²⁷¹ Another used cognitive, behavioural and family therapy to improve adjustment and symptoms of anxiety.²⁷² A third reported the benefits of a reunion workshop to provide support for psychosocial adjustment.²⁷³

3

The lack of evidence in this area should be an impetus for future research. Carefully designed prospective studies using standardised assessment measures are the best way to provide evidence about the efficacy of any intervention.

8 Patient issues

8.1 PATIENT INFORMATION

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.

8.2 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 2.3*). 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.

8.3 USEFUL CONTACT DETAILS

This section contains contact details for organisations which provide different levels of support and further information for patients. There are also many small local charities that provide additional support. A list of these can be obtained from the UKCCSG website (www.ukccsg.org/pub.htm and click on the "Links" button).

Cancer and Leukaemia in Childhood (CLIC)

CLIC, Abbey Wood Business Park
Filton, Bristol, BS34 7JU
Tel: 0845 301 0031, Fax: 0117 311 2649
Email: clic@clic.org.uk, Website: www.clic.org.uk

Children with Cancer and Leukaemia Advice and Support for Parents (CCLASP)

Suite 5, Leith Walk Business Centre, 108/152 Leith Walk, Edinburgh, EH6 5DT
Tel: 0131 467 7420, Fax: 0131 467 7421
Email: cclasp@hotmail.com

Macmillan CancerLine

Macmillan Cancer Relief,
89 Albert Embankment, London, SE1 7UQ
Freephone (Mon - Fri 9am - 6pm): 0808 808 2020
Textphone: 0808 808 0121
Email: cancerline@macmillan.org.uk, Website: www.macmillan.org.uk

Maggie's Centres Scotland

The Stables, Western General Hospital, Crewe Road South, Edinburgh, EH4 2XU
Tel: 0131 537 3131, Fax: 0131 537 3130
Email: maggies.centre@ed.ac.uk, Website: www.maggies.ed.ac.uk

National Alliance of Childhood Cancer Parent Organisations (NACCPPO)

3 Churchview Close, Bestwood Country Park, Arnold, Nottingham, NG5 9QP
Tel: 0115 9673106
Website: www.naccpo.org

Sargent Cancer Care For Children (Scotland)

5th Floor, Mercantile Chambers, 53 Bothwell Street, Glasgow, G2 6TS
Tel: 0141 572 5700, Fax: 0141 572 5701
Email: glasgow@sargent.org

Tak Tent Cancer Support Scotland

Flat 5, 30 Shelley Court, Gartnavel Complex, Glasgow, G12 0YN
Tel: 0141 211 0122, Fax: 0141 211 3988
Email: tak.tent@care4free.net, Website: www.taktent.org.uk

Teenage Cancer Trust

38 Warren Street London W1T 6AE
Tel: 0207 387 1000, Fax: 0207 387 6000
Email: tct@teencancer.bdx.co.uk, Website: www.teencancer.org

The United Kingdom Children's Cancer Study Group (UKCCSG)

Aims to improve the management of children with cancer and to advance the knowledge and study of childhood malignancy.

Website: www.ukccsg.org

9 Research, implementation and audit

9.1 RECOMMENDATIONS FOR RESEARCH

This guideline systematically reviews the available literature and makes recommendations for the follow up of long term survivors of childhood cancer. The evidence base in this case is mainly composed of descriptive longitudinal studies. Rarely is there an appropriate control group available, so study populations are compared to population norms. Many studies report small groups of survivors from individual hospitals. The strength of these data lies in the meticulous attention to detail evidenced in reports from paediatric oncology centres. Many of the reported patients have been enrolled in national and international clinical trials. There remains a dearth of good interventional studies of therapies to prevent, treat or modify late effects in young survivors. Large multidisciplinary, national and international collaborative studies must be designed to improve the outcome for this large cohort of long term survivors. Provision of long term follow up clinics should be related to research into the long term effects of cancer and treatment.

Specifically, research is required in the following areas:

Growth:

- the safety of growth hormone treatment
- the indications for growth hormone therapy in adults with childhood onset growth hormone deficiency
- the multifactorial aetiology of obesity in children treated for childhood cancer.

Fertility:

- the benefit of fertility preservation for the prepubertal patient who will receive gonadotoxic treatment
- the mechanisms of chemotherapy induced ovarian damage
- the effectiveness of in vitro maturation of ovarian tissue
- the success rate of cryopreservation of prepubertal testicular tissue
- the role of physiological sex steroid replacement in the young woman with ovarian failure
- long term follow up and outcomes of treatment with assisted reproductive technology for those who have been treated for cancer in childhood
- long term follow up of children born to survivors of childhood cancer.

Dental growth:

- the impact of orofacial and dental growth problems on the quality of life
- the long term effects of treatment for childhood cancer on dental development.

Cardiac problems:

- the frequency of echocardiograms required to identify cardiac problems
- the cardioprotection afforded by ICRF-187 and how this can reduce the incidence of late cardiac complications in long term survivors of childhood cancer
- the effectiveness of liposomal anthracycline products
- the influence of scheduling/infusion of anthracyclines
- the effectiveness of ACE inhibitors in this patient group.

Cognitive impairment:

- the utility of standardised assessment measures
- the usefulness of regular follow up in detecting cognitive impairment due to treatment
- the efficacy of any interventions
- the impact of formal psychiatric illness, subsyndromal psychiatric illness, psychological problems and social disadvantage on the quality of life of survivors and their families.

9.2 LOCAL IMPLEMENTATION

Implementation of national clinical guidelines is the responsibility of local NHS organisations and is an essential part of clinical governance. It is acknowledged that not every guideline can be implemented immediately on publication, but mechanisms should be in place to ensure that the care provided is reviewed against the guideline recommendations and the reasons for any differences assessed and, where appropriate, addressed. These discussions should involve both clinical staff and management. Local arrangements may then be made to implement the national guideline in individual hospitals, units and practices, and to monitor compliance. This may be done by a variety of means including patient-specific reminders, continuing education and training, and clinical audit.

9.3 KEY POINTS FOR AUDIT

Follow up outcomes should be audited carefully. As information accumulates, it will be increasingly possible to determine and deliver appropriate levels of surveillance in relation to clinical need so as to deliver high quality care in a targeted, effective and cost effective manner.

Key areas for audit are:

- regular height, weight, pubertal staging and body mass index measurements, recorded on appropriate charts
- appropriate follow up of patients at risk of late effects
- referral to specialists and treatment outcomes
- dental advice being given
- at-risk patients receiving appropriate cardiac monitoring
- annual thyroid function test being performed
- review for educational and psychosocial dysfunction or morbidity being undertaken.

10 Development of the guideline

10.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals, and patient organisations, funded by NHS Quality 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

10.2 THE GUIDELINE DEVELOPMENT GROUP

Dr Hamish Wallace (<i>Chair</i>)	<i>Consultant Paediatric Oncologist, Royal Hospital for Sick Children, Edinburgh</i>
Dr Chris Kelnar (<i>Methodologist</i>)	<i>Reader in Child Health and Consultant Paediatric Endocrinologist, University of Edinburgh</i>
Professor Ann Barrett	<i>Professor of Oncology, University of East Anglia</i>
Mrs Jane Belmore	<i>Paediatric Macmillan Nurse, Royal Hospital for Sick Children, Glasgow</i>
Dr Jan Clarkson	<i>Honorary Consultant in Paediatric Dentistry and Senior Lecturer, Dundee Dental Hospital and School</i>
Dr Alison Cozens	<i>SIGN Fellow and Specialist Registrar in Paediatrics, Tayside University Hospitals NHS Trust, Dundee</i>
Dr Ali El-Ghorr	<i>Programme Manager, SIGN</i>
Dr Brenda Gibson	<i>Consultant Haematologist, Royal Hospital for Sick Children, Glasgow</i>
Dr Robert Grant	<i>Macmillan GP Facilitator, Kirkcaldy</i>
Mr Robin Harbour	<i>Information and Quality Director, SIGN</i>
Dr Peter Hoare	<i>Honorary Consultant Child and Adolescent Psychiatrist, Royal Hospital for Sick Children, Edinburgh</i>
Dr Stewart Irvine	<i>Consultant in Obstetrics and Gynaecology, Centre for Reproductive Biology, Edinburgh</i>
Dr Paul Lim	<i>General Practitioner, Falkirk</i>
Mr Gordon MacKinlay	<i>Consultant in Paediatric Surgery, Royal Hospital for Sick Children, Edinburgh</i>
Mrs Ethel McNeill	<i>Endocrine Nurse Specialist, Royal Hospital for Sick Children, Glasgow</i>
Ms Lynn Myles	<i>Honorary Consultant Neurosurgeon, Western General Hospital, Edinburgh</i>
Dr Robert Simpson	<i>Consultant Paediatrician, Dumfries and Galloway Royal Infirmary</i>
Ms Anne Thomson	<i>Patient Representative, Kirkcaldy</i>
Dr Brenda Wilson	<i>Associate Professor, Department of Epidemiology and Community Medicine, University of Ottawa, Canada</i>
Dr John Wilson	<i>General Practitioner, Selkirk</i>

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. Declarations of interests were made by all members of the guideline development group. Further details are available from the SIGN Executive. Guideline development and literature review expertise, support, and facilitation were provided by the SIGN Executive.

10.3 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. The nature of the subject, the comparatively small amount of relevant literature, and the large number of questions to be addressed made this review particularly difficult. The final search strategies were developed by the SIGN Quality and Information Director together with a member of the guideline development group. These strategies are listed on the SIGN website, in the section covering supporting material for guidelines. The outputs from these searches were sifted by the guideline development group, and all potentially relevant material evaluated.

Systematic searches were carried out on the Cochrane Library, Embase, Medline, and Psychlit and covered the period from 1993 to 2000. The main searches were supplemented by material identified by individual members of the development group. This allowed the inclusion of older seminal publications and of material published during the guideline development process, although not systematically.

10.4 CONSULTATION AND PEER REVIEW

10.4.1 NATIONAL OPEN MEETING

A national open meeting is the main consultative phase of SIGN guideline development, at which the guideline development group presents its draft recommendations for the first time. The national open meeting for this guideline was held on 27 March 2002 and was attended by around 80 representatives of all the key specialties relevant to the guideline. The draft guideline was also available on the SIGN website for a limited period at this stage to allow those unable to attend the meeting to contribute to the development of the guideline.

10.4.2 SPECIALIST REVIEW

The guideline was also reviewed in draft form by a panel of 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. SIGN is very grateful to all of these experts for their contribution to this guideline.

Dr Alan Begg	<i>General Practitioner, Dundee</i>
Dr Allan Merry	<i>General Practitioner, Ardrossan</i>
Dr James Beattie	<i>Director of Guidelines Development, Royal College of General Practitioners, Scottish Council</i>
Dr Smita Bhatie	<i>Paediatric Physician, City of Hope National Medical Centre, California, USA</i>
Mr Robert Carachi	<i>On behalf of the Academy of Royal Colleges and Faculties in Scotland</i>
Professor Alan Craft	<i>Consultant in Paediatrics, Royal Victoria Infirmary, Newcastle upon Tyne</i>
Professor Hilary Critchley	<i>Professor of Reproductive Medicine, New Royal Infirmary, Edinburgh</i>
Dr Helena Davies	<i>Consultant in Late Effects/Medical Education, The Children's Hospital, Sheffield</i>
Professor Tim Eden	<i>Consultant Paediatric Haematologist / Oncologist, Royal Manchester Children's Hospital</i>
Professor Ian Gilmore	<i>Registrar, Royal College of Physicians, London</i>
Ms Wendy Hobbie	<i>Late Effects Nurse Practitioner, Children's Hospital of Philadelphia, USA</i>
Dr Gill Levitt	<i>Consultant in Oncology, Great Ormond Street Hospital for Children, London</i>
Ms Morag McIntosh	<i>National Organiser (Scotland), Sargent Cancer Care for Children, Glasgow</i>

Dr Anna Meadows	<i>Director, Survivorship Program, Division of Oncology, Children's Hospital of Philadelphia and Professor of Paediatrics, University of Pennsylvania School of Medicine, USA</i>
Professor Kevin Oeffinger	<i>Professor of Family Practice and Paediatrics, University of Texas, Dallas, USA</i>
Dr Cindy Schwartz	<i>Associate Professor of Oncology and Paediatrics, Johns Hopkins Hospital, Baltimore, USA</i>
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Comments were also received from the Scottish Cancer Group.

10.4.3 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. The Editorial Group for this guideline was as follows:

Dr James Beattie	<i>Royal College of General Practitioners Scottish Council</i>
Dr Keith Brown	<i>Royal College of Psychiatrists</i>
Dr Grahame Howard	<i>Royal College of Radiologists, Faculty of Clinical Oncology</i>
Professor Gordon Lowe	<i>Chair of SIGN, Co-editor</i>
Professor Nigel Pitts	<i>Dental Health Services Research Unit, University of Dundee</i>
Dr Safia Qureshi	<i>SIGN Programme Director, Co-editor</i>
Dr Sara Twaddle	<i>Director of SIGN, Co-editor</i>
Dr Pete Wimpenny	<i>Centre for Nursing Practice Development, Robert Gordon University</i>

Each member of the guideline development group then approved the final guideline for publication.

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Abbreviations

ALL	Acute lymphoblastic leukaemia
ACTH	Adrenocorticotrophin
ART	Assisted reproductive technology
EEG	Electroencephalography
FSH	Follicle stimulating hormone
GH	Growth hormone
ICSI	Intra-cytoplasmic sperm injection
LH	Luteinising hormone
NHL	Non-Hodgkin's lymphoma
RCT	Randomised controlled trial
SIGN	Scottish Intercollegiate Guidelines Network
SMR	Standardised mortality ratio
TSH	Thyroid stimulating hormone

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Update to printed guideline

4 Mar 2005

Section 8.3 paragraph 1 changed from -

This section contains contact details for organisations which provide different levels of support and further information for patients. There are also many small local charities that provide additional support. A list of these can be obtained from the UKCCSG website (www.ukccsg.org/pub.htm and click on the "Links" button).

to

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Cancer and Leukaemia in Childhood (CLIC) website changed from -

www.clic.uk.com

to

www.clic.org.uk

Maggie's Centres Scotland website changed from -

www.maggies.ed.ac.uk

to

www.maggiescentres.org

National Alliance of Childhood Cancer Parent Organisations (NACCPO) website changed from -

www.naccpo.org

to

www.naccpo.org.uk

4 Mar 2004

Section 5.1

Withdrawal of drug Liposomal daunorubicin. Footnote added to guideline to advise guideline users.

LONG TERM FOLLOW UP

- ☑ All survivors of childhood cancer should be actively followed up for life.
- ☑ At the end of a course of cancer treatment, patients, their carers and general practitioners should be given a summary of the treatment and a list of signs of late effects to look out for.

- ☑ Each patient should have access to an appropriate designated key worker to coordinate care.

With appropriate training, specialist nurses can make a significant contribution to the care of these patients.

Levels of follow up

Level	Treatment	Follow up method	Frequency
1	<ul style="list-style-type: none"> ■ surgery alone ■ low risk chemotherapy 	postal or telephone	1-2 years
2	<ul style="list-style-type: none"> ■ chemotherapy ■ low dose cranial irradiation ≤ 24 Gy 	nurse or primary care led (using protocols)	1-2 years
3	<ul style="list-style-type: none"> ■ radiotherapy, except low dose cranial irradiation ■ megatherapy 	medically supervised late effects clinic	annual

GROWTH PROBLEMS

- B All children who have survived childhood cancer should have their height measured regularly until they reach final adult height.
- B Children with craniopharyngioma should be tested at presentation for growth and other pituitary hormone deficiencies, and at regular intervals thereafter.
- C Children with impaired growth velocity should be referred to a paediatric endocrinologist for growth hormone level measurement.
- 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.

Obesity

- B 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.

GROWTH PROBLEMS (CONTINUED)

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

Dental and facial problems

- B 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.

PROBLEMS WITH PUBERTY AND REPRODUCTION

- Male puberty and fertility
 - ☑ 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, LH, testosterone, inhibin B
 - semen analysis.

Female puberty and fertility

- ☑ Men who have evidence of impaired fertility should be referred for specialist assessment as they could benefit from assisted reproductive technology (ART).
- ☑ Fertility counselling should be provided to survivors of childhood cancer.
- ☑ Cryopreservation of semen should be offered for young male patients whose cancer therapy will include potentially gonadotoxic treatments.
- C Girls treated with cranial irradiation should have their pubertal status assessed three to four times a year from the end of treatment as part of a routine clinical assessment.
- C Women who have evidence of impaired fertility should be referred for specialist assessment as they could benefit from assisted reproductive technology.

CARDIAC PROBLEMS

- C Healthcare professionals should be aware that:
 - effective doses of anthracyclines for the treatment of childhood cancer may cause congestive cardiac failure later in life.
 - mediastinal irradiation over 30 Gy is a risk factor for cardiac disease in later life and monitoring is necessary.
- These potential problems should be assessed during regular review.

- ☑ Children with satisfactory left ventricular function on simple echocardiographic measures who have received modest cumulative anthracycline doses (< 250 mg/m²) may benefit from three-yearly echocardiogram surveillance.

- ☑ Survivors of childhood cancer who are pregnant, considering becoming pregnant, or wishing to take part in competitive sports should have a detailed cardiological assessment.

- ☑ Survivors of childhood cancer should be advised from a young age to:
 - follow a healthy diet
 - take regular exercise
 - avoid taking up smoking or to aim towards smoking cessation.

THYROID DYSFUNCTION

- B Survivors of childhood cancer who received radiotherapy to the neck, spine or brain should have thyroid function checked after completion of treatment and regularly thereafter. Survivors are likely to require lifetime surveillance.

- ☑ Survivors should be advised of the risk of thyroid cancer and to seek urgent medical attention if they notice palpable neck masses
- Annual thyroid function tests are recommended for survivors at risk of thyroid dysfunction.

Thyroid hormone replacement therapy is generally safe and effective. Thyroxin may need to be introduced gradually in people with potential cardiac dysfunction (eg in patients who have received anthracycline).

COGNITIVE AND PSYCHOSOCIAL OUTCOMES

- D Healthcare and education professionals should be aware that the treatment of childhood cancer may have an impact on neurological, educational and social function in later life, particularly if irradiation of the brain occurs at a young age.
- D Regular review for such a deficit should be part of normal follow up.
- D If a problem is suspected, the patient should be referred for a cognitive or other appropriate assessment.
- ☑ Children with cancer who are due to receive cranial irradiation should undergo a cognitive assessment with a standard measure (eg an abbreviated version of the Wechsler Intelligence Scale for Children) at the start of treatment. The assessment should be repeated annually.