The long term survivors

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Recent research indicates that approximately 60% of children diagnosed with cancer in Britain are cured and as a result, about 1 in a 1000 of the general population will soon be survivors of childhood cancer. Unfortunately some elements of the therapies which are responsible for this remarkable success are associated with serious complications, sometimes decades after their administration. Therefore, a comprehensive knowledge of the risks and benefits of different therapies will only be obtained by monitoring the health of survivors indefinitely. With such therapeutic success, increasingly the composition of future treatment protocols will be influenced by knowledge of the risks of long term morbidity and mortality associated with past therapies. An awareness of the long term risks of complications of treatment is also important for estimating the future demand on the health services of this increasing proportion of the general population who together represent many life years of care. This chapter reviews what is known concerning the long term risks of complications of different treatments. Appropriate strategies for future clinical and epidemiological follow-up of the survivor population are discussed and the need for indefinite follow-up of the survivor population is emphasised.

Increased survival and the need for long term follow-up

Only 26% of children diagnosed with cancer in Britain during the period 1962–70 survived at least 5 years from diagnosis, whereas the corresponding percentages for children diagnosed during 1971–85 and 1986–88 were 50% and 65% respectively. This outstanding improvement in survival was mainly attributable to the introduction of chemotherapy; although increased centralization of treatment and improved supportive care have also contributed. As survival has greatly improved, the need to assess the quality of survival has increased correspondingly. It has become essential to know the risks of long term complications of childhood cancer and its treatment, and to understand the extent to which specific elements of therapy and biological
characteristics of survivors (particularly genetic factors) are involved in the development of such complications. Such information would provide a sound basis: for counselling survivors and their families; for targeting surveillance of groups of survivors at particular risk with a view to early diagnosis and intervention; and for planning the composition of future treatment protocols to achieve an optimum balance between the risks and benefits of different treatment strategies.

In the past almost all studies of survival following childhood cancer have tended to concentrate on the proportion of patients surviving to 5 years from diagnosis, with little consideration given to what happens subsequent to 5 years' survival. With most patients surviving beyond this point, two important clinical concerns needed to be addressed. Firstly, had the modern treatments which greatly improved survival to 5 years truly cured most children or merely postponed death from recurrent tumour? Secondly, whilst many modern anti-cancer therapies were known to have toxic 'side-effects', in the short-term, almost nothing was known concerning the risks of fatal toxic effects of treatment in the long term. A recent large population-based study in Britain, which was primarily established to investigate these two concerns, has provided reassurance in relation to both\(^1\). The study compared long term survival of 9000 5 year survivors diagnosed during 1971–85 and 4000 5 year survivors diagnosed during 1940–70. The early 1970s was the period when chemotherapy was widely introduced into the treatment of childhood cancer in Britain. The risk of dying of recurrent tumour, in the 10 years subsequent to 5 year survival, fell from 12% among those diagnosed during 1940–70 to 8% among those diagnosed 1971–85; the corresponding risks of dying of a treatment-related death rose only slightly from 1% to 2%\(^1\). Therefore modern therapies, involving the widespread use of chemotherapy, have resulted in cure for a greater proportion of 5 year survivors than was possible before introduction of such therapies. The extra costs associated with these benefits, in terms of increased treatment-related mortality, are comparatively small. Of course, further follow-up is required to fully assess the extent of treatment-related mortality in the long term.

The clinical objective in treating a child with cancer has become cure at minimum risk to the patient's subsequent health. Therefore, in addition to fatal complications, it is important to assess the risk of specific morbidities which may be influenced by childhood cancer or its treatment. Although such complications may not lead to death, the quality of survival is likely to be affected. In the remainder of this chapter we assess the evidence of increased risk, and aetiology, of specific morbidities following childhood cancer and its treatment and explore the clinical implications and the implications for survivors. In conclusion we shall attempt to establish clinical and research priorities for the future.
We carefully distinguish the needs and priorities for clinical and epidemiological long term follow-up of survivors.

Recent survival statistics in Britain indicate 65% of children diagnosed with cancer survive at least 5 years from diagnosis, and that 92% of these children are cured, therefore the best current estimate of the percentage of children cured is 60%. The overall risk of developing childhood cancer by age 15 years is 1/600 and assuming about 60% are cured means that approximately 1 in 1000 of the population in Britain will soon be survivors of childhood cancer. So, although childhood cancer is a relatively rare malignant disease, the outstandingly good survival prospects mean that the survivor population is becoming appreciable. This poses an increasingly important issue for health care provision.

Second cancers

Second cancer is arguably the most devastating complication to develop in someone already apparently cured of one cancer. It has been known for many years that survivors of childhood cancer are at an increased risk of developing another cancer in comparison with that expected from general population rates of cancer. It is, therefore, important to obtain unbiased and reliable estimates of the risks of occurrence of different types of second cancer; also to identify elements of therapy and genetic constitution which are associated with the increased risk.

In Britain, the existence of national registries enables the study of second cancer among all children diagnosed with cancer. Such large population-based series of survivors have two important advantages: firstly, being population-based ensures selection factors which sometimes bias treatment-centre based series are avoided; secondly, as a result of including large numbers of survivors reliable estimates of risk are obtained.

Population-based and treatment-centre based studies

Estimates of the risk of second cancer from large population-based studies tend to be substantially lower than those from large treatment-centre based studies. There have been two large population-based studies published: one from Britain, the other from the Nordic countries. The most informative large treatment-centre based studies of second cancers have been produced by the Late Effects Study Group (LESG). The percentage of patients developing any type of second cancer within 25
years of diagnosis of all types of childhood cancer considered together was 3.7%, 3.5% and 12.1% from the British, Nordic and LESG studies, respectively. These risks correspond to 6, 4 and 15 times the risk expected from the corresponding general populations, respectively. In Table 1 we give the relative risks of specific types of second cancer from these three studies. The risks from the LESG are consistently substantially greater than those from the population-based studies. To what extent these differences are a consequence of differences in underlying aetiological factors, or result from the influence of selection factors (bias) is unknown. However, it is very unlikely that an appreciable number of second cancers were not ascertained within the British study.

**Second bone cancer**

From Table 1, it is apparent that second bone cancer accounted for the highest relative risk of any specific type of second cancer from both the British and LESG studies. As a consequence, these two groups of investigators each carried out a specifically designed case-control study to identify elements of therapy for initial childhood cancer which might be associated with the increased risk. The conclusions from these two case-control studies were broadly similar.

From both studies the risk of second bone cancer increased substantially with the increased exposure to radiation which bone had received during radiotherapy for the initial childhood cancer. There was also agreement concerning evidence that the risk of bone cancer declined at the highest levels of exposure. There was firm agreement from...
both studies that children whose bone was exposed to less than 10 Gy had, at worst, only a small increased risk of bone cancer, and possibly no increased risk. There was evidence from both studies of an association between exposure to alkylating agents and a subsequent risk of bone cancer which was independent of radiation exposure; there was also agreement that this association was considerably weaker than that with radiation exposure.

Important clinical implications emerge from these studies. From the British study the percentage of 3 year survivors developing bone cancer within the subsequent 20 years did not exceed 0.9%, except for those diagnosed with heritable retinoblastoma, Ewing’s sarcoma and other malignant bone tumours for whom the risks were 7.2%, 5.4% and 2.4%, respectively\(^7\). The higher risks of bone cancer following these three rare types of childhood cancer, which accounted for only 11% of the 3 year survivors, provides a rational basis for closer surveillance of these particular survivors in long term follow-up clinics. Both studies provide information relevant to the likely risk of bone cancer after a specified level of exposure to radiation and should help in decisions of whether to include radiotherapy in future treatment protocols\(^6,7\). The tendency for an increased risk of bone cancer with increased exposure to alkylating agents taken together with known leukaemogenicity of these drugs indicates that cumulative doses should be kept as low as is possible without compromising the prospects of cure.

Second leukaemia

Second leukaemia has also been thoroughly investigated using case-control studies by both the British and LESG investigators\(^8,9\). The LESG reported that 0.8% of 2 year survivors developed second leukaemia by 20 years from diagnosis, corresponding to 14 times the expected risk from the general population\(^8\). Treatment of the original childhood cancer with alkylating agents was associated with 5 times the risk of second leukaemia associated with not being so exposed\(^8\). A strong dose-response was observed between cumulative exposure to alkylating agents and the risk of second leukaemia\(^8\). The risk of second leukaemia among those exposed to the highest cumulative doses of alkylating agents was 23 times the risk among those not exposed to alkylating agent\(^8\).

The British study reported that no more than 0.5% of 1 year survivors developed second leukaemia within the subsequent 5 years, except that after non Hodgkin’s lymphomas the corresponding figure was 1.4%\(^9\). The risk of secondary leukaemia increased substantially with increased cumulative exposure to epipodophyllotoxins: the risk of secondary
leukaemia among those exposed to more than 1200 mg/m\(^2\) was about 20 times the risk among those not exposed to epipodophyllotoxins\(^9\). Chromosomal translocations involving 11q23 were associated with a third of the second leukaemias for which there were successful cytogenetic studies after administration of an epipodophyllotoxin\(^9\). The risk of second leukaemia increased with increased dose of radiation received by the patient’s active bone marrow\(^9\).

Treatment schedule, that is the interval between successive doses of drug, also appears to be an important predictor of the risk of subsequent epipodophyllotoxin related leukaemia\(^10\). Furthermore, other topoisomerase II inhibitors, including doxorubicin, appear to be associated with an increased risk of second leukaemia\(^11\).

**Other second cancers**

The thyroid gland is particularly sensitive to the carcinogenic effects of radiotherapy and is the only organ with convincing evidence for increased risk at an exposure as low as 0.10 Gy\(^12\).

A retrospective study of 9720 children diagnosed with acute lymphoblastic leukaemia followed-up for a median period of 4.7 years identified 43 second primary neoplasms (24 of the central nervous system, 10 new leukaemias and lymphomas and 9 other neoplasms)\(^13\). This was 7 and 22 times the expected number of all cancers and of tumours of the central nervous system, respectively. The cumulative risk of a second neoplasm was 2.5% at 15 years from diagnosis. All central nervous system tumours developed in irradiated children.

A recent report from the LESG provides further follow-up on their cohort of 1380 children treated for Hodgkin’s disease\(^14\). There were 88 second primary neoplasms observed compared with 4.4 expected from the general population rates indicating an excess risk of 18 times that expected\(^14\). In addition to confirming an excess of second leukaemia 79 times expected, the remarkable finding was that breast cancer was the most common solid second cancer with 17 cases observed and only 0.2 expected which corresponded to 75 times the expected risk. The percentage of woman developing breast cancer by 40 years of age was estimated to be 35%. Treatment at older ages and higher exposure to radiation were each associated with the increased risk. These findings are worrying, but require confirmation in other studies.

A recent report from the National Wilms’ Tumour Study Group included 5278 patients among whom 43 second primary neoplasms were observed, 5.1 were expected from general population rates, this corresponded to 8 times the expected risk\(^15\). By 15 years from diagnosis,
1.6% of patients had developed a second cancer. Abdominal irradiation and doxorubicin were each associated with the excess risk.

**Growth and endocrine sequelae**

**Growth and final adult height**

The risk of abnormal growth and endocrine function is well recognised, particularly following radiotherapy to the pituitary, thyroid and gonads. Patients with obvious endocrine insufficiency can be successfully managed with endocrine replacement therapy but other issues, including poor nutrition, corticosteroids and factors which influence the timing and pace of puberty, may also have important influence on growth and final adult height. Furthermore, direct damage to bone and soft tissues within radiation fields may have a significant impact on final height or induce limb or spinal asymmetry.

Growth hormone (GH) deficiency is the most common cause of growth abnormality in patients who have received radiotherapy to a pituitary field—this may include nasopharyngeal and other head and neck fields as well as treatment directed at the brain, and TBI for BMT conditioning. There is a strong correlation between the pituitary dose received and both the risk and time of onset of symptomatic GH deficiency. Young age at treatment may also increase the risk of damage. Patients with growth hormone deficiency from direct pituitary irradiation may subsequently demonstrate sequential loss of TSH, gonadotrophin and (rarely) ACTH production requiring replacement therapy.

Although GH deficient growth failure can be successfully treated by GH supplementation with achievement of satisfactory final adult height, it is important to recognise that GH is involved in a number of other physiological processes and there is emerging concern that some patients could benefit from replacement therapy in adult life.

There is now adequate experience of growth and development in children undergoing TBI for BMT conditioning. Most experience significant growth retardation after 10 Gy given as a single fraction, but fractionation of the dose may reduce this risk. Other factors implicated in the growth problems induced by TBI include thyroid dysfunction, radiation induced skeletal dysplasia and chronic GVHD and its treatment.

Although some studies have suggested that chemotherapy has no effect on growth, clinical observations often demonstrate treatment related growth impairment followed by catch up growth and the intensity of chemotherapy may matter. Studies of more recently treated patients
receiving multiagent chemotherapy for leukaemia without cranial radiotherapy will be of particular interest.

Children with chiasmatic and suprasellar tumours as well as those with craniopharyngioma often present complex and multiple endocrinopathies for which joint management with an endocrinologist is essential.

**Thyroid dysfunction**

There is no evidence that chemotherapy alone is toxic to the thyroid but all patients receiving radiotherapy to a field incorporating or bordering on the thyroid (including TBI) must be monitored for the onset of compensated (normal T4, increased TSH) or true primary hypothyroidism. Furthermore, even scatter dose from radiotherapy fields has been implicated as a cause of thyroid damage. Monitoring must include careful clinical examination of the thyroid as these patients are also at risk of thyroid carcinoma.

**Puberty and secondary sexual development**

The risk of damage to the gonadal function by both chemotherapy and radiation therapy is well recognised. Depending on the extent of damage to gonadal tissue, it may be necessary to intervene medically to allow children to achieve normal sexual development, but most drugs that induce gonadal toxicity, including the alkylating agents, have a major effect against fertility rather than gonadal steroidogenesis. Children who receive direct gonadal irradiation are likely to also require life-long sex hormone replacement therapy to initiate and maintain progress through puberty and induce secondary sexual characteristics. Patients who experience complete ovarian failure require oestrogen replacement, not merely to induce development of secondary sexual characteristics, but also to relieve symptoms of oestrogen deficiency and to protect against premature onset of osteoporosis and ischaemic heart disease.

Children who receive high dose radiotherapy to the hypothalamic pituitary axis, and girls who have received prophylactic low dose cranial radiation for ALL appear to be at risk of early onset of puberty. The consequent acceleration of bone maturation when combined with suboptimal growth hormone production may result in unanticipated and inadequate final adult height.
There have been few large epidemiological studies of fertility after childhood cancer. The most informative such study was carried out in relation to 2283 long term survivors of childhood and adolescent cancer diagnosed during the period 1945–75 in five cancer centres in the US. Patients were diagnosed before age 20 years, survived at least 5 years and attained the age of 21. The control population consisted of 3270 siblings. An interviewer administered questionnaire was used to collect information; the response rate was 91%. Survivors were 15% less likely than siblings to have ever begun a pregnancy. Both male and female survivors who had previously received abdominal irradiation were 25% less fertile than siblings. Male survivors who had received alkylating agent therapy were 60% less fertile than siblings, irrespective of whether they had also received abdominal irradiation. Females who had received only alkylating agent therapy experienced no appreciable effect on fertility.

A further study of premature menopause in this same study population has also been reported. This further study was restricted to 1067 female survivors who were still menstruating at age 21. Menopause status in survivors was compared with that in 1599 female siblings. Women diagnosed before age 13 were not found to be at greater risk of menopause than their siblings. Women who had been diagnosed between 13 and 19 years, had 4 times the risk of menopause experienced by siblings during ages 21 to 25 years, the discrepancy diminished at older ages. Among survivors diagnosed between age 13 and 19 years, the risk of menopause during their early 20s was 4 and 9 times higher than in siblings after radiotherapy alone and alkylating agents alone, respectively. At ages 21 to 25 years, among women treated with abdominal irradiation and alkylating agents, the risk of menopause was 27 times that in siblings. By age 31 years, 42% of survivors had experienced menopause compared with 5% of siblings. The authors commented on the clinical implications and concluded that treatment for cancer during adolescence is associated with a considerable risk of premature menopause among women menstruating age 21 years. With increasing use of more gonadal toxic therapy in more recent years than for the patients included in this study, and the tendency for women in general to delay childbearing, means that women should be advised of the shorter period during which they are likely to be fertile.

The only British data which give some insight into fertility are concerned with the observed and expected numbers of live births to female survivors of childhood cancer treated in Britain and born before 1963. The expected live births were derived from general population...
age specific fertility tables for different calendar years. Only 57% of the expected live births were observed. The deficit was greatest among the young, in that, among those aged below 20, 20–24, 25–29 and 30–34 years old the percentage of expected live births actually observed was 51%, 58%, 57% and 64%, respectively.

**Pregnancy**

For those survivors of childhood cancer who conceive, or cause their partner to conceive, the prospects for the pregnancy and its outcome appear to be broadly similar to those experienced in the general population with one established and one potential problem being exceptions.

The established problem concerns woman who, as part of their treatment for childhood cancer, received abdominal irradiation, those abdominally irradiated for Wilms’ tumour are particularly affected. These woman have a substantially increased risk of miscarriage and of producing low birthweight offspring. The offspring produced experience a substantially increased risk of dying in the perinatal period. The mechanism underlying this phenomenon remains obscure. However, it seems unlikely to be due to germ cell mutation. The clinical implications of these findings are that any pregnancy in a woman abdominally irradiated in childhood should be regarded as being at high risk of an adverse outcome and monitored accordingly. The findings provide a basis for counselling such patients who are considering pregnancy.

The potential problem concerns the possible increased risk of cardiac problems during pregnancy among woman survivors who were treated with anthracyclines. This is anecdotal and no satisfactory data are currently available.

**Offspring**

An anxiety expressed by many survivors of childhood cancer concerns the possibility that their offspring may inherit cancer. Adverse outcomes of pregnancy or impaired health of offspring could in theory be related to constitutional genetic abnormalities in survivors associated with their cancer, or to germ cell mutagenesis from radiotherapy or chemotherapy. In a recent review it was noted that only three large cohort studies of offspring of survivors of childhood cancer had been published. Among the smaller (<200 offspring) cohort studies, no cancer had been observed in the offspring. On combining the three large cohorts, 7
cancers were observed and about 5 expected, after excluding definitely heritable cancers. Therefore, there was no evidence of an appreciable excess risk. Some of the parent/offspring pairs of cancer were consistent with the Li-Fraumeni syndrome. Only 1 of the 7 survivors producing affected offspring had received therapy which was potentially germ cell mutagenic. However, even with this number of offspring a doubling in the risk of the generality of childhood cancers could not be detected with confidence. Since that review, two further cohorts of offspring have been published. No cancer was observed in 382 offspring of survivors of childhood leukemia and non-Hodgkin's lymphoma. Three of 146 offspring produced by survivors of Wilms' tumour developed Wilms' tumour which gave an actuarial estimate of 3% of offspring being affected by age 10 years, consistent with a larger risk than had been apparent from previous studies.

Serious congenital malformations in offspring are another indicator of a possible germ cell mutagenic effect of therapy. However, the large studies reported so far have found no evidence of an increased risk associated with treatment potentially mutagenic to germ cells.

Cardiac dysfunction

After chemotherapy

It has been known for about two decades that there is an increased risk of acute cardiac toxicity following cumulative doses of anthracyclines which exceed 500 mg/m<sup>2</sup>. However, only recently have the longer term cardiotoxic effects of anthracycline therapy begun to be identified; particularly among children exposed to cumulative doses less than 500 mg/m<sup>2</sup>. In 1991, two studies were published which aroused particular concern.

In one study from the Memorial Sloan-Kettering Cancer Center, 47 of 201 children (23%) who had received cumulative doses of between 200–1275 mg/m<sup>2</sup> (median 450 mg/m<sup>2</sup>) had abnormal cardiac function as assessed by echocardiogram testing at 4–20 years (median 7 years) after completion of anthracycline treatment. The increased risk of cardiac abnormalities was associated with the cumulative dose of anthracyclines, length of follow-up and mediastinal irradiation.

The other study was of 115 children treated for ALL who were evaluated (using 24 h electrocardiogram, exercise testing and echocardiography) 1–15 years from treatment involving doxorubicin. Three (17%) of the 18 patients who received a cumulative dose of 45 mg/m<sup>2</sup> had mild but detectable cardiac abnormalities. In contrast, 65% of
patients who had received 228–550 mg/m² (median 360 mg/m²) revealed evidence of cardiac abnormalities. In a further study, these investigators included additional patients with osteosarcoma who had been treated with doxorubicin. They examined echocardiograms from 120 children and adults who had received cumulative doses 244–550 mg/m² of doxorubicin a mean interval of 8.1 years previously. A group of 296 normal subjects provided control data. All echocardiographic parameters measured were on average statistically abnormal among the survivors of malignant disease a minimum of 2 years after the end of therapy, with more frequent and severe abnormalities in female patients. It was concluded that female sex and higher rates of administration of doxorubicin were independent risk factors for cardiac abnormalities, and that the prevalence and severity of abnormalities increased with longer follow-up.

Nevertheless, at present, the relation between the measures of cardiac abnormality identified by screening patients during and after therapy and the long term risk of serious cardiac disease is very uncertain. This is a priority area for further research and it is essential to monitor all survivors treated with anthracyclines.

In addition to avoiding or limiting the use of anthracyclines, there is interest in cardioprotective drugs of which ICRF-187 is best evaluated. Recently the results have been published of the first randomized clinical trial to assess the possible cardioprotective effect of ICRF-187 in paediatric sarcoma patients treated with doxorubicin. Although based on only 38 patients, the results were impressive in that ICRF-187 treated patients were less likely to develop subclinical cardiotoxicity (22% vs 67%, \( P < 0.01 \)). The authors concluded that ICRF-187 reduces the risk of developing short-term subclinical cardiotoxicity in patients receiving up to 410 mg/m² of doxorubicin. Reassuringly, response rates to chemotherapy, event-free and overall survival, and noncardiac toxicities appeared unaffected by the use of ICRF-187. However, larger trials are required to fully investigate these questions.

Cyclophosphamide in high doses may be associated with acute cardiac problems, most studies involved high dose preparatory regimens for bone marrow transplant. The possible long term effects of lower doses are uncertain.

**After radiotherapy**

The cardiotoxic effects of radiotherapy in childhood and adolescents have been clearly demonstrated among survivors of Hodgkin’s disease. A cohort of 635 patients treated for Hodgkin’s disease before 21 years of
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age at Stanford University between 1961–1991, and followed up for an average interval of 10.3 years, yielded 12 deaths from cardiac disease. This was 30 times the number of such deaths expected from the death rates of general population of the US. Acute myocardial infarction accounted for 7 of the deaths which corresponded to 42 times the number expected. Six of these 7 deaths occurred after treatment not involving chemotherapy. These authors concluded that mediastinal irradiation of 40–45 Gy increases the risk of death from coronary artery and other cardiac diseases, and that the risk increases within 5 years of irradiation. They also noted that their study suggested the use of combined modality, low dose radiation regimens in children and adolescents, and suggested the need for careful cardiac screening of survivors at increased risk.

Pulmonary toxicity

Consequences of pulmonary radiotherapy

In contrast to the fibrotic changes noted in patients damaged by radiotherapy to the chest during adolescence or adult life, the problems experienced by survivors of treatment during childhood may result from a restriction in the growth of the whole chest, as well as effects on the lung. Histologically, late radiation injury in the lung is characterised by progressive fibrosis and obliteration of alveolar structure. Clinical symptoms are proportional to the extent of lung tissue involved, but most patients who manifest abnormalities on formal pulmonary function studies are asymptomatic. Important effects are rare at doses below 30 Gy but interaction with chemotherapy may potentiate acute radiation effects and result in unexpected long term damage. Even spinal radiation fields may impose a risk of radiation damage. No therapy is available to reverse the fibrotic damage once established.

Chemotherapy induced lung toxicity

Bleomycin toxicity is typically acute and associated with increasing cumulative dose. It may be potentiated by exposure to high levels of oxygen or coexistent infection. Such episodes may be fatal but withdrawal of the drug may lead to reversal of the changes although some patients will persist with X-ray and/or pulmonary function changes.
Toxicity due to BCNU is dose related and occurs late. Evidence of fibrosis has been reported in over 50% of patients receiving cumulative doses greater than 1500 mg/m². Discontinuation of therapy may not prevent progressive deterioration. There are also reports of toxicity with other nitrosoureas and with cyclophosphamide, busulphan, melphalan and methotrexate. Damage from methotrexate, is rare, but there is concern that exposure at a young age may have a direct adverse effect on lung growth.

Other risk factor

Loss of lung volume from surgery for pulmonary metastases may be an additional risk factor for pulmonary toxicity. Particular care should be taken in advising patients not to smoke and caution may be needed with general anaesthesia. Further research is required into the combined effects of known treatment risk factors and smoking and occupational risk factors.

Renal and genitourinary toxicity

Long-term effects on the kidney

The consequences of unilateral nephrectomy are generally considered to be unimportant. Compensatory hypertrophy of the remaining kidney is seen but as an increased risk of hypertension, proteinuria and even mild reduction in GFR has been reported, long term surveillance of renal function in this population is generally justified. Irradiation of the kidney is tolerated to a dose of approximately 20 Gy, less if chemotherapy is given concurrently. The use of such doses to the whole kidney is unusual and the incidence of important sequelae from radiation alone is small.

The most important chemotherapy agents which cause renal damage are cisplatin and ifosfamide. Experience with very long term follow-up (i.e. greater than 20 years) is limited with cisplatin and non-existent with ifosfamide, yet there is ample data about their acute effects. Cisplatin causes both glomerular and tubular damage, the latter characteristically resulting in chronic hypomagnesaemia. Partial recovery has been reported and whilst damage is dose related, it is not progressive once treatment has been discontinued.

Ifosfamide has been in wide use only since the mid 1980s, but there is considerable literature describing its nephrotoxic effects. Tubular
damage (affecting both proximal and distal tubule function) is the most frequent and clinically important element, although glomerular damage also occurs. Renal Fanconi syndrome has been described, as has serious interference with bone mineralisation, progressing in a few patients to renal rickets. Toxicity is dose dependant and the risks may be greater in young children and in those who have been previously exposed to other renal toxicities (cisplatin, renal radiotherapy or unilateral nephrectomy). Importantly, renal function may continue to deteriorate after cessation of therapy although spontaneous improvement has also been described.

Although other drugs, including carboplatin, high dose cyclophosphamide and methotrexate are also implicated in effects on renal function, it is often supportive care drugs (e.g. aminoglycoside antibiotics and amphotericin) which have important renal toxicity and therefore research is needed into the combined effects of anti-neoplastic and supportive care drugs.

**Bladder and urinary tract**

Radiotherapy to the bladder can induce fibrosis with loss of bladder volume and disturbance of voluntary sphincter control. The effect depends on both the volume and dose of radiation. This may also result in a risk for second malignancy. Furthermore, treatment given early in childhood may interfere with the growth of the bladder compounding the reduction in volume caused by fibrosis.

Haemorrhagic cystitis from the use of cyclophosphamide and ifosfamide has been abolished by the concurrent use of mesna uroprotection but there are many survivors of the pre mesna era, some of whom may also have received pelvic radiotherapy. The consequences may be cumulative and similar damage may affect the ureters and urethra but only at very high radiation doses. Cystoscopy should be considered whenever survivors experience haematuria because of the concern about second malignancy.

Radiation effects on other pelvic organs are less well described but fibrosis and growth impairment are characteristic of all radiation field injuries.

**Neurological and neuropsychological sequelae**

Evaluation of children treated for ALL has provided the best data for understanding the risk of neuropsychological damage after cranial radiation. After doses up to 24 Gy, many children appear to function in the normal range, although formal testing shows neuropsychological test scores below those of control groups, including other patients with cancer.
not receiving CNS therapy. Deficits are generally greater in terms of attention span and cognitive processing skills, rather than in verbal skills\textsuperscript{51} – hence many such children may demonstrate specific difficulties with educational tasks such as maths and spelling whilst otherwise showing normal performance. Young age at treatment is probably the most important risk factor\textsuperscript{52} but dose itself is important, as indicated by the adverse outcome for children receiving higher doses for treatment of brain tumours and for children who receive a second course of cranial radiation after CNS relapse. The benefit of a reduction in prophylactic radiation dose for childhood leukaemia from 24 Gy to 18 Gy or by its substitution with intrathecal and high dose intravenous methotrexate has not yet been adequately assessed. The possibility that systemic chemotherapy plays a role in interacting with CNS radiotherapy in leukaemia needs to be considered but most studies conclude that radiation is of primary concern.

Children with brain tumours may be disadvantaged by the direct effects of the tumour and by the consequences of its surgical resection, in addition to the use of radiotherapy at high doses. The overall effects can be very damaging\textsuperscript{53}. The implications of the radiation damage are worse for those who receive treatment to the whole brain and particularly for those treated at a young age but postsurgical complications and concomitant chemotherapy have both been implicated.

In a minority, chronic neurotoxicity from cranial radiation may go on to manifest evidence of leucoencephalopathy with severe intellectual, sensory and physical handicaps. The risk is greatest in those who have received more than one course of cranial radiotherapy, usually in combination with intrathecal and systemic methotrexate\textsuperscript{54}. Correlation of neurological outcome with structural abnormalities seen on CT or MRI scans is notoriously unreliable. Symptomatic changes from leucoencephalopathy do not usually arise in the spinal cord but at particularly high doses (50 Gy) there is a risk of radiation myelopathy.

Long term neurological damage from chemotherapy other than methotrexate is very rare despite the occurrence of various acute neurological effects.

The major practical concerns for the care of the child with neurological and neuropsychological deficits is to maximise rehabilitation and educational progress by ensuring that appropriate assessments are undertaken early and remedial help offered.

\textbf{Other toxicities}

\textbf{Gastrointestinal and liver damage}

The overall incidence of late gastrointestinal and liver toxicity is remarkably low considering the frequency with which acute toxicity is
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experienced during treatment. Chemotherapy induced late effects are rare and it is likely that the risk of late sequelae from radiotherapy is increased after the occurrence of acute toxicity during treatment. Radiation may also enhance the risk of obstruction from adhesions in children who have undergone laparotomy and at high dose result in bowel stricture and retroperitoneal fibrosis.

Chronic radiation damage to the liver is recognised and could result in fibrosis and portal hypertension. Hepatic fibrosis may arise from administration of methotrexate but the risk is greatest in relation to chronic oral administration for prolonged periods. The risk from the weekly oral dose schedules used in leukaemia therapy or from high dose intravenous methotrexate seems small. There is no convincing evidence to suggest that the transient acute changes in liver function encountered during chemotherapy are relevant to late sequelae if normal liver function tests are documented at the end of therapy. In patients who have undergone allogeneic BMT, chronic GVHD is the most likely cause of chronic liver disease. Increasingly the risk of symptomatic or sub clinical liver damage may be linked to transfusion related infection (hepatitis B and C or CMV).

Musculoskeletal and soft tissue damage

Even low doses of radiation will have a deleterious effect on skeletal growth and although the functional effect also reflects the size of the radiation field, fractionation schedule and the age of the child at the time of treatment. Concomitant chemotherapy may accentuate the effect by enhancing the acute radiation reaction but rarely accounts for bone or soft tissue damage alone. Steroids are implicated in osteoporosis and avascular necrosis of bone, and recent reports of metabolic bone damage following ifosfamide induced renal tubular toxicity are a reason for caution with this drug.

Inclusion of epiphyses within the treatment volume will have a major impact on limb growth and may also predispose to the risk of slipped epiphyses. Exostoses (osteocartilaginous outgrowths) are said to be relatively common within radiation fields but perhaps now occur less frequently with mega voltage techniques.

The risk of scoliosis from spinal growth asymmetry is minimised by the practice of including the full width of the vertebral column in any radiation field including or adjacent to the spine but unilateral hypoplasia or fibrosis of adjacent soft tissue may contribute to the development of a spinal curve. Regular inspection is required to detect and monitor the early occurrence of any spinal curvature and is particularly important.
during the adolescent growth spurt. Disproportion in sitting to standing height arises when a significant length of vertebral column is irradiated, particularly at a young age. It is estimated that a dose of 35-40 Gy to the whole spine before the age of 5 years may result in an average height loss of up to 16 cm.

Soft tissue hypoplasia after radiotherapy is difficult to quantify and usually associated with underlying skeletal damage. The overall effect is usually more cosmetic than functional but fibrosis may restrict adjacent joint movement and cause pain.

The developing breast may be damaged by relatively small doses of radiotherapy—10 Gy will result in hypoplasia and failure of lactation, and over 20 Gy can ablate breast development entirely, requiring surgical augmentation in adult life. Accelerated vascular degeneration is at least of theoretical concern when major arteries are included in radiation fields.

Severe cosmetic damage can result from direct radiation fields to the face or orbit and it is important to recognise that the consequent effects will not be maximally apparent until pubertal growth is complete.

**Haematological and immunological late effects**

These are areas which have attracted little attention given the importance of the changes in the bone marrow and immune function during therapy. There is documentation of persistent subclinical bone marrow damage even after conventional chemotherapy and similar changes are reported after radiotherapy. These observations may also be of relevance to the risk of treatment induced secondary leukaemia.

Splenectomy (after staging for Hodgkin's disease) is a long term risk factor for sepsis and splenic damage from radiotherapy has been reported. Prolonged immunosuppression is a major issue for survivors of BMT, especially those with chronic GVHD. Re-immunisation is usually recommended but this is generally not considered necessary for survivors of conventional chemotherapy and radiation.

**Ears, eyes and teeth**

Cisplatin is a well recognised cause of hearing loss and the effect may be potentiated by radiation, a particular risk in children receiving combined modality treatment for brain tumours. The importance of cisplatin induced deafness in likely to be more profound in children damaged in
early life before speech is fully developed and in those whose loss extends below the high frequency range.

Chemotherapy is rarely, if ever, implicated in late effects against vision, except the well known association between steroid therapy and cataract formation. However, late radiation damage may affect all parts of the eye, the orbit and surrounding soft tissue. The most important consequences are cataract and dry eye. Cataract formation depends on dose and fractionation but the lens is the most radiosensitive region of the eye and scatter from cranial radiation (e.g. for CNS prophylaxis in ALL or from the whole CNS field in medulloblastoma) may be sufficient to cause damage. Evidence of cataract may emerge within 2 or 3 years of treatment especially after TBI although fractionation of the dose may reduce the risk. Direct high doses given for orbital sarcoma inevitably adversely effect the lens. Dry eye is a consequence of damage both to tear production and to the cornea and conjunctiva. Trauma and infection must be managed aggressively and the use of artificial tear drops is required.

Direct irradiation to the mouth is damaging to developing teeth and to salivary glands and taste buds. As expected, effects are dose and field size related but even patients receiving whole CNS treatment may receive a significant dose to the parotid glands in addition to an ‘exit’ dose to the mouth from the spinal field. The combination of reduced salivary function, with dry mouth, and a direct dose to teeth may result in accelerated caries in addition to disrupted dental development.

**Psychosocial issues**

The increasing success achieved in treating cancer in childhood should shift the perspective from threat of death to the issues involved in survival. Nevertheless, all families must confront the possibility of death from disease at the time of first diagnosis and the fear of this lives on, often manifesting itself in an overprotective response by parents towards the affected child. The consequences of living with uncertainty, together with memories of the experience and perhaps the need to cope with long term sequelae, will inevitably influence the attitude of the survivor into adult life. This is not necessarily an entirely negative experience. Positive aspects of survival are well documented and there is certainly a need to recognise the generally well adjusted status of most survivors. Nevertheless, there is good evidence that some survivors experience difficulties in adult life, including problems with employment, insurability and in establishing close relationships. The importance of educational achievement on self esteem, employability and earnings potential justifies
considerable effort to ensure that schooling is supported at the time of treatment and thereafter.

**Organisation of follow-up and the education of survivors**

It is important to recognise that patients are not necessarily best categorised by their primary diagnosis and that strategies for the surveillance of survivors must be based on the treatment each individual actually received. A record of cumulative drug and radiation exposure should be compiled for each patient at the end of treatment and a surveillance plan evolved to match the risk factors identified. Inevitably, some groups of survivors will share particular difficulties, for example those treated for brain tumours who may be particularly disadvantaged.

Empowering survivors to cope with their real or potential problems involves developing a clear strategy for their education about their disease, its treatment and the long term implications. Strategies include emphasis on 'exit' interviews both at the end of treatment and on the threshold of adult life. The provision of written information which contains details of the individual's disease and treatment history, including individually relevant recommendations for follow-up should form part of an ongoing contact with a long term follow-up programme. The aim of such programmes should be to follow long term survivors into adult life and to continue to support and inform them as individuals whilst collecting long term data which will be important in influencing the design of future treatments and in advising later cohorts of survivors.

Long term, important and potentially life threatening consequences of treatment used for cancer in childhood will continue to evolve as survival patterns change, particularly if this is achieved in association with more aggressive therapies. These issues will become an increasing focus for attention within society and clinicians themselves may face medico-legal challenges as a result of their efforts to cure. New treatment trials should be extended to answer late effects questions in addition to evaluating overall survival and there is a real need to develop methodology which can measure the quality of survival, as survival itself is no longer a valid measure of success for many diseases.

Reduction in the incidence of serious late effects may require a trade off between alternative toxicities in the design of treatment schedules (for example, the risks of infertility from alkylating agents versus cardiotoxicity from anthracyclines) or even an acceptance of a limit on possible survival. Such a debate can only be informed by continuing surveillance.
of all survivors, by careful documentation of the sequelae of their treatment and by the development and application of methods to assess the quality of survival achieved.

Priorities for the future

With 60% of children diagnosed with cancer being cured, and the likelihood that this figure will continue to improve, increasingly important determinants of future treatment protocols are late adverse outcomes associated with different therapies and identified through long term follow-up. Long term follow-up involving the determination of the risks and causes of such adverse outcomes is likely to provide benefits for both existing and future survivors. Existing survivors should benefit through targeted surveillance of groups of survivors known to be at increased risk and the opportunity for early diagnosis and clinical intervention. Future survivors should benefit from treatment protocol modifications which achieve an improved balance between the long term risks of adverse outcome and prospects for cure associated with different treatment strategies.

What is the most efficient and effective way to structure long term follow-up? To begin to answer this it is essential to distinguish between clinical and epidemiological follow-up of survivors. Each is important and each provides different but complementary information.

The advantages of epidemiological long term follow-up, in Britain, relate to the existence of various national registries and opportunity for record linkage between them. The National Registry of Childhood Tumours (NRCT) and the National Health Service Central Registers are the two key registries. All survivors of childhood cancer in Britain, identified through the NRCT, are routinely linked with the NHSCR and this provides continuing and automatic notification of cancers and deaths among survivors, the easy identification of the general practitioners of survivors and hence the current addresses of most survivors. Previous epidemiological studies of survivors in Britain have not involved direct contact with survivors, but have relied heavily on information supplied by general practitioners. This has limited the number of questions which could be satisfactorily addressed and it is likely that some important outcomes may have been under ascertained—for example, the number of offspring produced by male and older female survivors. A pilot study is underway which is testing the feasibility of study methods required to execute a questionnaire postal survey of the 17,000, 5 year survivors of childhood cancer diagnosed in Britain between 1940–1990.
National population-based epidemiological follow-up provides the only practicable way of monitoring the entire survivor population for adverse outcomes of treatment. For adverse outcomes which occur rarely in the generality of survivors, but much more commonly among subgroups at particular risk, such population-based monitoring provides the only realistic means to comprehensively assess the risks of adverse outcomes and aspects of treatment related to such risks. The reasons for this relate to the following: not all treatment centres clinically follow-up survivors indefinitely; survivors tend to geographically mobile—partly due to their young age; such epidemiological follow-up is considerably less expensive than clinical follow-up. Two current issues generating much clinical concern are the long term risks of serious cardiac disease among survivors exposed to anthracyclines; and the long term risk of solid cancers among survivors, particularly in view of the recent report that 35% of girls treated for Hodgkin’s disease developed breast cancer by age 40 years \(^{14}\). Population-based epidemiological monitoring provides the only realistic means of ultimately answering these questions of critical importance to decisions concerning future treatment protocols. The justification for continuing national epidemiological surveillance of survivors is compelling.

Clinical follow-up provides an opportunity for direct contact between hospital consultants, other health care professionals and survivors. Therefore, any complications of childhood cancer or its treatment which require some direct medical investigation of the survivor for assessment can only be satisfactorily studied in this setting. Clinical follow-up, particularly in the initial years after treatment, is essential for all patients. Particularly because of the high risk of relapse, recurrence and metastases during this period.

However, beyond 5 years from diagnosis, the risk of dying of recurrent disease is probably less than 8%. At this stage is the clinical follow-up of all survivors of equal priority or should there be groups with higher priority? There are two issues: providing optimum clinical care for each survivor and maximising the information gained from each survivor concerning late effects. We suggest that clinical long term follow-up should be prioritised and the top priority should be focussed on two groups of survivors: those known and those suspected to be at increased risk of some adverse outcome. For those known to be at increased risk it is clinically important that early diagnosis of such adverse outcomes is achieved and the effectiveness of different clinical interventions investigated. For those who are suspected of being at increased risk it is prudent and only through the study of such cases will clarification of the role of treatment emerge. In particular, if the study of a particular suspected adverse outcome requires clinical investigations of individual patients, then this needs to be studied in a clinical setting.
Collaboration between several treatment centres may be necessary to provide sufficient numbers to adequately address the question. Increasingly studies of late effects in survivors will require the measurement of biological characteristics of survivors, particularly genetic constitution and, therefore, such clinical studies will be increasingly common.

In summary, for the future it is essential to epidemiologically follow-up, for life, all survivors of childhood cancer in Britain and investigate the risks and causes of all possible adverse outcomes of cancer and its treatment. Clinical long term follow-up of survivors known or suspected to be at increased risk is the top priority, as is the execution of studies of the risk and causes of adverse outcomes which are suspected to be related to treatment and which can only be satisfactorily studied in a clinical setting.

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The long term survivors

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