Late Complications of Cancer in Childhood and Adolescence

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Abstract

Overall survival for all childhood cancers has substantially increased with nearly 80 % of children surviving to five years following diagnosis, compared with 30 % 50 years ago. Unfortunately this comes at a cost; the overall Standardised Mortality Ratio (SMR) was 8.4 for childhood cancer survivors compared with the general population and increases in cause-specific mortality were seen for deaths due to second malignancy and cardiotoxicity. The incidence of chronic morbidities in the US Childhood Cancer Survivor Study (CCSS) cohort was 62.3 % after follow-up for 26.6 years. While many children will escape these organ toxicities, a significant proportion will require surveillance and management of treatment morbidities. It is the responsibility of those who treat childhood cancer to understand the effects of treatment and provide effective services to maximise the potential of these young people.

Keywords

Childhood, cancer, survivor, late effects, cardiac, second malignancy, endocrinopathy

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Since the 1960s, overall survival for all childhood cancers has substantially increased such that currently nearly 80 % of children will survive to five years following diagnosis, compared with 30 % 50 years ago. For most childhood cancers, survival at five years from therapy does not decrease significantly, and the vast majority of these children will be long-term survivors of their disease and go on to live normal and fulfilling lives, this being a true reflection of treatment success. The Automated Childhood Cancer Information System (ACCIS) contains data regarding cancer incidence and survival of children and adolescents registered to approximately 80 population-based cancer registries in Europe. The actual number of survivors within Europe is unknown but is estimated to be between 300,000–500,000, which in Western Europe translates to one in 750 young adults being survivors of childhood cancer. A similar statistic has been quoted for North America (see *Figures 1* and *2*).

Amid the devastation that comes to a family with the news that their child has a diagnosis of cancer, there is the definite hope of a cure. However, the path that the child must tread to achieve survival is fraught with the possibility of future morbidity. The burden of their disease may cause organ compromise but, more importantly, organ toxicity may result from the effect of multiple modality treatment on the developing child. Cause-specific late mortality was studied among 20483 5-year survivors who were part of the US Childhood Cancer Survivor Study (CCSS).[1] The overall Standardised Mortality Ratio (SMR) was 8.4 compared with the general population, with increases in cause-specific mortality seen for deaths due to second malignancy and cardiac causes. The incidence of chronic morbidities in the CCSS cohort of 10397 survivors was 62.3 % after follow-up for 26.6 years, with 27.5 % having a severe or life-threatening condition.[2] While many children will escape these organ toxicities, a small proportion will require careful ongoing surveillance and management of treatment morbidities, including a careful plan to minimize their effects.

Current treatment protocols for childhood cancer aim to anticipate and mitigate the late effects of treatment while maintaining optimal survival rates for each disease group. This has been possible because of the growing interest in long-term follow-up including good studies highlighting the adverse effects of treatment which are subsequently fed back to the protocol designers. To serve survivors well there must be an understanding of the challenges faced by this population of young adults survivors, both in terms of physical, as well as psychologic and social morbidity, and the burden that these place on the individual and on financially constrained adult and pediatric health services.

This paper will not be exhaustive in describing the extent of late complications of childhood cancer but will describe three areas where modality and intensity of treatment has generated potential significant late toxicity. These areas are: cardiac toxicity, gonadal toxicity, and risk for second malignancy. Although endocrinopathies, including growth hormone dysfunction and thyroid and hypothalamic–pituitary axis abnormalities, will not be discussed here they do comprise the largest group of morbidities.[3] Children at risk need to be identified early and carefully assessed and managed by an expert team. Growth failure, due to both endocrine dysfunction and skeletal/soft tissue radiation-induced hypoplasia both symmetrical and asymetrical, together with other late effects of cancer treatment, may be associated with poor body image and psychologic morbidity. This may in turn impact on quality of life.[4,5] Other

morbidities include bladder and renal damage, respiratory problems, ocular and hearing problems and gastrointestinal damage. Excellent textbook references include *Late Effects of Childhood Cancer* by Wallace and Green.[3]

To achieve optimal care, evidence-based models of care must be developed that address the needs of these adolescents and adults. Collaboration between pediatric oncologists and adult physicians remains key to achieving good care. A final section will be devoted to the requirements necessary to provide effective aftercare along with the challenges.

Cardiac Complications of Treatment for Childhood Cancer

GH illustrates a case of rare severe cardiotoxicity from childhood cancer treatment. He was diagnosed at age 9 years with orbital embryonal rhabdomyosarcoma. At initial presentation, GH was treated with nine courses of ifosfamide, vincristine, and actinomycin D and external beam radiotherapy, 4500 c Gy, to his right orbit. At the age of 11 years his first relapse was treated with vincristine, carboplatin, etoposide, and epirubcin (total dose 450 mg/m^2) and resection of the tumor. He tolerated chemotherapy well with no acute cardiotoxicity. He re-presented with a second local relapse of rhabdomyosarcoma 5 years from initial diagnosis and underwent exenteration of the right eye to achieve complete excision of the tumor and further chemotherapy with vincristine, actinomycin D and cyclophosphamide.

He was seen in the long-term follow-up clinic at the age of 21 years, when he was well with no cardiac symptoms and enjoyed normal activities at university. A routine echocardiogram showed a significantly reduced shortening fraction (SF) of 23 % and a mildly dilated left ventricle with moderate septal hypokinesis and mild overall reduction in systolic function. He was referred to adult cardiology services and cardiac MRI showed a left ventricular (LV) end-diastolic volume at the upper limit of the normal range with moderate impairment of systolic function, with LV ejection fraction (LVEF) of 46 % (normal range 55–70 %). He was started on angiotensin converting enzyme inhibitors and beta blockade for high frequency ventricular ectopy. His cardiac dysfunction progressed over the next 4 years and by 25 years of age he required full anti-cardiac failure medication to which he responded well. A Holter monitor showed multifocal ventricular ectopy and an echocardiogram showed a LVEF of 10 % with biventricular severe impairment with minor mitral regurgitation and triscupid regurgitation. These findings were corroborated by a cardiac MRI although there was no fibrosis. He is now proceeding with a cardiac resynchronisation defibrillator and is undergoing evaluation for cardiac transplantation.

The risk for cardiovascular disease in childhood cancer survivors is increased by the independent or combined exposure of radiotherapy to the thorax and anthracycline chemotherapy. Cardiotoxicity may present acutely following the start of therapy, or show early or late onset.

Anthracyclines are used effectively in the treatment of the majority (>60 %) of childhood cancers and include doxorubicin, daunorubicin, epirubicin, and idarubicin. However, these drugs are known to cause myocardial damage by destroying myocardial cells, which results in areas of myocardial fibrosis. Myocardial damage may be present in asymptomatic patients, and over years progress to a wide spectrum

Figure 1: Age-specific Cancer Incidence Among Children in Europe as a Whole by Single Year of Age, Separately for Boys and Girls, 1988–1997 Source: ACCIS (Stiller 2006)

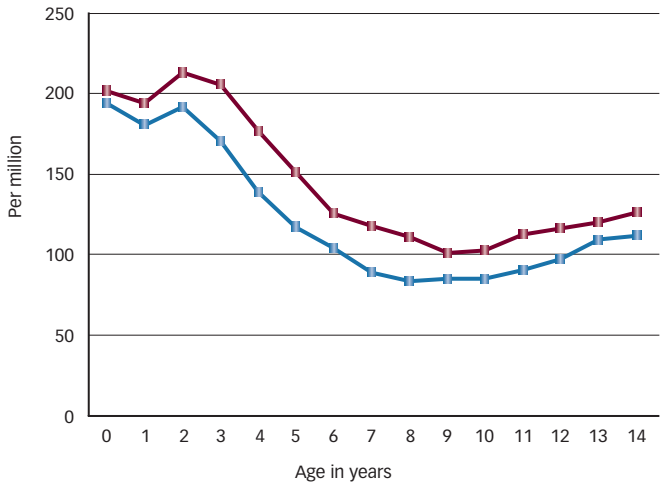
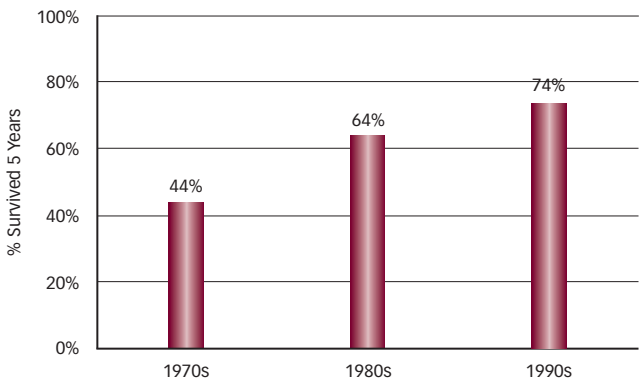


Figure 2: Overall 5-year Survival after Cancer during Childhood and Adolescence in Europe by Era of Diagnosis, Averaged over East and West Europe 1978–1997 Source: ACCIS (Stellarova-Foucher 2006)



of cardiac dysfunction including progression and irreversible cardiac failure, resulting in early mortality or necessitate cardiac transplantation.[6] The noted rise in incidence of transplantation over the last 30 years will need to influence the planning of therapy for children who may receive anthracyclines or cardiac irradiation.[7] Liposomal anthracyclines, including liposomal daunorubicin, liposomal doxorubicin (D-99), and pegylated liposomal doxorubicin, have been studied in several clinical trials and are thought to offer a more favorable cardiac safety profile.[8,9]

Radiotherapy to the myocardium is known to potentiate the cardiotoxic effects of anthracyclines, and independently causes pericarditis, pancarditis, myopathy, coronary artery disease, and conduction defects.[10] The mechanism of injury from irradiation is thought to involve damage to the fine vessels of the heart. Survivors previously treated for childhood Hodgkin's disease with radiation are at greatest risk for cardiac disease including fatal coronary artery disease, symptomatic, and subclinical

heart disease, with all but one of 48 patients having cardiac abnormalities on screening among a group of survivors who had received a median of 40 Gy mediastinal irradiation.[11] The risk for congestive heart failure in Wilms tumor patients receiving either chest radiotherapy or left abdominal radiotherapy in conjunction with anthracyclines was shown to increase by a factor of 1.6 and 1.8, respectively, for every 10 Gy of radiation received.[12]

The SMR for overall mortality and cardiac mortality in patients who have survived childhood cancer is 10.8 and 8.2 and is similar across the USA and Europe[13,14] and represents a significant disease burden. Long-term cardiac mortality was related to radiation dose received by the heart, and to cumulative anthracycline dose in a large cohort of 4122 survivors of childhood cancer diagnosed before 1986 in France and the UK followed for 27 years.[15] The overall SMR was 8.3 compared with the general population, and the relative risk (RR) of dying from cardiac disease was 4.4 for individuals who had received a cumulative dose of anthracycline of above 360 mg/m^2. Radiation dose to the heart above 5 Gy resulted in a RR of cardiac death of 12.5 for doses 5 to 14.9 gy, and of 25 for doses above 15 Gy. Regarding morbidity, the incidence of anthracycline-induced clinical heart failure in children has been reported as 16 % at 0.9 to 4.8 years after treatment,[16] and the prevalence of asymptomatic cardiac dysfunction as high as 57 % 6.4 years after treatment.[17]

Risk factors that increase the severity of cardiotoxicity from anthracycline therapy and radiation include higher cumulative anthracycline dose (particularly greater than 360 mg/m^2),[18–20] amount of radiation delivered to different depths of the heart, volume of myocardium irradiated, and other vascular structures involved, fractional irradiation dose, younger age at exposure,[19] longer latency period since therapy,[17,20] female gender,[21] and possibly increased rate of administration of anthracycline.[22,23]

Children treated for Hodgkin's disease in the past were often exposed to mediastinal irradiation using techniques that were less refined in terms of sparing normal tissue, and were also exposed to anthracycline chemotherapy. This group of patients remains particularly at risk for cardiovascular disease. It is hoped that in the future this risk will be reduced through a reduction in the use of radiotherapy and its dose intensity, more advanced techniques that spare normal tissue, and current chemotherapy protocols that conserve the use of anthracyclines.

Echocardiography has been the most frequently used method of screening for cardiac disease. LVEF as well as SF is measured together with systolic and diastolic function. However, echocardiography is operator-dependent and may not detect changes in myocardial structure that may predict earlier or later cardiotoxicity. In addition to clinically overt disease, a proportion of patients receiving low to moderate doses of anthracycline (90–270 mg/m^2) up to 10 years off treatment show signs, on detailed echocardiograms, of subclinical cardiac damage.[24] Evidence is lacking as to the clinical significance of these findings and prognosis for these patients, as well as the optimal screening schedule in this situation and its true value. Guidelines published vary in their recommendations between regular three to five yearly echocardiogram monitoring.[25–27]

In addition to echocardiography, ECG and the infrequent use of radionuclide angiocardiography, there has been much interest in the possibility of serum biomarkers to predict cardiac impairment and these may, in the future, contribute to a profile that includes improved imaging techniques to predict cardiomyopathy in at risk patients. Biomarkers that have been studied include B-type natriuretic peptide (BNP), N-terminal pro-BNP (NT-pro-BNP), cardiac troponin T (cTnT), and cardiac troponin I (cTnI).[28–30] To date cardiac MRI has not been shown to be a useful tool but newer techniques may offer a role as an imaging biomarker of disease. In tandem with these markers is the need to explore whether certain patients have a genetic susceptibility to anthracycline therapy, and this will allow modification of protocol and doses for those at greater risk for developing cardioxicity.

Pregnancy poses a particular challenge to women previously treated with anthracyclines.[31] Although a Dutch epidemiologic study shown no evidence of increased risk during pregnancy,[32] there is anecdotal evidence of cardiac compromise and the incidence will need to be assessed in large, adequately powered studies. Cardiotoxicity may be clinically unapparent until a stressful situation such as pregnancy causes cardiac decompensation which may occur in the third trimester and first two postpartum months. Pregnancy outcome was found to be favorable in 29 women with previous anthracycline exposure whose cardiac SF was above 30 % before pregnancy, but the eight women with LV dysfunction at baseline were at increased risk for further cardiac compromise during pregnancy and adverse pregnancy outcome.[33] Close liaison between an experienced obstetrician and cardiologist and care geared toward a high-risk pregnancy is essential, with regular echocardiography and appropriate follow-up postpartum.

Gonadotoxicity and Fertility in Survivors of Childhood Cancer

The majority of patients will have had therapy with radiotherapy and cytotoxic agents ,which will not have affected reproductive potential.[34] The ability to have families of their own is a parameter by which the success of survival and quality of life after pediatric cancer can be measured.

However, the impact of therapy on reproductive potential remains a significant concern for survivors, and it is a question frequently raised by parents at the start of treatment and during their child's journey. Among a cohort of 5-year survivors of solid tumors and Hodgkin's disease in the 1970s, a 15 % incidence of impaired fertility was demonstrated with a greater prevalence in boys.[35] Further studies including those who have undergone bone marrow transplant (BMT) for childhood cancer have correlated the incidence of impaired fertility with age at the time of therapy, type of therapy, and gender.[36–38]

The following case is unusual but highlights the difficult situation that some survivors may face in relation to their reproductive potential.

JB presented at the age of 4 years with bladder rhabdomyosarcoma, and completed treatment 1 year later. Therapy comprised multi-agent chemotherapy with alkylating agents and he received a nongonadotoxic total dose of 54 g/m^2 of ifosfamide.[39] He underwent cystoprostatectomy with urinary diversion and Mitrofanoff procedure followed by pelvic radiotherapy to a total dose of 45 Gy in 23 fractions with his testes shielded to a degree. Consequences of therapy included small testes with normal virilisation and erectile dysfunction requiring medical augmentation with

invasive penile injections prior to intercourse and he continued under uroandrology care. Sperm analysis had not been undertaken. As a young man he had outwardly sustained high spirits and had been successful in his academic pursuits, while appearing to enjoy a positive relationship with his girlfriend. The underlying distress at the difficulties of his situation was expressed suddenly and almost catastrophically. The burden of his sexual dysfunction and anxiety regarding future reproductive potential led him to end his relationship and he presented to clinic at the request of his mother with a profoundly flat affect and a complex emotional state for which he urgently needed psychologic support.

This case illustrates the burden and complexity of issues related to the late effects of cancer therapy on a vulnerable reproductive system. In addition to the medical aspects of managing expectations and compromised fertility, the psychologic and psychosexual consequences of difficulties in reproduction are extremely important to address at the same time.

For male survivors, chemotherapy and radiotherapy may compromise fertility by impairing the production of spermatozoa and the production of male sex steroid hormones required for normal male sexual development. The testicular germinal epithelium is particularly sensitive to the effects of chemotherapy and radiotherapy and irreparable damage may result with consequent infertility. Reduced testicular volume, elevated follicular stimulating hormone (FSH), low inhibin B, and impaired spermatogenesis are measurable indicators of germinal epithelial dysfunction. Chemotherapy agents that have a deleterious effect on germinal epithelial function include alkylating agents, cyclophopsphamide, ifosfamide, carmustine, lomustine, chlorambucil, melphalan, and busulfan. Procarbazine has been used in combination with alkylating agents in the treatment of Hodgkin's disease with great efficacy. However, the majority of males treated with these drugs subsequently developed permanent azospermia.[40–42] The extent of damage is related to the agent and dose received,[43,44] while regimens omitting alkylating agents and procarbazine were significantly less gonadotoxic with temporary azospermia in one-third of survivors and oligospermia in one fifth which subsequently recovered.[40] Current European protocols for Hodgkin's disease (EuroNet Paediatric Hodgkin's Lymphoma study) aim to minimize the late effects of therapy on fertility while maintaining successful survival by investigating the use of dacarbazine instead of procarbazine in a randomized controlled trial.

Testosterone-secreting Leydig cells are much less sensitive to gonadotoxic agents although direct radiation to the testes in sufficient dosage may result in hypogonadism requiring testosterone replacement. Reduced concentrations of testosterone and elevated luteinizing hormone (LH) are indicators of Leydig cell dysfunction. Although unusual, subtle Leydig cell dysfunction may result from gonadotoxic regimes for Hodgkin's disease resulting in compensated Leydig cell dysfunction with elevated LH and normal testosterone concentrations.[43,45] Conditioning regimes for BMT may include high-dose cyclophosphamide and busulfan causing impaired germinal epithelial function but Leydig cell function appears to be retained.[46]

Radiotherapy affects testicular function by both impairing germ cells which are exquisitely sensitive, as well as somatic cells. However, a greater dose of radiation is required to cause Leydig cell dysfunction and impaired production of testosterone. The degree of radiotherapy damage to the germinal epithelium is dependent on the field, total dose, and fractionation schedule. Impairment of spermatogenesis can occur at radation doses as low as 0.1–1.2 Gy, while doses above 4 Gy cause permanent azoospermia. Leydig cell dysfunction however is seen at doses of 20 Gy in prepubertal boys, and 30 Gy in sexually mature males.[47–49] Fractionation is an important factor in the degree to which dividing spermatogonia are damaged and permanent azospermia may result with fractionated doses greater than 1.2 Gy.[50] The concept of scatter to the testes during craniospinal irradiation must also be considered and was reflected in the incidence of primary germ cell dysfunction in a cohort of acute lymphoblastic leukemia (ALL) survivors receiving 24 Gy craniospinal irradiation without abdominal radiotherapy.[51] The potential for primary gonadal failure as a result of radiotherapy must be considered in boys who have received radiotherapy for disease control or total body irradiation (TBI) prior to allogeneic BMT. Subclinical dysfunction is also well documented with elevated LH levels and normal testosterone concentrations in children conditioned with TBI who proceeded to a normal male phenotype.[52] Testosterone replacement will be required in the prepubertal child with Leydig cell failure to augment puberty and growth, and in the older child to minimize symptoms of testosterone deficiency and risk for reduced skeletal mineralization and altered body composition.

For female survivors, infertility may occur as a result of adverse effects of radiotherapy and chemotherapy on the ovaries, the hypothalamic–pituitary–ovarian axis, or on the uterus. The fixed pool of primordial follicles present in the ovary at infancy may be prematurely depleted or its numbers more rapidly reduced over time as a result of cytotoxic injury. Depending on the age of the child at the time of treatment and the insult, primary ovarian failure may occur resulting in impaired fertility together with failure of normal pubertal development, in contrast to males whose pubertal progression is generally unaffected as a result of Leydig cell resistance. Less severe insult to the ovaries may present with early menopause. Ovarian failure is assessed by the presence of elevated gonadotrophins, FSH and LH, and low levels of estradiol (<40 pmol/L). Levels of anti-Mullerian hormone (AMH) appear to correlate most consistently with reduced ovarian reserve in women with raised FSH levels, and appeared to predict reduced reserve in survivors of Hodgkin's disease.[53–55] The use of AMH as a potential tool to predict premature menopause in survivors of childhood cancer is an exciting possibility that requires further evaluation. Ovarian failure is managed with estrogen replacement to induce puberty in primary ovarian failure, to relieve symptoms of estrogen deficiency and to maintain the protective effect of female sex hormones on the cardiovascular system and bone mineral density and survivors will need to be counseled regarding their risk for premature menopause.

Cytotoxic injury from radiotherapy may result from a direct effect on the ovaries or uterus if these organs are in the primary field or receive scatter and must be considered in girls who have received local treatment for solid tumors or TBI prior to BMT. Whole abdominal radiotherapy at 20–30 Gy resulted in 71 % of pre-pubertal girls failing to enter puberty, and 26 % entering into premature menopause.[56] Older women have a greater susceptibility to radiotherapy-induced ovarian failure as a result of an already reduced ovarian reserve, and the dose required to destroy 50 % of oocytes has been estimated as greater than 6 Gy compared with greater than 20 Gy in younger women.[57]

Hypogonadotrphic hypogonadism may occur as a result of cranial radiotherapy. Gonadotrophin deficiency is dose-dependent, infrequent when the hypothalamic–pituitary axis is irradiated at doses below 40 Gy, but increasing frequency at doses above 50 Gy, with an increase in prevalence over time postirradiation.[58,59] A spectrum of biochemical abnormalities and clinical severity may result. Abnormalities of gonadotrophin secretion may be detected only on dynamic pituitary function tests, and associated with either none or subclinical abnormalities only. In more severe cases, clinical secondary ovarian failure may occur with diminished estradiol concentrations and basal LH and FSH deficiency, or with abnormalities following dynamic pituitary function tests. Pulsatile stimulation with gonadotrophin-releasing hormone may potentially restore gonadal function and fertility.[60]

Chemotherapy-induced gonadal damage in females is caused by similar agents to those affecting males, but the ovaries are less sensitive than the testes. Alkylating agents and procarbazine are the main group with some evidence that vinblastine, cytarabine and cisplatin may affect ovarian function. The older the child at the start of therapy, the lower the doses of chemotherapy required to induce ovarian failure.[61] Women who had previously been treated for Hodgkin's disease with procarbazine and alkylating agents showed a variation in incidence of ovarian failure from 19–63 % of cases.[43] Multivariate analysis of 215 (6.3 %) participants of the CCSS who developed acute ovarian failure showed that increasing doses of ovarian irradiation, exposure to procarbazine at any age, and exposure to cyclophosphamide at ages 13–20 years were independent risk factors for ovarian failure.[62] In 103 females receiving high-dose cyclophosphamide alone (200 mg/kg), 54 % retained ovarian function, but this proportion fell significantly with the addition of busulfan (16 mg/kg) to the conditioning regime for BMT.[46] The risk for premature menopause in a large cohort of 518 females of median age 25 years, previously treated for Hodgkin's disease, was found to be 64 % after cumulative doses of cyclophosphamide greater than 8.4 g/m^2, and 15 % at doses of procarbazine less than 4.2 g/m^2. Current evolving protocols for the treatment of childhood cancer increasingly incorporate multi-agent regimens and newer biological agents and their effect on reproductive potential will need careful continued follow-up.

In addition to viable sperm and oocytes, conception requires delivery of sperm to the uterine cervix, patency of the fallopian tubes for fertilization to occur, and appropriate conditions in the uterus for implantation. Male sexual function may be impaired as in the case described above by surgical procedures involved in tumor resection and subsequent pelvic radiotherapy which damage the autonomic nervous system or reduce the blood supply to the penis. Complications include retrograde ejaculation or varying degrees of erectile dysfunction requiring sexual rehabilitation which may involve invasive techniques to sustain erection. The psychosexual difficulties that accompany these late effects cannot be underestimated.

In addition, the developing uterus will be damaged if exposed to both high-dose abdominal radiation and low-dose TBI with impairment of uterine length, blood flow, and endometrial thickness. These effects may lead to subsequent compromise of uterine function leading to an increased risk for early pregnancy loss, premature labour, and low-birthweight babies.[63] Importantly, there is no evidence that the offspring of patients previously treated for cancer are at greater risk for congenital malformations or cancer.[64]

Patients at risk for infertility should be offered information regarding fertility preservation prior to commencement of treatment. Sperm cryopreservation has long been an effective means of preserving fertility in males and can be offered with psychologic support to pubertal and postpubertal males. For prepubertal boys at present there is no effective technique although some centers are cryopreserving testicular material in the hope that in the future there will be a positive outcome, but this is still highly experimental.

For females the options differ.[65,66] In adult practice, cryopreservation of embryos may be successful, while cryopreservation of mature oocytes is less successful in terms of pregnancy outcome. Options are limited in prepubertal girls. Oophoropexy may be used in children to displace ovaries outside of the planned irradiation field, but the uterus may still be damaged. Cryopreservation of ovarian cortical tissue in which oocytes remain within primordial follicles is an emerging technique. This subsequently allows orthotopic or heterotopic re-implantation into the survivor after cure. Although a surgical procedure is required and caution needed regarding potential contamination of ovaries by some cancers, no ovarian stimulation is required prior to harvesting tissue, and it may therefore offer a potential solution to prepubertal girls and adolescents. A small group of children have undergone this procedure in some centres,[67–69] but there remains variation in tissue licensing requirements and the amount of tissue taken. There have been at least 13 pregnancies worldwide to women who have undergone this technique but none using prepubertal tissue, and its role in children remains experimental requiring further procedural and ethical clarity. Harvesting and storage of ovarian tissue must be carried out in accordance with standards for best practice, and guidelines have been published in the UK. Future advances may avoid the need for re-implantation of tissue by utilising in vitro growth and maturation procedures for nongrowing follicles which would avoid issues of re-introduction of tissue with possible malignant contamination.[65] It is hoped that prepubertal and adolescent girls and their parents will continue to be counseled appropriately regarding their fertility risk at the earliest opportunity, and in the future entered into an appropriate clinical trial where they will have the opportunity for ovarian preservation conducted in an ethical manner with careful follow-up regarding outcome.

Second Malignant Tumors

One of the most devastating consequences of curative cancer therapy is the development of a subsequent malignant tumor. The incidence and risk for developing a second malignant tumor (SMN) 5 years or more after initial diagnosis of childhood cancer was studied in 14,359 survivors as part of the CCSS.[70,71] Cumulative incidence of a second tumor at 30 years after initial cancer diagnosis was 20.5 %, with an incidence of 7.9 % for SMN. Second cancers following a primary childhood cancer include acute leukemias, mainly acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS), or solid tumors such as carcinomas or sarcomas.

SMN occurred with a sixfold increase in incidence compared with the general population, and excess risk was highest for a primary diagnosis of Hodgkin lymphoma (standardized incidence ratio [SIR] 8.7). Further risk factors were treatment with radiotherapy, female gender, older age at diagnosis, and treatment according to earlier protocols. This risk continues to increase as the cohort ages as seen in Hodgkin's disease survivors.[72]

In primary childhood cancers not associated with a genetic predisposition, the primary diagnosis is unlikely to be an independent risk factor but risk is influenced by previous treatment. Numerous studies have described the incidence and range of SMN in large cohorts of patients treated for childhood Hodgkin's disease. The risk for solid tumors remained elevated with RR of 6.6 among 20-year survivors in a cohort of 5925 patients diagnosed before 21 years of age and treated on early protocols between 1935 and 1994.[73] A RR of 4.6 persisted 25 years on and the range of cancers included sarcomas and carcinomas of thyroid, breast in females, bone and connective tissue, stomach, and esophagus, and in a number of cases reflected the radiotherapy fields used. Thyroid and respiratory tract tumors were particularly prevalent in children who had been treated with radiotherapy before the age of 10 years.

There is, additionally, a recognized interaction between specific cancer therapies precipitating SMN in patients with a genetic cancer predisposition, suggesting that germline mutations in tumor suppressor genes might interact with chemotherapy and radiotherapy insults to initiate second tumors. Patients with hereditary retinoblastoma who have a germline mutation of the RB1 tumor suppressor gene have an increased risk for SMN, particularly osteosarcoma and soft tissue tumors, and these are exacerbated by the use of irradiation.[74] Patients with Li Fraumeni syndrome who have germline P53 gene mutation are at risk for developing multiple subsequent cancers, and this risk is greatest in survivors of childhood cancers.

Therapy-related AML/MDS (t-AML/MDS) occurs following a short latency period from treatment and is associated with alkylating agents and topoisomerase II inhibitors. The alkylating agent-induced leukemias, often with a myelodysplastic stage, are associated with abnormalities involving chromosomes 5 and 7, and occur with a short latency of up to 5 years.[75] Incidence is less than 5 % and risk factors include increased age at exposure and higher cumulative dose of the alkylating agent. Therapy-related AML/MDS associated with topoisomerase II inhibitors occur following a shorter latency period of 6 months to 3 years and are associated with translocations involving the MLL gene to form a fusion product with a partner gene.[75,76] Risk factors include increased dose intensity of the topoisomerase inhibitor.[77] Both types of AML/MDS have been reported after treatment for Hodgkin's disease, acute lymphoblastic leukemia, and bone sarcoma, and are more resistant to therapy than de novo leukemias.

Solid SMNs are mainly related to the use of radiation, and risk factors include increased total dose of radiation, exposure at an early age, and increased latency period from first diagnosis.[70] As noted above, breast cancer is one of the most frequent second cancers in patients treated with radiotherapy for Hodgkin's disease and tumors develop within or at the edge of the radiotherapy field with a latency of 15 to 20 years, with the risk greatest for the youngest children, and cumulative incidence approaching 20 % at 45 years for patients treated with chest radiation below 16 years of age.[72] The high risk for breast cancer in susceptible survivors who have received chest radiation requires a vigilant screening program including regular mammography or MRI in the younger age group.[78] In addition, second malignancy of the digestive organs are directly related to radiation and the incidence has been shown to be in excess of the risk for having two first-degree relatives with bowel cancer, and therefore patients who have received significant abdominal radiation should be entered into a screening program.[79,80]

The thyroid is a particularly radiosensitive organ[70] and risk factors include radiation exposure at a young age, and increasing dose.[81] Data from the CCSS describe an 18-fold increase in the risk for thyroid cancer in at risk groups compared with the general population.[82] Careful physical examination of the thyroid is extremely important in this group of patients but routine ultrasound examination is not advised.

The risk for bone tumors in a cohort of 9170 patients who had been treated for childhood cancer was 133-fold greater than the general population with a 20 year cumulative risk for 2.8 %.[83] Children whose primary tumor was hereditary retinoblastoma or a bone sarcoma were at increased risk, and both increased radiation dose and cumulative alkylating agent dose were risk factors for developing a second bone tumor.[84]

The risk for developing a central nervous system tumor following childhood cancer was studied in a large cohort as part of the The British Childhood Cancer Survivor Study.[85] The study described an incidence of 137 meningiomas and 37 gliomas in a population of 17,980 survivors, and the risk for developing meningioma increased rapidly with increased dose of radiation to meningeal tissue, and increased dose of intrathecal methotrexate.

Smoking in adults who have previously been treated with lung irradiation for a Hodgkin's disease has been related to an increased risk for second lung cancer, and the risk for this malignancy after chest irradiation also rises with increased follow-up.[86]

With the use of modern protocols to treat childhood cancer in which the role of radiotherapy is more conservative than in the past, and the techniques used more advanced, it is hoped that future cohorts of Hodgkin's disease and other patients will show a reduction in the incidence of second cancers. The role of both primary and secondary prevention including careful lifestyle choices, in addition to appropriate screening programs, will, it is hoped, contribute to the reduction in the incidence of these tumors.

Service Provision

The perceived dictum has been that all childhood cancer survivors should be followed up for life, though whether this is necessary or appropriate is up for debate. However there is general consensus that follow-up programs should provide surveillance and management for late effects, support for psychosocial issues and education regarding lifestyle, employment, and financial issues[87] with the aim of reducing mortality, morbidity, and improving quality of life.

To provide this effective aftercare for childhood cancer survivors a number of factors need to be considered. Firstly, there is the evolving population and its needs. There is an ever-increasing population with age range extending widely from young children, through adolescence into adulthood, with adult survivors now contributing to more than half of the population. As illustrated above the late sequelae can be very diverse, presenting during treatment (cisplatin-induced hearing loss, neurologic deficiency post brain tumor surgery) or many decades later (SMN, cardiovascular disease). The symptoms can remain static or present as progressive disease. In addition, the risk for late effects varies from those patients who remain well requiring no medical or social support to the other extreme of those with multiple comorbidities and life-threatening conditions.

Secondly, the health care system and its capabilities must be considered. The patient's journey needs to be mapped out with flexibility to provide different models of care tailored to fit the differing requirements of the survivor over time.

For some, hospital-based multidisciplinary expert care may be required, but for many supported self-management may be the method of choice as for other chronic diseases. Depending on the health care system this support could come from informed primary physicians, community nurses, or care coordinators within the principal treatment centers. In addition, to provide early detection of sequele, remote surveillance may be useful as in the case of breast cancer surveillance in the female mediastinal radiation group.[78] Similarly, there is recent evidence to support bowel cancer surveillance in those who received abdominal radiation[80].

In 2006 the Institute of Medicine (IOM) report *From Cancer Patient to Cancer Survivor: Lost in Transition*,[88] recommended implementation of treatment summaries and survivorship care planning. Since then various groups have been working on treatment summaries and care plans (Childrens Oncology Group, National Cancer Survivorship Initiative, European Network for Cancer research in Children and Adolescents). These documents could empower the survivors and support self-management by providing relevant information about their past treatment, late effects, and future planning of care. Late effect guidelines have been published from different groups and work is in progress to provide international harmonization of the guidelines to provide, as far as possible, evidence to support care plans and to stratify the risk for late effects for individual patients[25,26,89–91] This information can be used to provide an appropriate level of care assisting in defining type and frequency of follow-up.

While survivors are in their childhood, they are served by the pediatric community but as adults their requirements change. Transition to adult services is a vital part of aftercare. It should be seen as an active process that changes care from paternalistic driven care (health care professional or parents) to supported self-management within adult services. This process has to run in parallel with the changing physical and emotional development that goes with the progress through childhood to adulthood. Effective transition has many components and should facilitate safe self-management and provide information to those that require more structured multidisciplinary care.[92] The real challenge is to provide an effective adult late-effects service.

In summary, late effects of cancer treatment is a vital issue for all those who treat childhood cancer, and it is their responsibility to acknowledge and understand the effects of the treatment and provide effective services to maximise the potential of these young people. ■

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