

# CHALLENGES FACING SURVIVORS OF CHILDHOOD AND ADOLESCENT CANCER

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## Abstract

The last 40 years have seen major changes in the treatment of childhood and adolescent cancers. From a nearly uniform fatal outcome to an expectant 80% probability of cure, the number of long-term survivors has dramatically increased. During the last 20 years the significant consequences of surgery, radiotherapy and chemotherapy have become apparent. Permanent complications as a result of the tumour itself and initial surgery are aggravated by long-term effects of radiotherapy and chemotherapy. The assumption that cancer cure leads to the end of medical surveillance is being overturned as more research regarding long-term and late effects is reported. The effect on psychosocial development of children and adolescents is increasingly being recognised and this has implications well into adulthood. With the increasing number of survivors of childhood and adolescent malignancies in the community, medical and allied health professions should develop a knowledge of the implications of having had these diagnoses and their subsequent treatments. The challenges in creating a robust, sustainable model of ongoing care for these patients is significant, with options ranging from discharge to family doctors, who are provided with information, through to totally tertiary referral centre based care.

In many pursuits, the 'finishing line' is not always where you think it is. For many years the 'finishing line' for children and adolescents with cancer was being told that they were cured – usually after four to five years of disease-free survival. It is now apparent that the consequences of having had a malignancy, especially in childhood, can impact many years later. In the greater scheme of things, curing significant numbers of childhood cancers has been a relatively recent phenomenon, namely over the last 35-40 years. This period has seen a phenomenal change in outcomes for childhood malignancies. When Farber first used methotrexate to treat children with leukaemia in 1948, short remissions resulted, but ultimately all patients succumbed to the disease. His initial report in the *New England Journal of Medicine* in 1948<sup>1</sup> was met with derision, as the prevailing view was that leukaemias were incurable and that the children should be allowed to 'die in peace'. Indeed, in the 1960s parents were often told to take their children home and to love them, as there were no sustained remissions.

The use of multi-agent chemotherapy in the late 1960s led to the first reported durable remissions for children with acute leukaemias and lymphomas. The 1970s saw a dramatic rise in cure rates for many malignancies. It is humbling to realise that many of these children are now in their 40s and 50s - in many respects still relatively young.

Until this watershed, the only long-term survivors of childhood malignancy resulted from curative surgery or curative radiation. The numbers were small, but even

then there was a recognised cost seen in these long-term survivors with growth effects, neuro-cognitive and neuro-endocrine complications and the suggestion of increased second malignancies. In his seminal paper on the role of radiotherapy in medulloblastoma, Bloom noted that children under two years of age often required ongoing institutional care after receiving craniospinal radiotherapy.<sup>2</sup> Prior to this, Lampe expressed concern regarding brain damage that could result from high doses of radiation to brains of younger patients.<sup>3</sup>

It was hoped that chemotherapy would eliminate the need for radiation and be free of long-term consequences, but unfortunately this was not to be. Until the 1990s, once a patient was deemed cured they were usually discharged from the primary treating institution and told to live a normal life with reasonable expectation that they would. There has been an increasing recognition over the last 20 years of the many complications that may result from anti-cancer treatments. As a profession, we have an obligation to screen for and deal with these problems. This paper reviews the challenges facing childhood cancer survivors considering the physical, psychological, social and financial implications.

## Epidemiology of cancer in children

According to the Surveillance, Epidemiology and End Results data, the incidence of cancers in young people less than 20 in the US, has remained static between 12.9 and 16.7 per 100,000 during the last 30 years.<sup>4</sup> During

this time, the mortality incidence has decreased from 5.2 to 2.6. The most common malignancies are leukaemias (45/100,000), central nervous system malignancies (28/100,000), lymphomas (24/100,000), soft tissue sarcomas (12/100,000), germcell/trophoblastic tumours/neoplasms of the gonads (11.6/100,000), malignant bone tumours (9/100,000), neuroblastomas (8/100,000) and renal tumours eg. Wilms (6/100,000).<sup>5</sup>

As a result of this improvement in treatment, it is now expected that 80% of childhood cancer patients will become long-term survivors.<sup>6</sup> One in 640 young adults 20-39 are cancer survivors and this means that the average general practice would be expected to have at least two of these patients per physician.

Treatments for childhood and adolescent cancers are diverse. The most common malignancy in this group is leukaemia (as above) and the chemotherapy for this condition can often continue over 18 months, possibly requiring total body irradiation and bone marrow transplantation. Lymphomas are treated predominantly with chemotherapy, with radiation used in a number of cooperative group protocols, albeit at much lower doses than adult patients receive. Brain tumours are usually treated with up-front surgery followed by up to 59 Gy of radiation. Sarcomas are usually treated with surgery and subsequent chemotherapy, often with the role of radiotherapy dependant on the histology and surgical clearance pathologically. The doses of radiotherapy for this group are variable, ranging from a modest 36 Gy to a radical 50.4 (Rhabdomyosarcoma) or 55.8 Gy (Ewings). At the other end of the spectrum, Wilm's tumour in the early stages is treated with a short course of chemotherapy and radiotherapy usually of very small doses (10.8-21.6 Gy).

The gist of the European cooperative group studies has been to avoid radiation unless the local control with surgery comes with unacceptable toxicities. The North American cooperative groups in contrast have aimed to reduce the doses of radiotherapy, but the result is that more children are receiving it. Not surprisingly, over the last decade many treatment protocols for diseases such as Wilms tumour are converging on the role and dose of radiotherapy, allowing cross group studies to be entertained.

### Physical effects from the cancer itself

The tumour itself can cause significant long-lasting problems prior to any therapeutic intervention. In brain tumours, there is good evidence that having a tumour itself can cause disturbance of the hypothalamic pituitary axis prior to surgery or radiotherapy.<sup>7</sup> Likewise, the development of hydrocephalus is recognised to be an independent cause of significant neurocognitive decline in patients with brain tumours, previously attributed solely to radiation therapy.<sup>8</sup> Damage to neurones may not be repairable and so often timely intervention is crucial in the setting of cord compression (eg. osteosarcoma or Ewing's), or the optic chiasm (craniopharyngiomas and optic pathway gliomas).

### Surgery

Clearly, the need for cancer resections of bony structures may have significant cosmetic effects and impacts on

growth, especially if the growth plates are involved. The issue of rehabilitation involved after amputations is significant. Those patients who have undergone splenectomy, as performed at staging laparotomy for Hodgkin's disease in the 1970s and 80s, are at risk of pneumococcal and meningococcal infections and as such require life-long surveillance and vaccinations.<sup>9</sup> Long-term neurocognitive insult and neuronal injury are a possible complication of major brain tumour resections. Nephrectomy patients develop compensatory hypertrophy of the remaining kidney and run the risk of earlier onset hypertension, with its related health issues and proteinuria.<sup>10-12</sup>

### Late effects from radiotherapy and chemotherapy

The most famous first victim of radiation late effects was probably Marie Curie, who discovered radium along with her husband Pierre. She also went on to develop the first mobile X-ray station in France in World War I. Marie died of aplastic anaemia, most likely as a result of her long-term radiation exposure. Her daughter Irene, also a Nobel Prize winning radiation physicist, developed and died from acute leukaemia. Pierre Curie however, was spared a similar fate – he was run over by a horse drawn cart on the streets of Paris in April of 1906.

The most studied modality producing late effects is radiation. The first patients were treated in the late 1890s and until the advent of chemotherapy, it was the only effective non-surgical treatment for cancer available. However, from relatively early on the effects of radiotherapy were appreciated.

*"The dangers from the use of X-rays may be grouped as immediate and remote. During the actual exposure, the possibility of making contact with a high-tension lead carrying a very high voltage has to be guarded against. An accident of this kind may easily be fatal...constitutional disorders, anaemia and sterility not infrequently arise in operators who are constantly exposed to X-rays."<sup>13</sup>*

In 1935, the concept of immediate and long-term or late effects was very simple. It is now thought that late effects refer to complications that arise many months to many years after the completion of therapy.

Indeed, much of the significant early data regarding adverse effects from radiotherapy is not from therapeutic radiation exposure - rather from the Hiroshima and Nagasaki atomic bomb data, industrial accidents and use in benign conditions. For example, in the 1940s and 50s, superficial irradiation was a commonly used treatment for tinea capitis, with doses of 0.04-0.45 Gy used.<sup>14</sup> Early reports from the 1960s suggested an increase in leukaemias, other malignancies and interestingly 'mental disorders'. The incidence of thyroid, brain and other head and neck cancers was also found to be increased in the large cohort of Israeli immigrants treated for tinea in the 1940s and 50s.<sup>15</sup>

Much of the current data regarding late effects of cancer treatments has been developed for the retrospective cohort of ~ 10,000 patients with matched sibling controls in the Childhood Cancer Survivors Study group.<sup>6,16-19</sup>

Much of this data and other published literature has been brought together in the formation of the long-term follow-up guidelines of the Children's Oncology Group ([www-survivorshipguidelines.org/](http://www-survivorshipguidelines.org/)). These guidelines are used as the basis for many long-term follow-up programs both in the US and internationally.

It is beyond the scope of this paper to exhaustively detail the physical effects of chemotherapy and radiotherapy, however, a brief overview follows.

### **Head and neck region**

Alopecia is physically perhaps the most insignificant side-effect of cancer treatment, but psychosocially, one of the more distressing, particularly for teenage girls. Cranial radiation often leads to temporary hair loss in field and the degree of permanent effect relates to total dose. It is apparent that combined chemoradiation (such as in medulloblastoma) can lead to more pronounced permanent thinning of the hair, or indeed complete alopecia.<sup>20</sup>

The lens of the eye is very sensitive to the effects of radiation and to steroid administration, which both lead to cataractogenesis.<sup>21</sup> In conditions such as medulloblastoma and leukaemia requiring prophylactic cranial irradiation, it is difficult to adequately cover the cribriform plate without giving some dose to the lens. In itself, cataract removal is a fairly straightforward procedure, but the dose to the anterior chamber of the eye also increases the later risk of developing glaucoma.<sup>22</sup>

The hypothalamic-pituitary axis is often compromised if it is involved in the surgical resection of tumours (particularly craniopharyngioma). Both surgery and radiotherapy to the hypothalamus can lead to hypothalamic obesity or metabolic syndrome, which is thought to be due to an abnormality in the normal satiety response to food. Radiotherapy effects to this axis present with a median time of three years post therapy. The thyroid axis is usually affected first, followed by growth hormone, the sex hormones (sometimes presenting as precocious puberty) and less commonly Adrenocorticotrophic hormone, leading to Addisonian syndromes. The thyroid gland itself may suffer primary failure if it is in the primary radiation field. In conditions requiring cranio-spinal irradiation, it may prove difficult to distinguish between central failure and peripheral (glandular) failure. Central infertility may also result from radiation, however, this may be negated by the use of gonadotrophic releasing hormone agonists to induce gonadal stimulation.<sup>23-26</sup>

Often the most devastating long-term effects is the functional neurological compromise suffered by patients who have had brain tumours or cranial irradiation.<sup>27</sup> As mentioned previously, there is evidence that hydrocephalus itself can aggravate neurocognitive compromise.<sup>8</sup> Merchant et al have demonstrated that IQ decline is proportional to the volume of brain treated, especially the temporal lobes and the dose these volumes received.<sup>28</sup> Palmer et al found that there appears to be a constant decline until age 12, after which the IQ remains stable. There is however, a progressive reduction in short-term memory and concentration span through the teenage years.<sup>29</sup> Some evidence suggests medications such as dexamphetamine and/or cognitive remediation programs may improve academic performance and overall quality of life in some with a history of brain

tumours.<sup>23,24,30,31</sup> Similar, but not as profound effects can be seen in patients who have had intrathecal methotrexate, especially if cranial radiotherapy is also given.<sup>25,32</sup>

Radiation can age the brain and there is a small risk of focal radionecrosis in high dose regions,<sup>33</sup> as well as a general increased risk of cerebrovascular accidents. Radiation to the neck and mediastinum can increase the rates of cerebrovascular disease in five-year survivors from Hodgkin's disease.<sup>34</sup> For this reason, many late effects services take an aggressive approach to management of hypercholesterolemia, hypertension and other reversible risk factors for cerebrovascular disease.

### **Cardiac effects**

Both radiotherapy and chemotherapy have significant impacts on cardiac function. High-dose anthracyclines (eg. > 350 mg/m<sup>2</sup> equivalent doxorubicin), can induce cardiac failure during treatment.<sup>35</sup> There is also a recognised decrement in cardiac function which may present years later.<sup>36,37</sup> In female patients, cardiac failure may be unmasked during pregnancy. It is advisable for pregnant women with a history of cardiac irradiation or anthracycline chemotherapy to undergo cardiac function assessment during pregnancy and monitoring during labour and delivery. Radiotherapy to the chest increases the risk of ischaemic heart disease by 2-5%.<sup>19,38</sup> These patients also have an increased rate of valvular abnormalities, usually presenting with stenotic rather than incompetent valvular heart disease. Renal irradiation may cause cortical scarring or fibrosis, increasing the risk of Angiotensin converting enzyme driven hypertension, aggravating both the cerebral and cardiac risk profile.<sup>10</sup>

Intriguingly, there is data that implicates higher doses of cisplatin used in the treatment of testicular cancers in the development of the metabolic syndrome. This clearly has ongoing implications for the cardiovascular health of these patients.<sup>39</sup>

### **Pulmonary effects**

Radiation doses above about 20 Gy induce variable degrees of pulmonary fibrosis in the radiation field, which if marked, may lead to a restrictive pattern on lung function testing and a decrease in overall diffusing capacity.<sup>32,40</sup> This is particularly relevant in patients with mediastinal lymphoma, and needs to be considered in some with a history of neuroblastoma. Bleomycin chemotherapy is a potent inducer of interstitial fibrosis and pneumonitis.<sup>33,41</sup> These problems are aggravated by tobacco and marijuana smoking, so smoking cessation is essential for people with these prior exposures.

### **Gastrointestinal effects**

High dose radiation to the gastrointestinal tract can lead to localised strictures, gastrointestinal tract blood loss from telangiectatic blood vessel formation in the walls and/or chronic loose motions or diarrhoea.<sup>1,42</sup> There are reports of radiation induced bowel cancers in people treated for Wilm's tumour or rhabdomyosarcoma.<sup>43</sup>

### **Genitourinary effects**

High dose cyclophosphamide may induce haemorrhagic cystitis despite routine intravenous hydration prior to chemotherapy. Cyclophosphamide in childhood increases

the risk of later bladder malignancies.<sup>44</sup> High dose irradiation may induce scarring in the bladder, causing reduced bladder volume, which may result in urinary frequency and urge incontinence. Many chemotherapies, particularly potent alkylating agents (especially nitrogen mustard), can induce infertility in later life.<sup>45</sup> Chemotherapy (especially cyclophosphamide) may be associated with premature menopause. This is related to chemotherapy dose and age at treatment. Radiation has been found to reduce uterine blood flow, and in doses above 16-20 Gy may induce hypoplasia and fibrosis, resulting in miscarriage or inability to carry a pregnancy to term. Radiotherapy doses of 2-4 Gy to the testes and 4-6 Gy to the ovaries may induce sterility, and at higher levels (~20 Gy) may result in loss of hormonal function.<sup>46-48</sup>

### Musculoskeletal hypoplasia

As depicted in figure 1, the threshold dose for hypoplasia induced by radiation appears to be about 16 Gy, with the plateauing of effect seen at about 25 Gy. If there is inhomogeneity across growth plates (as in vertebral bodies), asymmetric growth may lead to impaired cosmetic outcomes, such as kyphoscoliosis, facial asymmetry and pelvic tilt. Associated with this could be effects on neuronal, glandular and mechanical functions as described above. Clearly another mechanism of impaired growth is from the effects on growth hormone production from hypothalamic/pituitary irradiation. Chemotherapy itself may cause overall growth failure, with twin studies showing that bone marrow transplanted patients are

reliably shorter than their siblings. Radiation can lead to late osteoporosis in field and in some cases radionecrosis in high dose areas. Likewise, high total dose corticosteroids may induce osteoporosis and more worryingly avascular necrosis of the head of the femurs.

### Second malignancies

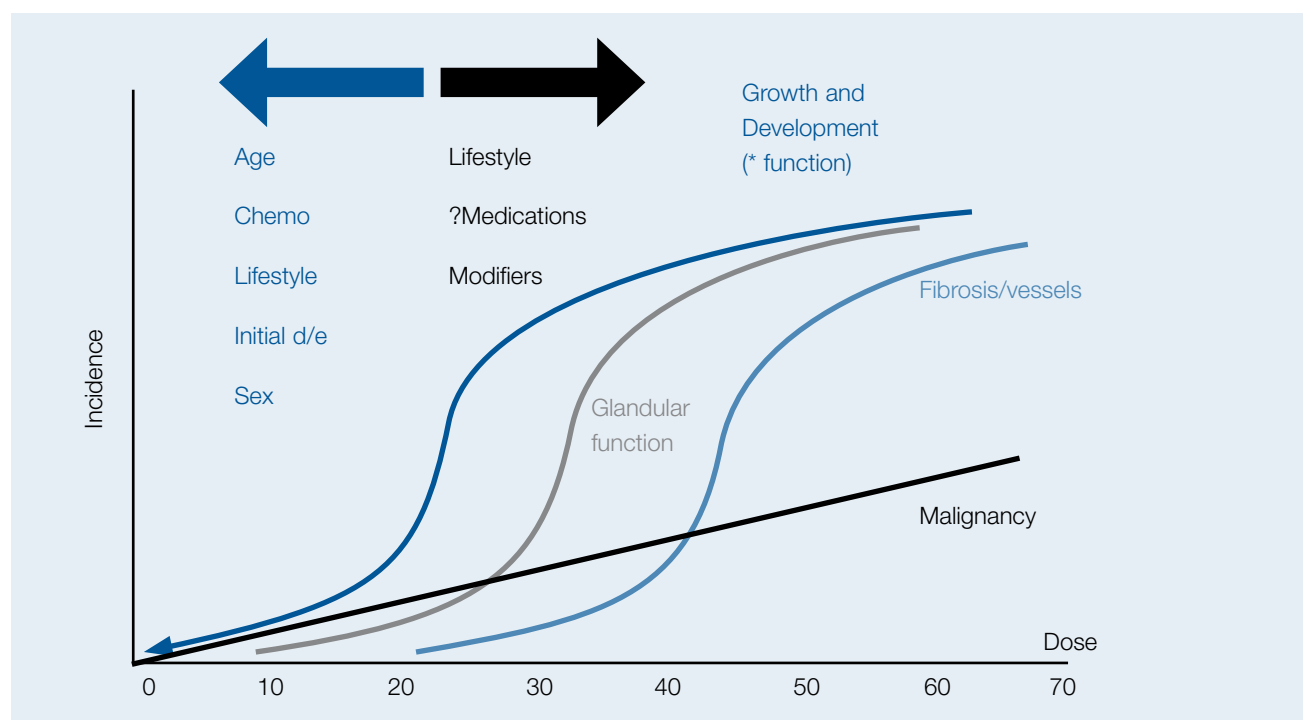
One of the most concerning complications of cancer treatment, both for the patient and the treating clinicians, is second malignant neoplasms.<sup>49</sup> Some primary tumours in themselves are associated with an increased risk of other malignancies, such as retinoblastoma, or lymphoma. Intensive chemotherapy, particularly etoposide-like drugs, carry a risk of induced leukaemias and myelodysplastic syndromes.<sup>50</sup> The second malignancy risk from radiotherapy has a dose response, with the exception of thyroid cancers, which seem to plateau at a dose of approximately 15 Gy. Concurrent chemotherapy, particularly doxorubicin, increases the risk of developing a radiation induced second malignancy.

It has been appreciated for many years that treatment for Hodgkin's lymphoma using mediastinal radiation increases the risk of breast cancer.<sup>51</sup> More recently, the induction of meningiomas and more rarely gliomas in the central nervous system with antimetabolite maintenance chemotherapy in acute lymphoblastic leukemia is apparent. Retinoblastoma patients who have had irradiation have a significant risk of a second malignant neoplasm, especially osteosarcomas in the treatment field. The prognosis from

**Figure 1** – Schematic representation of the late effects of radiotherapy

*Legend: The shape of these curves indicate an initial gentle rise in incidence with increasing radiotherapy doses. The steeper sections represent the critical regions of dose where there is a rapid increase in the incidence of growth retardation/glandular function/fibrosis and vascular complications; at higher dose levels the incidence tends to plateau. In planning radiotherapy for children it is preferable to dose critical structures below that where the curves steepen. There is a near linear development of second malignancy to dose.*

*(Incidence – reflects the incidence or severity of the complication; Dose – in Gray; d/e – disease; Sex – male or female gender; \* function- surrogate for function; Malignancy – radiation/treatment induced second malignancy (excluding disease recurrence)).*



these tumours is grim. Development of skin cancers within a previous radiation field is common. Infield lung cancers have been reported with an observed to expected ratio of 7.0, and in this study,<sup>52</sup> all were smokers. Eighty per cent of secondary malignancies are either in the field of radiotherapy or at the margins, strongly implicating the role of radiation in the pathogenesis of these conditions.<sup>53-59</sup>

### Psychological and social effects

It has become increasingly apparent that having had a cancer can have a profound impact on psychosocial development. Survivors of cancer in childhood or adolescence are much less likely than their peers to marry, hold a job, reach the same socioeconomic status, hold insurance or complete tertiary education.<sup>60-64</sup> The most obvious impacts relate to failure to socialise due to brain injury, whether it be surgical insult (such as posterior fossa syndrome or hemiplegias), or failure to concentrate and follow game commands due to prior radiation. Damaged frontal lobe function often impacts on group play, and children may be ostracised as a result. More subtle impacts are seen when children lose touch with their peers during long absences caused by treatment. Social awkwardness engendered by lack of hair or just the fact of having their peers feeling awkward about their diagnosis of cancer can impede normal interactions. They are also often caught between wanting to be 'normal', yet having a life-changing event acknowledged in some way (see Carl's story).

#### Carl's story

Carl was found to have a medulloblastoma in his second last year of high school. He found that once the diagnosis was known, especially once his hair began to fall out, he felt cocooned from his friends, that they didn't see him in the same way and often would tiptoe around him with their jokes and stories in case they offended him.

He found however, that their conversations were more inane and juvenile: "I'd faced a life threatening illness and they were concerned about who said what to who; it just didn't seem important anymore." He repeated his second last year of school to catch up on the work he had missed out on while undergoing treatment. When he was in his final year he found it hard to be motivated as all his friends were at university and having a great time, while he was still stuck with the 'kids'.

While wanting to get on with a normal life he became increasingly concerned about minor symptoms in case they represented disease recurrence. The periods between his scans and obtaining the results were also extraordinarily stressful for him. A referral to a psychology and counselling service in concert with regular medical check-ups has helped this latter problem.

He is now in tertiary studies and pursuing a music career. His illness has given him a very different perspective on life and he remains anxious as to the possible late effects of treatment.

This can become particularly poignant once the treatment is completed and they look physically normal. Indeed, often adolescents and children find the academic dislocation hard to overcome, resulting in poor grades and worsening social isolation should they need to repeat a year of school.<sup>49</sup> As they transition into the period of adolescence and young adulthood, social awkwardness, along with the physical impact from cancer and its treatments, can provide additional stress on relationships. Having a healthy body image and self-esteem relies on accepting physical appearances, which in the maelstrom of surgery, chemotherapy and radiotherapy is hard for young people to achieve, especially with the change in the way people respond to them. Permanent physical treatment side-effects such as hair loss, amputation, scarring and fatigue, can result in reactive depression, anxiety and in some situations post-traumatic stress disorder.<sup>65,66</sup> Increased prevalence of somatic symptoms, depression and/or anxiety, attention deficit and anti-social behaviour among young cancer survivors, has been documented in those diagnosed with leukaemia. Central nervous system tumours and neuroblastoma are also deemed to be at particular risk.<sup>66,67</sup> Brain tumour patients in particular may have profound and often debilitating fatigue, which inhibits ability to work and particularly socialise after work if they are employed. In some patients, exogenous growth hormone or stimulants such as dexamphetamine may be useful adjuncts, and of course screening for hypothyroidism (either central or due to gland damage) is an important part of long-term surveillance.

Other causes of fatigue need to be considered and it is often an early sign of more significant issues, such as a reactive depression, post-traumatic stress disorder or general anxiety. Many long-term survivors have a marked anxiety about their health.<sup>66</sup> The wait for test results can be particularly onerous, while returning to the same institution where their initial treatment was given can bring distressing flashbacks or even responsive nausea and vomiting. Minor symptoms can bring on marked agitation about the possible cause, and it is beholden upon the caring team to put the risks of long-term problems in perspective. In other cases, patients may want to completely ignore what they have been through and refuse further follow-up. The extreme of this is to engage in risk taking behaviour such as tobacco and alcohol excess or illicit drug use.

Childhood cancer survivors often find long-term consequences in later life that are not directly related to the direct physical effects of chemotherapy or radiotherapy. In many countries (such as Australia), there are enormous hurdles to cancer survivors joining the military and developing further trade opportunities that could carry on into civilian life. Short-term memory impairment and concentration span problems, which may result from cranial radiation and intrathecal chemotherapy, reduce patients' ability to complete tertiary education or even vocational training assessments.<sup>60-64</sup> More subtle issues such as altered cosmetic outcomes or personality affects, may deny survivors of childhood and adolescent cancers promotion prospects or other advancement in their fields.

Life insurance policies are often very difficult to obtain, which is frequently an issue when they start their own

families. For instance, many policies issued in this setting exclude any malignancy, even if it were to develop outside the treatment field and have no obvious link to the treatment given or the primary condition. Likewise, health insurance in many spheres may be difficult to obtain and in many regions assisted fertility (eg. IVF) is not necessarily covered in public health programs. In regions where there is no universal health coverage this can carry significant implications for these patients, both for future health issues as well as the need for routine surveillance for long-term treatment related effects.

The increasing use of molecular genetics in the diagnosis of the primary tumour raises the spectre of future employers requesting the results as part of the employment process, potentially allowing discrimination. This is of most concern in jurisdictions where part of the employment conditions involve employer funded health insurance.

In the brain tumour survivor cohort treated to high doses of radiation to large volumes, or who have suffered significant initial injury from the tumour or surgery, there is the heart-rending situation where significantly neuro-cognitively impaired patients are reliant on their now ageing parents for many of their activities of daily living. These parents often struggle with the issue of who will care for their children when they die or become too frail to do it themselves.

Finally, one of the more insidious and common problems faced by cancer survivors is the lack of knowledge about the issues by both themselves and their treating medical practitioners. Clearly there needs to be a balance in informing survivors of their long-term risk and causing unnecessary concern. Many patients feel that they are a 'time bomb' waiting to develop a second cancer or other significant complication. The majority of patients will not develop a second cancer - their relative risks mandate an appropriate screening regimen, but an understanding of the risk is critical for their peace of mind. In a busy oncology clinic, the needs of acutely unwell and newly diagnosed patients generally take precedence over those who are apparently cured and healthy. In our practice, we find that a consult in our dedicated late effects clinic - with the same patient we saw last in an acute clinic, and often in the same clinic room - is profoundly different in the scope of issues covered. Indeed, we have a number of patients in whom there is a correspondence trail between their family doctor asking for advice about issues and the oncology team answering that it is not related to their cancer and thus not appropriate for them to address. How should these patients be cared for now?

At one end of the spectrum is the concept discussed above, whereby once a patient is deemed cured they are discharged into their family physician's care. The other end is regular detailed follow-up in a multidisciplinary long-term follow-up clinic. The problem with the first option is that it places a lot of reliance on the family doctor to keep up-to-date with a wide range of potential issues for what may be only a couple of patients in their practice. Compounding this is the mobile nature of the young adult population and patients' lack of knowledge about what treatment they received, let alone the likely toxicities. The second does

create its own issues. A dedicated paediatric late effects clinic can reach a steady state whereby the patients that are discharged when they reach adulthood (18 years old), are replaced by patients entering the long-term follow-up period - a revolving door concept. However, an adult clinic is more like a bucket. Patients enter the clinic either directly from their oncology team or from the paediatric long-term follow-up unit and, due to the high cure rates and low mortality from late effects, and with no ongoing plan will stay there. The clinic initially ran second monthly, but over the last 10 years is now bursting at the seams with a fully booked clinic every week.

### Shared care

Clearly a shared care model is appropriate.<sup>68</sup> The model that we are developing in our centre is based on a stratified shared care system. On entry to the clinic patients will be assessed as low, intermediate or high risk. Low risk patients would include such groups as a stage I Wilms tumour treated with surgery and simple chemotherapy. These patients would be able to be discharged into their family physician's care with important provisos. The first is that the patients are given a survivorship care plan which outlines the treatment they have received, the risks identified as a result of the treatment and the recommended screening investigations and lifestyle modifications. This would enable the patient to change doctors without compromising their ongoing care, and would also give the family doctors guidance. The second proviso is the need to have a feedback loop, so that the long-term follow up clinic knows who the local doctor is, what tests have been ordered and what the results are. This is necessary to ensure that the appropriate care is being delivered and to allow contact with both the patient and the family doctor should new information about potential late effects become apparent. In a survey of GPs from the Netherlands, 97% of GPs were willing to participate in the long-term care of survivors and 64% felt that it was their responsibility.<sup>69</sup>

The intermediate risk group would be patients who need regular surveillance and imaging, but not on an annual basis. This would include any patients who had had radiotherapy, high dose anthracyclines or endocrinopathies. Again a passport and management plan is essential, as is the feedback loop to a robust database. For instance, structural imaging for second malignancy surveillance or echocardiograms for delayed cardiotoxicity may be done every two to three years. Subsequent review in a multidisciplinary setting could alternate with yearly bloods, blood pressure checks and lifestyle modification counselling by the GPs.

The high risk group would be those who need annual multidisciplinary review in a tertiary centre. Again the passport and database would be essential to inform the GPs for the care between visits to the long-term follow-up clinic. Patients in this group would include brain tumour/cranial irradiation patients and bone marrow transplant recipients.

In the Netherlands survey, GPs felt that to participate in a shared care program they needed availability of guidelines (64%), sufficient information about the patient's

medical history (37%) and short communication lines (45%). The main barriers to participation were felt to be workload (16%), lack of knowledge (15%) and lack of communication from the parent institution.<sup>69</sup>

The challenges facing long-term follow-up programs mirror those of oncologists caring for adults, especially in diseases that have significant cure rates. Hopefully, a working model for childhood and adolescent cancer survivors will extrapolate easily to the appropriate care of cured adults.

As a profession, we have only been curing childhood cancers reliably for 30-40 years. This is the span of many of our senior colleagues' and mentors' working lives. We need to provide robust and thorough follow-up, both for our current patients' sakes, and through surveillance and research, patients that are yet to come through our doors. It may well be that in 200 years, our professional descendents look upon our crude therapies much as we look upon the gross surgeries performed without anaesthesia 200 years ago. The question for our profession is how we will be viewed with regard to the care we have provided for our patients.

## References

- Farber S, Diamond LK, Mercer RD, Sylvester RF, Jr Soliff JA. Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid. *N Engl J Med.* 1948 Jun 3;238:787-93.
- Bloom HJ, Wallace EN, Henk JM. The treatment and prognosis of medulloblastoma in children. A study of 82 verified cases. *Am J Roentgenol Radium Ther Nucl Med.* 1969 Jan;105:43-62.
- Lampe I. Radiation tolerance of the central nervous system. *Prog Radiat Ther.* 1958;224-36.
- National Cancer Institute. Surveillance Epidemiology and End Results. [Cited 2009 Jul]. Available from: [http://seer.cancer.gov/csr/1975\\_2006/browse\\_csr.php?section=28&page=sect\\_28\\_zfig01.html](http://seer.cancer.gov/csr/1975_2006/browse_csr.php?section=28&page=sect_28_zfig01.html).
- National Cancer Institute. Surveillance Epidemiology and End Results. [Cited 2009 Jul]. Available from: [http://seer.cancer.gov/csr/1975\\_2006/browse\\_csr.php?section=29&page=sect\\_29\\_zfig01.html](http://seer.cancer.gov/csr/1975_2006/browse_csr.php?section=29&page=sect_29_zfig01.html).
- Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al. Childhood Cancer Survivor Study. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med.* 2006 Oct 12;355:1572-82.
- Merchant TE, Williams T, Smith JM, Rose SR, Danish RK, Burghen GA, et al. Preirradiation endocrinopathies in pediatric brain tumor patients determined by dynamic tests of endocrine function. *Int J Radiat Oncol Biol Phys.* 2002 Sep 1;54:45-50.
- Merchant TE, Lee H, Zhu J, Xiong X, Wheeler G, Phipps S, et al. The Effects of hydrocephalus on intelligence quotient in children with localized infratentorial ependymoma before and after focal radiation therapy. *J Neuro Surg.* 2004 Nov;101(2 suppl):159-68.
- Mourtzoukou EG, Pappas G, Peppas G, Falagas ME. Vaccination of asplenic or hyposplenic adults. *Br J Surg.* 2008 Mar;95:273-80.
- Maas MH, Cransberg K, van Grotel M, Pieters R, van den Heuvel- Eibrink MM, Renin induced hypertension in Wilms tumour patients. *Pediatr Blood Cancer.* 2007 May;48:500-3.
- Finklestein JZ, Norkool P, Green DM, Breslow N, D'Angio GJ. Diastolic Hypertension in Wilms' Tumor Survivors: a late effect of treatment. A report from the National Wilms Tumor Study Group. *Am J Clin Oncol.* 1993 Jun;16:2001-5.
- Argueso LR, Ritchey ML, Boyle ET, Jr, Milliner DS, Bergstralh EJ, Kramer SA. Prognosis of Children with a solitary kidney after unilateral nephrectomy. *J Urol.* 1992 Aug;148:747-51.
- Various Authors. The Universal Home Doctor Illustrated, ODHAMS Press LTD 89 Long Acre, London, WC2. 1935 pg720.
- Albert RE, Omran AR, Brauer EW, Dove DC, Cohen NC, Schmidt H, et al. Follow-up study of patients treated by x-ray for tinea capitis. *Am J Public Health.* 1966;56:2114-20.
- Sadetzki S, Chetrit A, Freedman L, Stovall M, Modan B, Novikov I. Long-term follow-up for brain tumor development after childhood exposure to ionizing radiation for tinea capitis. *Radiat Res.* 2005 Apr;163:424-32.
- Oeffinger KC, Hudson MM. Long-term complications following childhood and adolescent cancer: foundations for providing risk-based health care for survivors. *CA Cancer J Clin.* 2004 Jul-Aug;54:208-36.
- Friedman DL, Meadows AT. Late effects of childhood cancer therapy. *Pediatr Clin North Am.* 2002 Oct;49:1083-106.
- Mertens AC, Yasui Y, Neglia JP, Potter JD, Nesbit ME Jr, Ruccione K, et al. Late mortality experience in five-year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study. *J Clin Oncol.* 2001 Jul;19:3161-2.
- Gurney JG, Kadan-Lottick NS, Packer RJ, Neglia JP, Sklar CA, Punyko JA, et al. Childhood Cancer Survivor Study. Endocrine and cardiovascular late effects among adult survivors of childhood brain tumors: Childhood Cancer Survivor Study. *Cancer.* 2003 Feb 1;97:663-73.
- Lawenda BD, Gagne HM, Gierra GP, Niemierko A, Wong WM, Tarbell NJ, et al. Permanent alopecia after Cranial irradiation: dose-response relationship. *Int J Radiat Oncol Biol Phys.* 2004 Nov 1;60:879-87.
- Ainsbury EA, Bouffler SD, Dórr W, Graw J, Muirhead CR, Edwards AA, et al. Radiation cataractogenesis: a review of recent studies. *Radiat Res.* 2009 Jul;172:1-9.
- Yamada M, Wong FL, Fujiwara S, Akahoshi M, Suzuki G. Non-cancer disease incidence in atomic bomb survivors, 1958-1998. *Radiat Res.* 2004 Jun;161:622-32.
- Hameed R, Zacharin MR. Long-term endocrine effects of cancer treatment: experience of the Royal Children's Hospital, Melbourne. *J Paediatr Child Health.* 2005 Jan-Feb;41:36-42.
- Duffner PK. Long-term effects of radiation therapy on cognitive and endocrine function in children with leukemia and brain tumors. *Neurologist.* 2004 Nov;10:293-310.
- Rutter MM, Rose SR. Long-term endocrine sequelae of childhood cancer. *Curr Opin Pediatr.* 2007 Aug;19:480-7.
- Cohen LE. Endocrine late effects of cancer treatment. *Endocrinol Metab Clin North Am.* 2005 Sep;34:769-89.
- Mulhern RK, Mercahnt TE, Gajar A, Reddick WE, Kun LE. Late Neurocognitive sequelae in survivors of brain tumours in childhood. *Lancet Oncol.* 2004 Jul;5:399-408.
- Merchant TE, Kienha EN, Li C, Shukla H, Sengupta S, Xiong X, et al. Modeling radiation dosimetry to predict cognitive outcomes in pediatric patients with CNS embryonal tumours including medulloblastoma. *Int J Rad Biol Phys.* 2006 May 1;65:210-21. Epub 2006 Feb 10.
- Palmer SL, Gajar A, Reddick WE, Glass JO, Kun LE, Wu S, et al. Predicting intellectual outcome among children treated with 35-40 Gy craniospinal irradiation for Medulloblastoma. *Neuropsychology.* 2003 Oct;17:548-55.
- Butler RW, Copeland DR, Fairclough DL, Mulhern RK, Katz ER, Kazak AE, et al. A multicenter, randomised clinical trial of a cognitive remediation program for Childhood survivors of a paediatric malignancy. *J Consult Clin Psychol.* 2008 Jun;76:367-78.
- Conklin HM, Khan RB, Reddick WE, Helton S, Brown R, Howard SC, et al. Acute neurocognitive response to methylphenidate among survivors of childhood cancer: a randomized, double blind, cross over trial. *J Pediatr Psychol.* 2007 Oct;32:1127-39.
- Iuvone L, Mariotti P, Colosimo C, Guzzetta F, Ruggiero A, Riccardi R. Long-term cognitive outcome, brain computed tomography scan, and magnetic resonance imaging in children cured for acute lymphoblastic leukemia. *Cancer.* 2002 Dec 15;95:2562-70.
- Ruben JD, Dally M, Bailey M, Smith R, McLean CA, Fedele P. Cerebral radiation necrosis: incidence, outcome, and risk factors with emphasis on radiation parameters and chemotherapy. *Int J Radiat Oncol Biol Phys.* 2006 Jun 1;65:499-508. Epub 2006 Mar 6.
- De Bruin ML, Dorresteyn LD, van't Veer MB, Krol AD, van der Pal HJ, Kappelle AC, et al. Increased risk of stroke and transient ischemic attack in 5-year survivors of Hodgkin lymphoma. *J Natl Cancer Inst.* 2009 Jul 1;101:928-37.
- Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. *J Am Coll Cardiol.* 2009 Jun 16;53:2231-47.
- Boucek RJ Jr, Steele A, Miracle A, Atkinson J. Effects of angiotensin-converting enzyme inhibitor on delayed-onset doxorubicin induced cardiotoxicity. *Cardiovasc Toxicol.* 2003;3:319-29.
- Van Dalen EC, Van Der Pal HJ, Kok WE, Caron HN, Kremer LC. Clinical heart failure in a cohort of children treated with anthracyclines: a long-term follow-up study. *Eur J Cancer.* 2006 Dec;42:3191-8. Epub 2006 Sep 20.
- Green DM, Hyland A, Chung CS, Zevon MA, Hall BC, Green DM, et al. Cancer and cardiac mortality among 15-year survivors of cancer diagnosed during childhood or adolescence. *J Clin Oncol.* 1999 Oct;17:3207-15.
- Haugnes HS, Aass N, Fosså SD, Dahl O, Klepp O, Wist EA, et al. Components of the metabolic syndrome in long-term survivors of testicular cancer. *Ann Oncol.* 2007 Feb;18:241-8. Epub 2006 Oct 23.
- McDonald S, Rubin P, Phillips TL, Marks LB. Injury to the lung from cancer therapy: clinical syndromes, measurable endpoints, and potential scoring systems. *Int J Radiat Oncol Biol Phys.* 1995 Mar 30;31:1187-203.
- Carver JR, Shapiro CL, Ng A, Jacobs L, Schwartz C, Virgo KS, et al. ASCO Cancer Survivorship Expert Panel. American Society of Clinical Oncology clinical evidence review on the ongoing care of adult cancer survivors: cardiac and pulmonary late effects. *J Clin Oncol.* 2007 Sep 1;25:3991-4008. Epub 2007 Jun 18.

42. Ransom JL, Novak RW, Kumar AP, Hustu HO, Pratt CB. Delayed gastrointestinal complications after combined modality therapy of childhood rhabdomyosarcoma. *Int J Radiat Oncol Biol Phys.* 1979 Aug;5:1275-9.
43. Densmore TL, Langer JC, Molleston JP, Dehner LP, Coffin CM. Colorectal adenocarcinoma as a second malignant neoplasm following Wilms' tumor and rhabdomyosarcoma. *Med Pediatr Oncol.* 1996 Dec;27:556-60.
44. Kersun LS, Wimmer RS, Hoot AC, Meadows AT. Secondary malignant neoplasms of the bladder after cyclophosphamide treatment for childhood acute lymphocytic leukemia. *Pediatr Blood Cancer.* 2004 Mar;42:289-91.
45. Green DM, Sklar CA, Boice JD Jr, Mulvihill JJ, Whitton JA, Stovall M, et al. Ovarian failure and reproductive outcomes after childhood cancer treatment: results from the Childhood Cancer Survivor Study. *J Clin Oncol.* 2009 May 10;27:2374-81. Epub 2009 Apr 13.
46. Wo JY, Viswanathan AN. Impact of radiotherapy on fertility, pregnancy, and neonatal outcomes in female cancer patients. *Int J Radiat Oncol Biol Phys.* 2009 Apr 1;73:1304-12.
47. Kalapurakal JA, Peterson S, Peabody EM, Thomas PR, Green DM, D'Angio GJ, et al. Pregnancy outcomes after abdominal irradiation that included or excluded the pelvis in childhood Wilms tumor survivors: a report from the National Wilms Tumor Study. *Int J Radiat Oncol Biol Phys.* 2004 Apr 1;58:1364-8.
48. Green DM, Whitton JA, Stovall M, Mertens AC, Donaldson SS, Ruyman FB, et al. Pregnancy outcome of female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Am J Obstet Gynecol.* 2002 Oct;187:1070-80.
49. Thompson K, Palmer S, Dyson G. Adolescents & young adults: Issues in transition from active therapy into follow up care. *European Journal of Oncology Nursing.* 2009; doi 10.1016/j.eon.2009.05.001.
50. Borgmann A, Zinn C, Hartmann R, Herold R, Kaatsch P, Escherich G, et al. ALL-REZ BFM Study Group. Secondary malignant neoplasms after intensive treatment of relapsed acute lymphoblastic leukaemia in childhood. *Eur J Cancer.* 2008 Jan;44:257-68. Epub 2007 Nov 5.
51. Bhatia S, Robison LL, Oberlin O, Greenberg M, Bunin G, Fossati-Bellani F, et al. Breast cancer and other second neoplasms after childhood Hodgkin's disease. *N Engl J Med.* 1996 Mar 21;334:745-51.
52. Tucker MA, Coleman CN, Cox RS, Varghese A, Rosenberg SA. Risk of second cancers after treatment for Hodgkin's disease. *N Engl J Med.* 1988 Jan 14;318:76.
53. Meadows AT. Risk factors for second malignant neoplasms: report from the Late Effects Study Group. *Bull Cancer.* 1988;75:125-30.
54. Bhatia S, Robison LL, Oberlin O, Greenberg M, Bunin G, Fossati-Bellani F, et al. Breast cancer and other second neoplasms after childhood Hodgkin's disease. *N Engl J Med.* 1996 Mar 21;334:745-51.
55. Meadows AT, Baum E, Fossati-Bellani F, Green D, Jenkin RD, Marsden B, et al. Second malignant neoplasms in children: an update from the Late Effects Study Group. *J Clin Oncol.* 1985 Apr;3:532-8.
56. Klein G, Michaelis J, Spix C, Wibbing R, Eggers G, Ritter J, Kaatsch P. Second malignant neoplasms after treatment of childhood cancer. *Eur J Cancer.* 2003 Apr;39:808-17.
57. Breslow NE, Takashima JR, Whitton JA, Moksness J, D'Angio GJ, Green DM. Second malignant neoplasms following treatment for Wilms' tumor: a report from the National Wilms' Tumor Study Group. *J Clin Oncol.* 1995 Apr;13:1851-9.
58. de Vathaire F, Hawkins M, Campbell S, Oberlin O, Raquin MA, Schlienger JY, et al. Second malignant neoplasms after a first cancer in childhood: temporal pattern of risk according to type of treatment. *Br J Cancer.* 1999 Apr;79:1884-93.
59. Relling MV, Rubnitz JE, Rivera GK, Boyett JM, Hancock ML, Felix CA, et al. High incidence of secondary brain tumours after radiotherapy and antimetabolites. *Lancet.* 1999 Jul 3;354:34-9.
60. Frobisher C, Lancashire ER, Winter DL, Jenkinson HC, Hawkins MM. Long-term population-based marriage rates among adult survivors of childhood cancer in Britain. *British Childhood Cancer Survivor Study.* *Int J Cancer.* 2007 Aug 15;121:846-55.
61. Crom DB, Lensing SY, Rai SN, Snider MA, Cash DK, Hudson MM. Marriage, employment, and health insurance in adult survivors of childhood cancer. *J Cancer Surviv.* 2007 Sep;1:237-45.
62. Gurney JG, Krull KR, Kadan-Lottick N, Nicholson HS, Nathan PC, Zebrack B, et al. Social outcomes in the Childhood Cancer Survivor Study cohort. *J Clin Oncol.* 2009 May 10;27:2390-5. Epub 2009 Feb 17.
63. Armstrong GT, Liu Q, Yasui Y, Huang S, Ness KK, Leisenring W, et al. Long-term outcomes among adult survivors of childhood central nervous system malignancies in the Childhood Cancer Survivor Study. *J Natl Cancer Inst.* 2009 Jul 1;101:946-58. Epub 2009 Jun 17.
64. Schultz KA, Ness KK, Whitton J, Recklitis C, Zebrack B, Robison LL, et al. Behavioural and social outcomes in adolescent survivors of childhood cancer: a report from the childhood cancer survivor childhood study. *J Clin Oncol.* 2007 Aug 20;25:3649-56.
65. Hobbie WL, Stuber M, Meeske K, Wissler K, Rourke MT, Ruccione K, et al. Symptoms of posttraumatic stress in young adult survivors of childhood cancer. *J Clin Oncol.* 2000 Dec 15;18:4060-6.
66. Langeveld NE, Stam H, Grootenhuys MA, Last BF. Quality of life in young adult survivors of childhood cancer. *Support Care Cancer.* 2002 Nov;10:579-600. Epub 2002 Oct 24.
67. Zebrack BJ, Zeltzer LK, Whitton J, Mertens AC, Odom L, Berkow R, et al. Psychological outcomes in long-term survivors of childhood leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma: a report from the Childhood Cancer Survivor Study. *Pediatrics.* 2002 Jul;110:42-52.
68. Oeffinger K, McCabe M. Models for Delivering Survivorship Care. *J Clin Oncol.* 2006;24:5117-5124.DOI: 10.1200/JCO.2006.07.0474.
69. Blaauwbroek R, Zwart R, Bourma M, Meyboom-de Jong B, Kamps I WA and Postma A. The willingness of general practitioners to be involved in the follow-up of adult survivors of childhood cancer. *J Cancer Surviv.* 2007 Dec;1:292-7. Epub 2007 Sep 27.