Monitoring after childhood cancer

An update for GPs

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BACKGROUND
The majority of children treated for a cancer will be long term survivors, with the potential to develop specific treatment related adverse health outcomes.

OBJECTIVE
This article describes the late effects of treatments for childhood cancer, and makes recommendations about appropriate surveillance.

DISCUSSION
With appropriate primary care input, long term morbidity and mortality for childhood cancer survivors can be reduced.

Approximately 750 children and adolescents are diagnosed with cancer in Australia every year. These cases exhibit a greater diversity of tissue type and anatomical location when compared to adult cancers where carcinomas (breast, lung, bowel genital) predominate (*Figure 1a, b*). Fortunately, with recent advances in treatment including the widespread use of cooperative clinical trials, aggressive multi-modality therapies, and improved supportive care, there has been a remarkable improvement in overall cure rates (*Figure 2*). Today, more than 80% of these patients are expected to be long term survivors,[1] resulting in one in every 900 Australians currently aged 16–44 years being a cancer survivor. This figure is likely to improve into the future, meaning health professionals will increasingly need to be aware of the specific health care needs of this cohort.

Overseas research suggests that almost half of childhood cancer survivors will have or will develop disabilities severe enough to affect quality of life.[2] Furthermore, the mortality rate for 5 year survivors of childhood cancer is greater than tenfold that of the normal age adjusted population.[3] The American Cancer Society,[4] the American Society of Pediatric Hematology/Oncology[5] and the European based International Society of Pediatric Oncologists[6] have each recently published standards of comprehensive care for children with cancer, and all included the need for long term follow up. The challenge for us is to provide optimal follow up in the Australian setting.

Models of long term follow up

The purpose of long term follow up is to:

- confirm continued cancer remission
- monitor for therapy related toxicity
- optimise mental health, social adjustment and educational/occupational achievements, and
- promote healthy lifestyle choices to minimise late effects.

A major contributor to the body of knowledge about specific late effects for survivors of childhood cancer has been the National Childhood Cancer Survivor study.[7] This longitudinal cohort study tracks the outcomes of over 14 000 long term survivors of childhood cancer and 5000 sibling controls. Based on these and other research findings, the Curesearch Children's Oncology Group (the world's largest paediatric oncology collaboration) recently published long term follow up guidelines for survivors of child, adolescent, young adult cancers (see *Resources*).[8] These

provide comprehensive recommendations for evaluation and management of childhood cancer survivors who may be encountered across a wide range of health care settings.

The relative risk for late effects relates in part to the type of cancer therapy (surgery, radiation or chemotherapy) and the patient's age at the time of treatment. The growing child is especially at risk for impaired growth, development and fertility. All childhood cancer survivors should therefore have regular medical checkups throughout their lives. For most, transition of care back to the community is not only appropriate, but may even be therapeutic. For a minority, there will be a need for additional input from a specialised late effects clinic (*Table 1*). To provide effective care, a summary of treatment and a list of possible late effects (*Table 2a–c*) needs to be provided to survivors, their carers and primary health care providers once active cancer treatment has ceased.

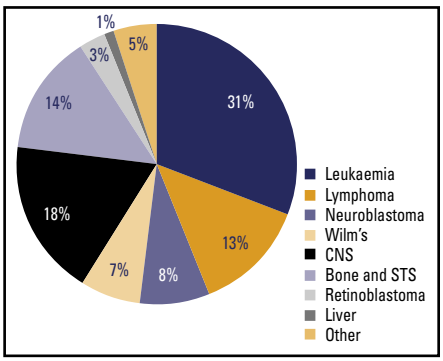

Figure 1a. Distribution of cancer types in children and adolescents

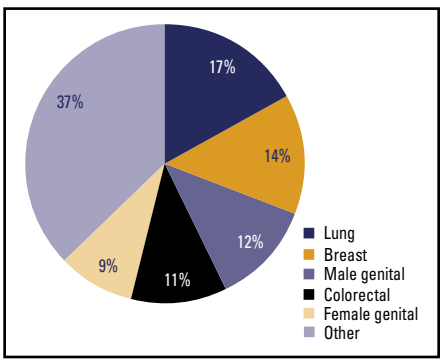

Figure 1b. Distribution of cancer types in adults

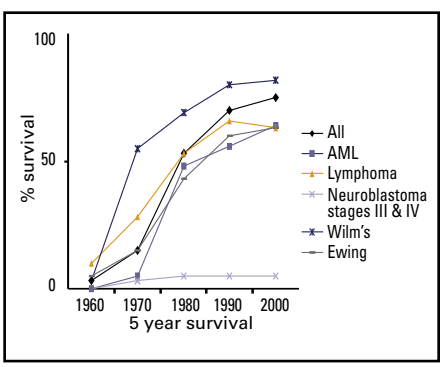

Figure 2. Improvement in cure rates for childhood cancers (1960–2000)

Specific issues in follow up

Anxiety

Anxiety about the risks of recurrence and serious late effects can be enough for survivors to avoid routine health care. It is important that practitioners and survivors alike understand that these problems only occur in a small minority, and that if this was to occur, early detection by way of regular checkups has the potential to prevent or reduce the impact of any episodes of ill health.

Cancer recurrence

Although not common, there are a number of cancers (eg. leukaemias, brain tumours) where recurrence 5 or more years after treatment is recognised.[9] The presentation may be similar to that at original diagnosis (and families are often very sensitive to this), or may be altogether different. When patients present with unexplained symptoms, it is important to consider a cancer recurrence in the list of differential diagnoses. Equally, many families will continue to be concerned about a recurrence long after its likelihood has diminished to a negligible level.

Second cancers

The cumulative lifetime incidence of second cancers approaches 5%, which represents a relative risk six times that of the normal population.[10] This reflects both a genetic predisposition (sometimes identifiable as in the cases of retinoblastoma, neurofibromatosis and Li-Fraumeni syndrome) and the effects of treatments such as radiation and chemotherapy (eg. epipodophyllotoxins and alkylators causing secondary myeloid leukaemias). The median time to development of a second cancer is shorter for chemotherapy related leukaemias (2–4 years)[11] than for radiation induced tumours (5–20 years).[12]

Physical problems

Physical effects vary from easily identifiable (eg. amputation), to quite subtle (eg. scoliosis) or only detectable on screening (eg. hypothyroidism).

Growth impairment

Growth impairment can result from numerous factors, including:

- the cancer itself
- complications of treatment (poor appetite, vomiting, infection, toxicity to growing tissue), and
- direct/indirect endocrine effects.

Cranial radiotherapy can lead to growth hormone deficiency and less commonly other pituitary hormone (TSH, ACTH, FSH/LH) problems. It can also lead to precocious or delayed puberty, which in turn affects growth potential. Chemotherapy alone can occasionally lead to significant effects on growth. Finally, localised tumour treatments may also affect growth and function of individual organs and the musculoskeletal system (skeletal and soft tissue hypoplasia).

Those at greatest risk for growth impairment include survivors of tumours located in the pituitary-hypophyseal region (eg. craniopharyngiomas), those who received craniospinal irradiation (>18 Gy) and those who have undergone allogeneic bone marrow transplantation.

Growth assessment requires ongoing integration of information including regular height measurements and puberty staging plotted onto standardised growth charts. Pre-pubertal children receiving cranial radiotherapy should be closely monitored for clinical signs of precocious puberty. It is important that early pubertal growth is not mistaken for 'catch up' growth. Children with impaired growth velocity should be referred to a paediatric endocrinologist. If growth hormone deficiency is demonstrated, replacement can be extremely beneficial. There is no evidence to suggest that the risk of cancer

recurrence is increased by the use of growth hormone therapy.[13]

Obesity

Obesity is a well recognised complication of a number of cancers, including leukaemia and craniopharyngioma. It is best documented using the standard body mass index (weight [kg]/height [m] >30). When relevant, contributory factors such as hypothyroidism should be addressed. Advice on healthy eating and regular exercise should be given early and reinforced regularly. In most cases, results will be better when the entire family participate in these healthy lifestyle changes.

Puberty and fertility

Both puberty and fertility may be affected by cancer treatments. Fertility counselling should therefore be provided to all childhood cancer survivors. Survivors who have impaired fertility may benefit from assisted reproductive technologies, and early referral should be made where issues of fertility arise.

Male

Fertility outcomes are generally good for boys treated for leukaemias and most solid tumours. However, pre- and post-pubertal testes are susceptible to high dose cytotoxic treatment by alkylating agents (eg. as used in the treatment of Hodgkin disease) or radiotherapy to the gonads. It is important to remember that spontaneous progression through puberty does not equate to normal fertility. When indicated, assessment of male pubertal development and fertility should include:

- assessment of testicular volume
- Tanner staging of secondary sexual development
- measurement of serum follicle stimulating hormone (FSH), luteinising hormone (LH), testosterone, and
- semen analysis.

Currently, cryopreservation of semen is offered to all postpubertal male patients whose cancer therapy is known to be highly gonadotoxic. Although there is evidence for impaired spermatogenesis both before and after treatment, there is no evidence to suggest an increase rate of abnormalities in the offspring of survivors.[14]

Table 1. A suggested schema for follow up of survivors of childhood cancer

Level	Treatment	Follow up	Frequency	Examples
I	• Surgery alone • Low risk chemotherapy	Primary care	As required	• Wilm's tumour stage I/II • Histiocytosis (single lesion)
II	• Chemotherapy • Low dose cranial irradiation (<18 Gy)	Primary care	Annual	• Majority of patients (eg. ALL in first remission)
III	• Radiotherapy (>18 Gy) • Megatherapy	Late effects clinic	Annual	• Stage IV tumours • Brain tumours • Bone marrow transplants

Table 2a. Potential late effects of treatment – surgery

Type of surgery	Late effect
Brain surgery (craniotomy)	Cranial nerve palsies
	Balance problems
	Motor weakness
	Vision/hearing
	Speech problems
	Seizures
Thoracotomy	Scoliosis
	Chronic lung problems
	Chronic pain
Laparotomy	Intestinal obstruction
Nephrectomy	Usually none
Splenectomy	Increased risk of sepsis
Hepatectomy (partial)	Usually none
Pelvic surgery	Bowel or bladder incontinence
	Sexual dysfunction
Amputation	Scarring/cosmetic deformity
Limb sparing surgery	Psychologic maladjustment
	Chronic pain
	Fracture

Female

Most girls who receive chemotherapy alone will retain their fertility. However, they may be at increased risk of a premature menopause and require hormone therapy.[15] In contrast, high dose busulfan and total body/pelvic irradiation are likely to result in impairment of ovarian function. Assessment of female pubertal development and fertility should include:

- Tanner staging of secondary sexual development
- menstrual history
- measurement of serum FSH, LH, oestrogen.

Pre- and post-pubertal ovarian tissue preservation is still in the experimental phases and ovarian function preservation with

the use of gonadotropin releasing hormone (GnRH) analogues is still an unproven therapy.[16] Spontaneously conceived offspring of patients treated for cancer in childhood have no excess of congenital anomalies or other diseases.[17]

Other endocrine problems

Thyroid

Children who have received radiotherapy to the brain, spine, face or neck are at risk of later thyroid problems. They should have their thyroid function tests done annually. In addition, careful examination for thyroid hyperplasia and nodules with ultrasound screening if exam is suspicious should be undertaken. While thyroid cancer is rare as a second primary cancer, its early detection can be life saving.

Cardiopulmonary problems

Most cardiovascular damage is the result of direct effects by chemotherapy, particularly anthracyclines, but injury to other organs can contribute indirectly. Effective doses of anthracyclines (100–450 mg/m2) may cause congestive cardiac failure later in life with the risk being dose dependant. Younger age at treatment and female gender are additional independent risk factors.[18] Mediastinal irradiation (particularly >30 Gy) is also a risk factor for late onset cardiac disease.

Children at risk may benefit from 2–3 yearly echocardiogram surveillance with early intervention where a decrease in ejection fraction is documented. Survivors with demonstrably impaired cardiac function may benefit from treatment with an after load reduction agent, such as an angiotensin converting enzyme inhibitor, although this is far from proven.[19] Unfortunately, some patients will deteriorate to a level requiring cardiac transplantation.

A detailed cardiology assessment is also appropriate for survivors who have other major cardiac risk factors, wish to take part in sport at an elite level, and those who are planning to get pregnant or are pregnant.

A number of chemotherapeutic agents (eg. bleomycin, carmustine [BCNU]) together with radiation are known to affect pulmonary function, usually with a restrictive disease pattern. When clinically indicated, a detailed assessment including chest X-ray and lung function tests may provide helpful information about the type of impairment and optimal treatment options.

Needless to say, a healthy diet, regular exercise, and nonsmoking should always be encouraged to minimise the risk of adult onset cardiopulmonary problems.

Table 2b. Potential late effects of treatment – radiation therapy

Organ/tissue	Late effect
All tissues	Second cancers
Bones and joints	Osteoporosis
	Reduced/uneven growth
	Scoliosis/lordosis
	Short height
	Cosmetic deformities
	Chronic pain
Muscle and soft tissues	Scarring
	Scoliosis/lordosis
	Short height
	Cosmetic deformities
	Chronic pain
Teeth and salivary glands	Abnormal dentition
	Xerostomia
	Cavities/gum disease
Brain	Cognitive defects
	Behavioural changes
Eyes	Cataracts
	Retinopathy
	Dry eyes
	Keratoconjunctivitis
	Light sensitivity
Ears	Scarring of eardrum
	Damage to middle ear (balance)
	Ear wax build-up
Heart and blood vessels	Coronary artery disease
	Myocardial infarction
	Constrictive pericarditis
	Valve problems
	Arrhythmias
Lungs	Fibrosis
	Diffusion abnormalities
Intestines/liver	Chronic diarrhoea
	Malabsorption
	Strictures
	Liver damage
Kidneys/bladder	Hypertension
	Renal insufficiency
	Scarring of bladder
Endocrine glands • Pituitary • Thyroid • Testes/ovaries	Dysfunction

Table 2c. Potential late effects of treatment – chemotherapy

Organ/tissue	Predisposing drug(s)	Late effect
Brain	Methotrexate (high dose)	Leukoencephalopathy
		Motor problems
		Behaviour/learning problems
		Seizures
Nerves	Cisplatin	Hearing loss
	Cisplatin, vincristine, vinblastine	Neuropathies
Heart	Anthracyclines	Cardiomyopathy
	Cyclophosphamide (high dose)	Cardiac failure
	Cardiac arrhythmias	
Lungs	Bleomycin, BCNU	Fibrosis
	Cyclophosphamide (high dose)	Inflammation
Liver	Methotrexate, BCNU	Hepatitis, fibrosis, cirrhosis
Kidney	Ifosfamide, cisplatin	Fanconi's syndrome
	Cisplatin, carboplatin	Reduced filtration
	Methotrexate (high dose)	Kidney failure (rare)
	Nitrosureas (BCNU, CCNU)	
Bladder	Ifosfamide, cyclophosphamide	Haemorrhagic cystitis
		Bladder cicatrisation
		Bladder cancer
Testes/ovaries	Alkylating agents	Gonadal failure
Bone marrow	Alkylating agents	Myelodysplasia
	Epipodophyllotoxins	Acute myeloid leukaemia
Bones	Corticosteroids, methotrexate	Avascular necrosis
		Osteoporosis

Genitourinary problems

Children with some embryonal cancers (eg. Wilms tumour of the kidney, neuroblastoma) may undergo a nephrectomy. In addition, both abdominal irradiation and some chemotherapy (eg. alkylators such as ifosfamide, cisplatin) can cause renal and bladder damage. These patients should have blood pressure and urinalysis for haematuria and proteinuria performed at each visit. Prevention or early treatment of both hypertension and diabetes mellitus is essential.

Neurological problems

Documentation of baseline focal deficits and persistent neuropathy (eg. secondary to vincristine chemotherapy) are important in order to detect new changes, which may result from vascular accidents (Moyamoya) or secondary malignancies.

Hearing loss can be a direct physical effect of the tumour or secondary to the use of radiation and/or oto-toxic drugs during treatment (eg. cisplatin, aminoglycosides). Appropriate advice about minimising background noise in the school and workplace, and avoidance of environments with overly loud noise can be beneficial. Likewise, visual problems such as cataracts (corticosteroids), optic atrophy, or retinopathy may be a primary or secondary phenomena. Early detection can lead to interventions that may preserve function.

Dental problems

Poor enamel and root formation, and reduced saliva secretion are common complications of radiation to the head and neck region. Referral to a dentist with a special interest in paediatrics is appropriate.

Infections

All children who complete a course of intensive chemotherapy should receive booster immunisations once their immune system is functioning (usually 6 months post-therapy). In addition, meningococcal and pneumococcal vaccines can be administered, and an annual influenza vaccine is recommended. Many survivors will have undergone multiple blood product transfusions throughout the treatment phases. While this is usually very low risk, screening for blood borne infections (hepatitis B, C, HIV) should be considered.

Cognitive and psychosocial problems

Despite periods of intense stress, most survivors achieve normal levels of psychological and social functioning, and families adapt well. A concise psychosocial history (school/work performance, peer relationships, depression screen) should be taken at each visit. Issues around body image should also be explored where relevant (eg. obesity, amputation, scars).

Unfortunately, some survivors do experience a range of educational, behavioural and social problems. Children may miss substantial amounts of schooling during treatment. In addition, families often allow their child a greater degree of behavioural freedom and are sometimes reluctant to re-integrate following the completion of treatment (eg. for fear of infections or difficulties with school refusal), thus further disrupting the child's social development. Appropriate interventions may include counselling, psychotherapy, and rarely antidepressant medications. Empathy, support and appropriate medical care for carers are also important health measures.

Cognitive impairment is one of the most debilitating late effects. Those most at risk are listed (*Table 3*). Children under the age of 3 years are particularly vulnerable to the effects of neurotoxic therapies such as craniospinal irradiation and high dose chemotherapy (eg. methotrexate). In addition to a general decline in intellectual function, some more subtle changes in attention span, motivation, mathematical reasoning and forward planning are often demonstrable with formal testing. When a problem is suspected, the patient should be referred to a neuropsychologist for formal assessment. It is important to optimise each survivor's potential to learn and

Table 3. Survivors at risk for cognitive impairment

Children with:

- Central nervous system (CNS) tumours
- Leukaemia/lymphoma who received CNS prophylaxis (radiation and/or chemotherapy)
- Tumours of the face, eye, skull that required external beam radiation
- Treatment that included total body irradiation and myeloablative chemotherapy as preparation for an allogeneic bone marrow transplant
- Treatment given during critical developmental periods

become a productive member of society. A standard measure such as the Weschler Intelligence Scale for Children (WISC) should be administered annually to those at risk of cognitive deficits. Where a child is shown to have a disability, governmental supports and the use of an integration aide or placement in a special education facility may be available (see *Resources*).

Health promotion

There is some evidence that adolescent and young adult cancer survivors, having beaten a life threatening illness, are greater risk takers.[20] A review of the adverse health effects of alcohol, tobacco and sun exposure, a discussion of routine health issues such as responsible sexual behaviour, alcohol and drug use, and where relevant a discussion of genetic issues (eg. retinoblastoma, neurofibromatosis, Li Fraumeni) is advisable.

All childhood cancer survivors should be educated in cancer prevention. This should include a review of the simple cancer screening tests such as breast and testicular self examination, a review of radiotherapy volumes with regular skin checks for naevi and soft tissue changes, and advocacy for Pap tests.

Conclusion

Australia's public health system provides us with an opportunity to provide optimal health care for all survivors of childhood cancer. With open communication between general practitioners and the relevant paediatric and adult medicine specialist services, most survivors should be able to live long and productive lives.

Summary of important points

- Health care for childhood cancer survivors should be considered a continuum from cancer diagnosis to eventual death, regardless of age.
- At the completion of active cancer treatment, patients, their carers and GPs should be provided with a summary of treatment and a list of late effects to look out for.
- Scheduled proactive care that includes a systematic plan of prevention and surveillance is likely to optimise health outcomes.
- A multidisciplinary team approach with communication between the primary health care provider, specialists of paediatric and adult medicine, and allied/ancillary service providers is optimal.

Resources

- Curesearch Children's Oncology Group Long term follow up guidelines for survivors of child, adolescent, young adult cancers: www.curesearch.org
- Government supports: www.healthinsite.gov.au/topics/Disability_Support_Services

Conflict of interest: none.

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