Paediatric Integrated Cancer Service

A statewide cancer service for children

Long Term Follow-up Project

Literature Review

Original report completed July 2007 by Addie Wootten

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1 Introduction

This literature review has been conducted to examine the long term follow-up (LTF) needs of individuals who have been successfully treated for paediatric cancer (survivors) and to inform decision making about the development of an agreed model of LTF care based on sound, evidenced-based information.

The complexities of LTF care of paediatric cancer survivors are well known by paediatric healthcare professionals. However, a comprehensive examination of the available literature will enable an evidenced based understanding of the long-term physical, emotional and social sequelae following paediatric cancer. An objective examination of the available service models and guidelines for care will also inform decision making about the development of an agreed model of LTF care for the Paediatric Integrated Cancer Service (PICS) in the state of Victoria, Australia.

The core questions guiding this review were:

1. What physical late effects are experienced by paediatric cancer survivors?
2. What psychological/emotional late effects are experienced by paediatric cancer survivors?
3. What social late effects are experienced by paediatric cancer survivors?
4. What are the rates of these late effects?
5. What treatment types lead to a higher risk of developing certain late effects?
6. What information is available about the level of LTF care required by paediatric cancer survivors?
7. What guidelines / models of care are currently available for the LTF of paediatric cancer survivors?

This review is structured in following parts:

- Background information
- A review of the late effects of paediatric cancer treatment
- A review of the level of care required for the LTF care of paediatric cancer survivors
- A review of the available guidelines and models of care for the LTF care of paediatric cancer survivors
- Summary and conclusions

1.1 Method

An organised review of available information was conducted utilising a number of search methods. A literature search was conducted utilising a range of scientific databases. These databases were included:

- Ovid Medline
- PsychInfo
- Cochrane Collaboration
- CINAHL (Cumulative Index to Nursing and Allied Health Literature)

Search terms included combinations of key words including: Late effects, Long-term follow-up, paediatric cancer, childhood cancer, oncology, survivors, psychosocial, psychological, cognitive, special education, allied health, chemotherapy, radiotherapy, long-term follow-up clinic.

All studies that included a combination of these key words were reviewed for relevant information. The age of articles was restricted to a publication date between 1990 and 2007.

A review of the reference lists of the relevant articles was then conducted and further articles were obtained if they had not been revealed in the original database searches.

2 Background information

Cancer is relatively uncommon among children, with less than 1% of all cancers occurring in children in 2001 [1]. In 2003 16% of deaths among children aged 1-14 years were attributed to cancer [1].

Australia wide the incidence rates of cancer in 2001 were 15.8 new cases per 100,000 for boys and 14.4 per 100,000 for girls aged 0-14 years [1]. Incidence was highest for children aged 0-4 years with 22.1 cases per 100,000 [1]. Table 1 lists the rates of new cancer diagnoses by type, age and sex, nationwide in 2001.

In 2004 in Victoria there were 79 male and 77 female new cancer diagnoses in the 0-14 year age group [2]. In the 15-24 year age group there were 107 males and 88 females who were diagnosed with a new cancer in 2004, in Victoria [2].

Table 1. Number of new cancer cases in Australia for children aged 0-14 years, selected cancers and total cancers by age group and sex, 2001[1].

	Males			Females			Total
Type of cancer	**0-4**	**5-9**	**10-14**	**0-4**	**5-9**	**10-14**	**0-14**
Leukaemia	63	33	26	47	30	26	225
Brain and other central nervous system	25	28	15	27	13	8	116
All Lymphomas	9	13	24	3	8	11	68
Connective and other soft tissue	13	3	2	11	1	7	37
Kidney, ureter and urethra	11	1	0	15	4	1	32
Other endocrine glands	10	3	0	7	1	0	21
Bone and articular cartilage	0	5	2	2	4	8	21
Eye	9	1	0	7	1	2	20
Skin (melanoma)	0	0	6	1	6	6	19
All cancers (except NMSC)	**156**	**89**	**79**	**128**	**72**	**79**	**603**

Note: NMSC – Non-melanocytic skin cancer

The most common types of new cases of cancer among children aged 0-14 years in 2001 nationwide were leukaemia (6.0 per 100,000 for boys and 5.3 per 100,000 for girls) and brain cancer (3.3 per 100,000 boys, 2.5 per 100,000 girls) accounting for 57% of cancers diagnosed in children in 2001 [1]. In Victoria in 2004, Leukaemia, brain and CNS and lymphoma were the top three most common cancer diagnoses for boys and girls in the 0-14 year age group [2].

Cancer incidence rates are projected to increase by 7% for females and 5% for males aged 0-14 years between 2002-2011 [3]. The most common cancers in 2011 are projected to be leukaemia, cancers of the brain and central nervous system, cancers of the bone and connective tissue, non-Hodgkin lymphoma and cancers of the urinary tract [3].

A two-pronged approach to the definition of survivor has been used in paediatric oncology. Patients will generally be defined as a ‘survivor’ when they have been deemed disease free for at least two (2) years after the cessation of treatment and/or are at least five (5) years post-diagnosis [4-6].

The paediatric cancer survival rate has substantially increased between 1994 and 2003 with 2.7 per 100,000 children dying from cancer in 2003 compared to 4.3 per 100,000 in 1994 [1]. This is a reduction of 60 deaths related to cancer in children aged 0-14 years (162 in 1994 to 102 in 2003). Having said this, cancer remains the most common cause of death from chronic disease in children aged 0-14 years [1]. In the UK and the USA 5-year survival rates are reported to be around 70% for all paediatric malignancies [7]. Another study has indicated that more than 80% of children with childhood cancers are expected to be long-term survivors [8].

Location of treatment can often vary with 83% of Victorian adolescents 10-15 years and 14% of those aged 16-19 years treated at paediatric institutions [9].

With the projected increase in incidence rates of paediatric cancer, coupled with the increasing survival rate, it is anticipated that a growing number of children diagnosed with cancer between the ages of 0-14 years will become survivors of paediatric cancer. Therefore, it is important to consider the long-term outcomes of this population.

3 Late effects of paediatric cancer

Late effects of cancer treatment in paediatric cancer survivors have been found to be substantial with considerable increased risk of morbidity and even mortality as a result of their previous cancer treatment [6]. In one study in the US it was found that survivors of paediatric cancer had a 10.8 fold mortality rate than the general US population as a whole [10].

A large UK cohort study of more than 2000 five-year survivors found that at least 60% of survivors had one or more chronic health problem and about 20% had three or more; CNS tumour survivors were most commonly affected [11]. CNS tumour survivors are also reportedly at high risk of death from progressive disease, especially within the first decade after diagnosis [12]. Chronic health problems in paediatric cancer survivors included seven specific domains.

- The growth/endocrine domain which includes chronic health problems such as thyroxine deficiency, growth hormone deficiency and infertility.
- The neurological domain included problems such as cerebral palsy, ataxia/dyspraxia and migraine.
- The organ/system domain included respiratory problems, organ removal (e.g. kidney) and cardiovascular problems.
- The special sense/dental domain included visual handicap, deafness and dental problems.
- The intellectual/psychological domain included learning difficulties, behaviour problems and anxiety/depression.
- The cosmetic effects domain included obesity and overweight, tissue atrophy and hypoplasia and skin problems.
- The orthopaedic domain included scoliosis, paraplegia/hemiplegia and amputation/endoprosthesis [10].

Another noteworthy piece of research was conducted by the childhood cancer survivor study (CCSS) which is a multi-institutional study that examined the health status of adults who were diagnosed with paediatric cancer between 1970 and 1986 in the U.S. and who have survived for at least 5 years after treatment [5]. This group of research collaborators have been able to provide very good scientific data on the late-effects of paediatric cancer in their large sample of participants. In comparing 10,397 survivors with 3034 siblings this group found that 62.3% of survivors reported having at least one chronic health condition and 27.5% reported a severe or life threatening condition [5]. In comparison, 36.8% of siblings reported having a chronic health condition of which 5.2% reported having a severe or life threatening condition [5]. After adjusting for group differences of age, sex or ethnic background survivors were found to be 3.3 times as likely as siblings to have a chronic health condition of any kind and 8.2 times as likely as siblings to have a severe or life threatening condition [5].

In this study, groups at highest risk for developing a severe or life threatening condition were survivors of bone tumours (relative risk 38.9), CNS tumours (relative risk 12.6) and Hodgkin's disease (relative risk 10.2) [5]. Female survivors were 1.5

times as likely as male survivors to have a severe or life threatening condition, 1.4 times as likely to have any condition and 1.5 times as likely to have multiple conditions [5].

Age at diagnosis also independently modified the risk of experiencing a health condition. For each cancer group, survivors who received treatment at an older age were significantly more likely to report any condition, conditions of a severe or life threatening nature or multiple conditions [5]. The cumulative incidence of a chronic health condition 30 years after diagnosis was 73.4%, with a cumulative incidence of 42.4% for a severe, disabling, or life threatening condition or death resulting from a chronic condition [5].

The nature (surgery, drugs, radiotherapy etc.) and amount (intensity and dose) of treatment has been linked to the type and severity of late effects experienced by the paediatric cancer survivor [5, 6]; although there has also been increasing interest in the role of genetic predisposition [13]. The risks of late-effects appear to be cumulative, with no evidence of a plateau effect [14]. The content of LTF has thus, commonly, been dictated by these same factors. The following sections outline the major late-effects experienced as a result of various treatment modalities. Table 2 gives a brief summary of the late effects of radiation and chemotherapy treatment.

Table 2: Selected late effects after radiation and chemotherapy

TYPE OF TREATMENT	LATE EFFECTS
Radiation Therapy	
Cranial radiation	**CNS** Neuro-cognitive defects Panhypopituitarism Seizures Strokes Brain Cancer **Growth and development** Obesity Short stature **Teeth and gums** Defective dentition Increased caries Root abnormalities Periodontal disease **Eye** Cataracts Keratoconjunctivitis **Thyroid** Hypothyroidism Hyperthyroidism Cancer
Thoracic radiation	**Heart** Coronary artery disease Valvular disease Pericardial disease Arrhythmias **Lung** Fibrosis Restrictive-Obstructive lung disease Interstitial pneumonitis Cancer **Thyroid** Hypothyroidism Hyperthyroidism Cancer **Skeletal** Abnormal chest-wall development **Breast** Cancer
Abdominal/Pelvic radiation	**Gastrointestinal tract** Gastrointestinal obstruction Cancer **Spleen** Asplenia **Kidney** Nephropathy **Cancer** **Bladder** Fibrosis Cystitis Dysfunctional voiding Cancer **Gonads** Ovarian failure Testicular failure Cancer **Muscle** Atrophy Cancer (Sarcoma)

Table 2 continued

TYPE OF TREATMENT	LATE EFFECTS

	Skeletal
	Osteopenia
	Osteoporosis
	Avascular necrosis
	Spinal deformities
	Cancer (sarcoma)
Any radiation	**Skin**
	Melanotic nevi
	Nonmelanotic skin cancer
	Melanoma
Chemotherapy	
Alkylating agents	**Gonads**
Nitrosourea	Infertility
Dacarbazine	Hypogonadism
Cytarabine	**Bone marrow**
Cyclophosphamide	t-AML/MDS
Ifosfamide	**Bone**
Chlorambucil	Cancer
Carmustine	**Bladder**
Lomustine	Cystitis
Thiotepa	Fribrosis
Procarbazine	Dysfunctional voiding
Melphalan	Cancer
Busulfan	**Lungs**
	Fibrosis
	Kidney
	Nephrotoxicity
	Eye
	Cataracts
Cisplatin	**Ear**
	Sensorineural high-frequency hearing loss
	Kidney
	Nephropathy
	CNS
	Neuropathy
Methotrexate	**Liver**
	Cirrhosis
	Skeletal
	Osteoporosis
6-Mercaptopurine	**Liver**
	Cirrhosis
Vincristine	**CNS**
	Neuropathy
Anthracyclines	**Heart**
Doxorubicin	Left ventricular dysfunction
Daunorubicin	Cardiomyopathy
Idarubicin	Arrhythmias
Epirubicin	**Bone Marrow**
Mitoxantrone	Leukaemia (?)
Bleomycin	**Lung**
	Fibrosis
	Interstitial pneumonitis
Corticosteroids	**Eye**
	Cataracts
	Skeletal
	Osteopenia
	Osteoporosis
Topoisomerase 2 inhibitors	**Bone marrow**
	t-AML/MDS

From: Dickerman, J. D., (2007). The late effects of childhood cancer therapy. *Pediatrics*, 119 (3), 554-568.

3.1 Heart

Anthracycline antibiotics have been found to have significant cardiovascular late effects in paediatric cancer survivors. With estimates of up to 60% of paediatric cancer patients being treated with anthracyclines, these late effects are especially noteworthy [15]. Late effects include cardiac toxicity, arrhythmias, cardiomyopathy, valvular disease and pericardial disease [15-18]. The risk of congestive heart failure after anthracycline use has been estimated at between 0%-16% and subclinical myopathy between 0%-57% [20]. The risk of cardiac damage is dependent on the cumulative dose of the anthracycline [19, 20]. Females have a higher risk of developing these late effects, as do patients treated when they were less than 5 years of age, or with a combination of anthracycline antibiotics and radiation to the heart or the use of other types of cardiotoxic chemotherapy [16-18, 21-23]. Thoracic radiation may also result in cardiovascular toxicity [24] and carotid artery disease [25, 26].

3.2 Vasculature

Myocardial infarction or arterial damage resulting in stroke has been reported as possible late effects of paediatric cancer treatment [19]. A report from the CCSS indicated that the relative risk (RR) of stroke for leukaemia survivors compared to siblings was 6.4 with 37 of 4,828 leukaemia survivors studied reporting a late-occurring stroke [27]. The relative risk of the brain tumour survivor group compared to the sibling group was 29.0 with 63 of 1,871 brain tumour survivors reporting a late-occurring stroke [27]. The dose of cranial radiation was significantly associated with risk of late-occurring stroke in both the leukaemia and brain tumour group with a dose of greater than 30 Gy associated with an increased risk. The mean interval from initial cancer diagnosis to stroke was 9.8 years for the leukaemia group and 13.9 years for the brain tumour group [27].

A recent pilot study has also found that anthracyclines could cause impaired endothelial function [28] which suggests that they may play a role in the progression of coronary disease [19].

3.3 Lung

Alkylating agents have been linked to pulmonary fibrosis [29, 30] post-treatment. Radiation to the chest or lung has been linked to possible late-occurring pulmonary toxicity including pulmonary fibrosis, interstitial pneumonitis, restrictive lung disease, or obstructive lung disease [31, 32]. The risk of these late effects increases at younger diagnosis [19]. A CCSS report [32] on 12,390 children 5 years after diagnosis demonstrated a significant association between lung radiation and lung fibrosis (RR 4.3), supplemental oxygen use (RR 1.8), emphysema (RR 2.0), recurrent pneumonia (RR 2.2), chronic cough and shortness of breath for more than one month (RR 2.0), exercise-induced shortness of breath (RR 1.8) and abnormal chest-wall development (RR 5.0). Chest radiation was found to be associated with a 3.5% cumulative incidence of lung fibrosis 20 years post-diagnosis [32].

3.4 Liver

There have been reported cases of infection of blood born viruses including hepatitis B [33-36], hepatitis C [35, 37-41] and HIV infection [42-44] following the use of blood/serum products in the treatment of paediatric cancer, especially if transfused prior to stricter screening of donated blood products. Certain health behaviours have also been linked to increased risk of developing these late-effects, not related to the cancer treatment directly, that health professionals should be mindful of. These health behaviours include IV drug use, multiple partners, unprotected or high risk sex behaviour, tattoos and body piercing.

3.5 Kidney

Alkylating chemotherapy agents have been linked to renal toxicity [45, 46] post-treatment. Heavy metal based chemotherapy agents have been found to have potential late effects including renal toxicity [47, 48] and dyslipidemia [49, 50]. Kidney damage can also be caused by radiation and ifosfomide as well as other antineoplastic drugs such as cisplatin [19].

3.6 Bladder

Alkylating chemotherapy agents have been linked to urinary tract toxicity [51, 52] and bladder malignancy [53, 54] post-treatment. Hematuria, cystitis, fibrosis and dysfunctional voiding can also occur and bladder damage can be caused by radiation, cyclophosphamide and ifosfamide [19].

3.7 Skeletal

Antimetabolites have been found to be related to the development of osteopenia or osteoporosis in both male and female paediatric or adolescent cancer survivors [55-57]. A higher risk factor for developing this late effect is older age at the time of treatment, growth hormone deficiency, hypogonadism, hyperthyroidism and the combined use of corticosteroids or cranial radiation as well as antimetabolites [55-57].

3.8 Muscle

Atrophy can occur after direct radiation to muscle [19].

3.9 Thyroid

Hypothyroidism or hyperthyroidism can occur after thoracic, cranial or neck radiation [19]. A report of the CCSS on 13,674 survivors of Hodgkin’s lymphoma indicated that there was an increased risk of hypothyroidism with increased dose of radiation (> 4.5 Gy), with older age (> 15 years), with female gender and less than 5-years post-diagnosis [58]. The RR for hypothyroidism in this study was 17.1, occurring in 25% of patients and 50% of patients more than 20 years post-diagnosis if treated with greater than 4.5 Gy dose [58]. The RR of hyperthyroidism was 8, occurring in 5% of the patients [58].

3.10 Growth and development

3.10.1 Obesity

Obesity after treatment for paediatric cancer, including lymphoblastic leukaemia, has been linked to cranial radiation (growth hormone deficiency), steroid therapy, physical inactivity and increased dietary intake. The prevalence of obesity has been reported to be between 16-56% [59]. Adult survivors of acute lymphocytic leukaemia who underwent cranial radiation greater than 20 Gy have been associated with increased risk of obesity particularly females treated between 0-4 years of age [11, 19]. Chemotherapy without cranial radiation has also been linked to obesity in survivors of acute lymphocytic leukaemia [19].

3.10.2 Short stature

Short stature has been found in survivors of acute lymphoblastic leukaemia and has been linked to cranial radiation, possibly due to growth hormone deficiency [19].

3.11 Gonads

Gonadal failure can occur, in men and women, following direct radiation therapy to the gonads or brain [19]. A higher occurrence of male gonadal (testicular) dysfunction has been reported in association with alkylating chemotherapy agents [60-63]. This gonadal dysfunction can include problems such as infertility, hypogonadism, delayed/arrested puberty, oligospermia and azospermia [60-63]. These late-effects more commonly occur in patients who have had higher cumulative doses of alkylating agents or a combination of alkylators [60-63]. If patients have also been treated with combined radiation to the abdomen/pelvis, testes or brain there is an increased risk of developing these late effects [60-63].

A higher occurrence of female gonadal (ovarian) dysfunction has also been reported in association with alkylating chemotherapy agents used in the treatment for childhood or adolescent cancers [63-67]. These problems include early menopause [66], infertility [63, 67] and delayed/arrested puberty [63-67]. As for male gonadal dysfunction, a higher risk for developing female gonadal dysfunction has been seen with higher cumulative doses of alkylators or a combination of alkylators [63-67]. A higher risk has also been found when this type of chemotherapy has been combined with radiation to the abdomen/pelvis, lumbar or sacral spine or the brain/cranium [63-67].

3.12 Central nervous system and peripheral nervous system

Plant alkaloids have been found to affect the peripheral nervous system with reported late effects including peripheral sensory or motor neuropathy including foot drop, weakness, areflexia and paresthesia's [68, 69]. Clinical leukoencephalopathy including spasticity, ataxia, dysarthria, dysphagia, hemiparesis and seizures has also been reported in survivors of paediatric cancer [70-72]. Higher risk for developing these late effects have been associated with a younger age at treatment, radiation dose higher than 24 Gy or fraction dose higher than 3 Gy and radiation in combination with dexamethasone, methotrexate and cytarabine [70-72].

Heavy metal based chemotherapy agents have been found to have potential late effects including peripheral sensory neuropathy [73]. Other central nervous system late effects of antimetabolites include clinical leukoencephalopathy which includes ataxia, spasticity, dysarthria, dysphagia, seizures and hemiparesis [74-77]. Younger age at treatment increases the risk of developing these late effects.

Antimetabolite chemotherapy agents have been found to have significant central nervous system late effects in children and adolescents. Neuro-cognitive deficits include functional deficits in executive function, sustained attention, processing speed, memory and visuo-motor integration [74, 76]. There can also be learning deficits, reduction in global IQ and behavioural changes [75].

Children at higher risk for developing these late effects are those treated at an earlier age (especially if treated when younger than 3 years of age), female and a pre-morbid or family history of learning difficulties [74-76].

3.13 Eye

Alkylating agents have been linked to cataracts (with higher risk when combined with corticosteroids or cranial, orbital or eye radiation) [78, 79] post-treatment.

3.14 Ear

Heavy metal based chemotherapy agents have been found to have potential late effects including ototoxicity (tinnitus, vertigo or sensorineural hearing loss) [80-82]. Sensorineural hearing loss is most commonly seen in a cumulative dose approaching 400 mg/m^2 of cisplatin therapy [19].

3.15 Teeth and gums

Dental abnormalities have been identified across all chemotherapy types with issues such as enamel dysplasia, root thinning/shortening and tooth/root agenesis [83-86]. Patients treated at a younger age (especially if treated below the age of 5 years) and those who had not developed permanent dentition at the time of treatment are more at risk for developing these problems post-treatment [83-86].

3.16 Skin

There is a significant risk of developing dermatologic changes including altered skin pigmentation, permanent hair loss, fibrosis and telangiectasias [87] as a result of radiotherapy. Treatment at an earlier age as well as higher doses of radiation are reported to increase the risk of developing this after effect [87].

3.17 Secondary cancers

Childhood cancer survivors are reported to be at a greater than 19-fold increased risk of developing a secondary malignancy [19, 88]. In a CCSS study of 13,518 paediatric cancer survivors 314 reported second malignant neoplasms; the largest excess was reported for bone cancers and breast cancer [89]. An increased risk was seen in females and those diagnosed at a younger age [89]. Across all participants in this study the cumulative estimated second malignancy incidence 20 years post diagnosis was 3.2% [89].

Radiation has been found to cause secondary malignant or benign neoplasms in or near the radiation field [89-91] in paediatric or adolescent cancer survivors. Higher cumulative radiation dose and large radiation treatment volumes increase the risk of developing this late effect.

3.17.1 Skin cancer

Skin cancer has been reported to be the most commonly occurring secondary cancer in paediatric cancer survivors [92]. Patients receiving any field of radiotherapy are at a higher risk of developing dysplastic nevi or skin cancer including melanoma, basal cell carcinoma or squamous cell carcinoma [90, 92-94]. This may be due to the result of decreased immuno-surveillance secondary to the radiation or chemotherapy coupled with sun exposure [19]. Radiation has been reported to show a 6.3 fold increased risk of skin cancer and secondary skin cancer will more commonly occur in the radiation field [92].

3.17.2 Breast cancer

Breast cancer has most commonly been seen following thoracic radiation for Hodgkin’s lymphoma [19]. The risk of secondary breast cancer after thoracic radiation for Hodgkin’s lymphoma in women under 30 years of age is elevated to 4-56 fold depending on the intensity of radiation and age at treatment [95, 96]. Higher doses of radiation increase the risk of developing breast cancer as well as treatment between the ages of 10-20 years.

3.17.3 Thyroid cancer

Survivors of paediatric cancer who underwent radiation to the head, neck or upper thorax have an increased risk of developing thyroid cancer [96]. A CCSS study reported an increased risk of thyroid cancer at radiation doses of 20-29 Gy but a decreased risk at 30 Gy or higher which the authors attributed to a cell killing effect [97]. Patients diagnosed and treated before the age of 10 were at a higher risk for developing thyroid cancer [97].

3.17.4 Leukaemia

The use of alkylating chemotherapy agents, heavy metals and non-classical alkylators in the treatment of childhood or adolescent cancer have been linked to the development of acute myeloid leukaemia or myelodysplasia [91, 98-100]. Epipodophyllotoxins chemotherapy agents have also been associated with acute myeloid leukaemia [101].

3.17.5 Sarcoma of bone and connective tissue

Radiotherapy has also been linked to the later development of bone malignancies [102, 103] with higher radiation doses and treatment during adolescence increasing the risk for developing this late effect.

3.17.6 Brain tumours

Radiation to the brain or cranium has been associated with a number of late-effects in paediatric cancer survivors. The development of brain tumours (benign or malignant) [89, 104, 105] increases with cranial irradiation especially if treated at a younger age or with higher radiation dose. Brain tumours secondary to cranial radiation have been reported to have a latency period of 9-10 years [19].

3.17.7 Bone marrow and stem-cell transplantation

In addition to the usual late effects associated with radiation or chemotherapy paediatric cancer patients undergoing transplantation are also at risk of developing chronic graft-versus-host disease and all its attendant complications post-transplant [19]. They are also at risk of developing secondary malignancies [19].

3.18 Psychological

Some form of psychological maladjustment has been reported in 10-20% of long-term paediatric cancer survivors [19], manifested as mood disturbance, behavioural problems or somatic distress [106, 107]. A CCSS study recently reported that 44% of long-term adult survivors experienced problems in at least one health status domain. These included general health, mental health, functional status, cancer related pain or cancer related fear/anxiety [106]. An increased risk was seen in female patients and those patients with lower income or educational status [106]. Patients were also more likely to report an adverse health status if they had survived bone tumour, CNS tumour, sarcoma or Hodgkin's disease [106]. While moderate to severe impairment in some aspect of mental health was seen across all diagnostic groups patients who had survived Hodgkin's disease, sarcomas and bone tumours had significantly higher rates of cancer-related anxiety and fears adversely affecting health status [106].

Self-esteem, anxiety and depression have been evaluated in survivors of paediatric cancer. One Swedish study found that children and adolescents off treatment reported higher depression and anxiety levels and lower psychological well-being and physical self-esteem (body image satisfaction) than the general population [108]. Survivors in this study, reported poorer psychological functioning than did children who were currently receiving treatment [108].

Another study of 30 survivors of childhood cancer found that poor individual coping was related to diagnosis, a shorter time of continuous complete remission, more severe illness and treatment impairments, and lower scores on a test of intellectual abilities [109]. In addition, a longer time of treatment tended to be followed by poorer coping [109].

Post-traumatic stress reactions have been reported in survivors of paediatric cancer [110, 111]. One study assessed the prevalence of post traumatic stress disorder (PTSD) in young adult survivors of paediatric cancer [110]. This study found that 20.5% of the sample met diagnostic criteria for PTSD at some point since the end of their treatment and PTSD was associated with elevated anxiety. The authors of this study concluded that cancer-related post traumatic stress may emerge in young adulthood and may effect the achievement of developmental milestones and orientation toward healthcare [110]. It has been reported that survivors suffering PTSD symptoms are reluctant to return to the place of cancer treatment and may avoid further follow-up [110, 111].

One study that examined psychiatric hospitalisations among paediatric cancer survivors reported that the risk of psychiatric hospitalisation was higher among cancer survivors than the general population but that the excess risk was restricted to survivors of brain tumour [112]. This study found an increased risk of psychoses of somatic, cerebral causes, psychiatric disorders in somatic disease, and schizophrenia and related disorders among survivors of brain tumours. Interestingly, there was no evidence of a significantly increased risk of major depression [112].

Positive psychological outcomes have also been reported. In terms of general quality of life (QoL) one study has reported that survivors of childhood cancer have significantly higher self reported QoL than healthy controls [113]. Another study supports this finding with evidence of thriving in survivors of paediatric cancer [114]. This study with 50 paediatric cancer survivors found that processes of coping, meaning making and psycho-spiritual growth are intimately related to long-term psychosocial well-being [114]. These studies highlight the range of outcomes experienced by paediatric cancer survivors.

A screening tool for use with paediatric oncology patients and their caregivers has recently been developed to assess psychosocial risk factors indicative of future psychosocial distress [115]. The Psychosocial Assessment Tool (PAT) is a 20 item self report questionnaire that is given to caregivers to complete at the time of diagnosis (taking approximately 10-15 minutes to complete). It assesses psychosocial risk across 10 domains: family structure; family resources; social support; child knowledge of cancer; school attendance; child cognitive, emotional and behavioural concerns; child maturity; marital or family problems; family beliefs; and other stressors [115]. The authors also indicate that oncologists and nurses can also complete this screening tool with good agreement across each individual in the study [115].

3.19 Neuro-cognitive

Neuro-cognitive deficits in the areas of memory, processing speed, executive function and visual-motor integration [75, 116-121] have been identified following radiotherapy to the brain or cranium, surgery or chemotherapy [122]. Higher risk of this late effect has been noted in survivors treated at a younger age (especially below 3 years of age), who have a head/neck tumour where the brain is in the radiation field, primary CNS tumour, radiation combined with dexamethasone, TBI, methotrexate, cytarabine, female or who have a premorbid family history of learning or attention problems [75, 116-121].

It is suggested that a standard measure such as the Weschier Intelligence Scale for Children be administered annually for those survivors at risk of cognitive deficits. If a problem is identified, referral to a neuro-psychologist is required [123].

3.20 Social/developmental

Social withdrawal and educational problems have been reported in survivors of paediatric cancer [124]. In a CCSS report on the utilisation of special education services by childhood cancer survivors 23% of survivors and 8% of siblings reported using special education services [124]. Survivors were more likely to utilise special education services if they were diagnosed before 6 years of age, were diagnosed with CNS tumours, leukaemia or Hodgkins disease [124]. Survivors of leukaemia, CNS tumours, non-Hodgkin lymphoma and neuroblastoma were significantly less likely to finish high school compared with siblings; however, when survivors received special education services, risk estimates approximated the sibling population [124].

A relatively small study examining the academic and cognitive late effects of survivors of acute lymphoblastic leukaemia who had received chemotherapy as CNS prophylaxis found that survivors scored significantly poorer in cognitive academic abilities when compared to norms, particularly in females [125].

Another study also identified a higher rate of behavioural problems in survivors of autologous bone marrow transplant compared to a normative sample, as reported by survivors' parents and teachers [126]. Of interest is the discrepancy between parent/teacher reports and survivor reports where survivors reported a significantly more positive level of adjustment than did parents/teachers [126]. The authors recommend utilising multiple sources of information in assessment of survivor psychosocial functioning [126].

4 Level of care required for long term follow-up

Estimates of up to 60% of paediatric cancer survivors experiencing some form of adverse late effect of paediatric cancer indicates the need for long-term follow-up (LTF) of these patients at least into young adulthood and possibly longer [4, 6, 14]. The range of late effects outlined above indicates the breadth of the problem and also highlights the need for input from a range of health professionals. The late effects of treatment are often life long [14].

There have also been suggestions made that survivors of paediatric cancer will be more susceptible to many age-related chronic health conditions, their risk magnified by their previous medical treatment [14]. As the population of paediatric cancer survivors age and advances in cancer treatments are made, the consequences of these newer cancer treatments will become increasingly clear, with the potential for a very different spectrum of late-effects arising [14].

The role of LTF of paediatric cancer survivors is to decrease the severity of late treatment complications by performing appropriate surveillance to detect insipient toxicity, and by facilitating timely diagnosis and management of emerging or established late adverse effects [6]. Surveillance may include clinical assessment by medical history and physical examination and/or the performance of appropriate investigations [6]. LTF can also deliver ongoing health education about the original malignancy and possible late effects as well as the provision of support and health promotion [6]. In this way LTF serves to decrease the morbidity related to cancer treatment and to increase quality of life of cancer survivors [13]. In this way LTF by specialist staff should not be relapse driven but, rather, wellness focussed [127, 128].

Paediatric oncologists and haematologists working in this field have reported that paediatric cancer survivors should be followed up for life [7]. Certain groups of paediatric cancer survivors have been identified as having greater LTF needs as a result of the malignancy site and/or treatment intensity [6]. These survivorgroups will require regular medically supervised LTF which will usually be hospital based and patients who have already developed adverse effects or are at high risk of developing an adverse outcome may require specialist follow-up in a number of locations depending on local circumstances [6].

Whilst certain malignancy types and treatment modalities have certainly been identified to result in specific late effects that require specialised LTF there are aspects of LTF that are applicable to all paediatric cancer survivors. These include the provision of health education, psychosocial support and health promotion advice [6].

The National Institute for Clinical Excellence, coordinated by the National Health Service (NHS) in the UK, have developed an approach to paediatric cancer care detailed in their documents titled “Improving outcomes in children and young people with cancer” [127]. These documents outline their approach to LTF in which they recommend that LTF involve a specialised multidisciplinary team including a lead clinician with expertise in LTF (usually and oncologist but not necessarily paediatric),

a specialist nurse, an endocrinologist, an appropriate allied health professional (e.g. social worker or speech pathologist) and a psychologist. It is also suggested that a 'key worker' should be assigned to each survivor on commencement of LTF to coordinate care, provide support and facilitate communication between each health professional [129].

There has also been suggestion that LTF should be survivor led [6]; that survivors should be encouraged to take increasing amounts of control over their follow-up needs, thereby fostering independence.

Box 1: Key aspects of long term follow-up care

- Comprehensive health care
- Health maintenance and education
- Reproductive counselling
- Educational and vocational counselling
- Psychosocial support
- Early detection and treatment of late effects
- Multidisciplinary approach to care
- 'Key worker' for each patient
- Open lines of communication between all involved parties
- Utilisation of a detailed summary of treatment that the has access to
- Wellness focussed

Adapted from: Keene N, Oeffinger KC. Comprehensive follow-up programs: A necessity not a luxury. National Journal of the Candlelighters Childhood Cancer Foundation 2002;Fall:3-5.

One research group in the UK have proposed a grading system be applied to paediatric cancer survivors to determine the level of LTF care required [7]. This system has been based on the evidence available for high and low risk treatment modalities.

Table 3: Proposed grading system for levels of LTF care more than 5 years post treatment

Level	Treatment	Level of LTF	Frequency	Examples of Tumour
1	Surgery alone	Post or telephone	1-2 years	Wilms' tumour stage I or II
	Low risk chemotherapy			Langerhans cell histiocytosis (single system disease)
				Germ cell tumours (surgery only)
2	Chemotherapy	Led by nurse or primary care doctor	1-2 years	Most patients (e.g. acute lymphoblastic leukaemia in first remission)
	Low dose cranial radiation (< 24Gy)			
3	Radiotherapy (except low dose cranial radiation)	Medically supervised late effects clinic	Annual	Brain tumours
				After bone marrow transplant
	Megatherapy			Patients with stage IV tumours (any tumour type)

From Wallace W, Blacklay A, Eiser C, Davies H, Hawkins M, Levitt GA, et al. Developing strategies for long term follow up of survivors of childhood cancer. British Medical Journal 2001;323:271-274.

One study that has examined the utility of this coding method in the hospital setting concluded that coding was relatively simple for experienced clinic staff and that consensus among coders was generally very high [130]. The ease with which coding was completed for patients depended on the quality of prior record keeping. There was a strong relationship between the assigned level and self-reported symptoms of late-effects [130]. However the authors note that it is important to maintain flexibility to allow movement between levels for individual patients and that the default should always be to the higher level [130].

A recent series of focus groups of paediatric cancer survivors was conducted in the UK [131]. These focus groups identified a number of needs for LTF care. These included the need for a positive relationship with healthcare professionals, feeling remembered by doctors was important; the need for information about their disease, treatment and ongoing care, with regular updates at each visit; a need for communication, where they could express their needs and concerns in a supportive environment; parental involvement need, where parents were provided with support and information; and the need for healthcare professionals to have appropriate knowledge [131].

These focus groups also identified survivor's views on the design and structure of LTF. There was a preference to see a specialist doctor over a generalist physician or nurse and that telephone, email or questionnaire follow-up was seen as no substitute for face-to-face communication due to its impersonal nature [131]. There was a strong desire for a 'key worker' to coordinate LTF with a clear preference expressed by survivors for a model of follow-up directed by the needs of the survivor rather than the treatment they had received [131].

5 Existing guidelines and recommendations

There is a range of evidence to help guide clinical practice and the models of care for long term follow-up services.

5.1 Review of existing guidelines

There have been three noteworthy practice guidelines for standardised screening of paediatric cancer survivors recently developed by the Children's Oncology Group (COG) and the Scottish Intercollegiate Guidelines Network (SIGN).

The **Children's Oncology Group (COG)** is a 238 member clinical trials group whose goals are to minimise the risk of long-term effects that may impact on quality and duration of life in paediatric cancer survivors [132]. COG recently developed risk-based, exposure related guidelines for use in directing LTF care of paediatric malignancies. These guidelines are entitled "Long-term follow up guidelines for survivors of childhood, adolescent and young adult cancers" [133]. The guidelines were developed under strict criteria and guidance from a range of specialists working in the area of paediatric cancer. The COG guidelines represent a hybrid of evidence-based and consensus driven approaches to guideline development, and consist of a set of comprehensive, clinically relevant screening recommendations that take into account the specialised healthcare needs of paediatric cancer survivors [132]. The guidelines are designed to standardise and direct follow-up care that facilitates early identification and intervention for treatment-related complications [132].

The **Scottish Intercollegiate Guidelines Network (SIGN)** develops evidence-based clinical guidelines aimed at reducing variations in clinical practice and outcomes for patients [132]. SIGN recently developed guidelines for paediatric cancer survivors entitled "Long-term follow-up of survivors of childhood cancer – SIGN 76" [132]. The SIGN guidelines provide a systematic review of the evidence available for several key areas of importance in the LTF of paediatric cancer survivors, including a detailed review of: assessment and achievement of normal growth; achievement of normal progression through puberty and factors affecting fertility; early identification, assessment and treatment of cardiac abnormalities; assessment of thyroid function; and assessment and achievement of optimum neurodevelopment and psychological health [132]. These guidelines do not address renal, pulmonary, gastrointestinal, ocular, auditory, and musculoskeletal systems as well as second malignancies. These guidelines also provide recommendations for the LTF care of patients based on the intensity of treatment received.

A third set of guidelines, or practice statement, is **The United Kingdom Children's Cancer Study Group**, Late effects group, "therapy based long term follow up". These guidelines provide another evidence-based risk assessment and screening strategy to reduce the impact of possible late effects of paediatric cancer treatment.

All three sets of guidelines provide recommendations for the LTF of paediatric cancer patients including medical screening, psychosocial assessment and support. The development of these guidelines has been a significant advance in the

understanding of the LTF needs of paediatric cancer survivors and is easily accessible to healthcare providers worldwide.

5.2 Review of existing models of care

The majority of LTF has been conducted by paediatric oncologists in the paediatric setting [134]. However, there have been a number of LTF models proposed for the continuing care of paediatric cancer patients [13]. These include specialised LTF clinics, transitional models, adult oncology based models and community based models.

5.2.1 Specialised LTF clinics

Specialised LTF clinics are predominantly specialised multidisciplinary care led by a paediatric or general oncologist who specialises in the LTF care of paediatric cancer survivors. Specialised LTF clinics are often conducted separately from the acute treatment or early follow-up clinics but are most commonly conducted in the same hospital and run by the same clinician [134]. Some age-appropriate clinics have been developed in the UK and US, however they are still generally conducted in the paediatric hospital [134].

This model of care is the most widely advocated model [135]. It has been reported that only 50% of childhood cancer treatment centres in the US and the UK have access to a dedicated LTF clinic [127] but there is very little information available about the use of this model of care in Australia. It has been advocated that a specialised LTF clinic be operated separately from the acute oncology department where patients may have received their treatment [127].

A recent review of 24 comprehensive LTF programs in the U.S. and Canada indicated the core staff of the LTF programs consisted of a physician, nurse and an administrative assistant with 83% of the program directors being paediatric oncologists [136]. A social worker was a part of 54% of the LTF programs and 33% of LTF programs had a psychologist as part of the team [136]. In 21% of the programs other physicians attended the LTF clinics, including radiation oncologist, endocrinologists, cardiologists, medical oncologists, and neurologists. The health services provided by the LTF program were reported to be relatively uniform across all programs. Upon entry to the LTF program the child's parents/carers are given a detailed summary of the child's cancer and cancer therapy. During the early stages of the LTF program (2-5 years) the focus of the LTF visit is on surveillance of disease recurrence and initiating screening for late effects [136]. As time progresses the focus shifts to include age and developmentally appropriate education on health behaviours and practices [136].

In the 54% of LTF programs which included a social worker a formal social evaluation was conducted at each annual visit. Although all programs reported some form of mood disturbance screen, only 50% of the programs reported a formal psychological evaluation at each annual visit and formal neuropsychological evaluations were reported to be conducted annually in 29% of the programs [136].

All program directors reported that care delivered through comprehensive LTF programs was time and labour intensive [136]. All program directors reported that survivors transitioned from primary oncologist to LTF care two (2) years after the completion of treatment or five (5) years after cancer diagnosis [136]. Nine of the LTF programs were conducted from a children's hospital or cancer centre, 12 were conducted from a cancer centre or a university hospital and 3 were dual programs linking the children's hospitals with the university hospital [136].

5.2.2 Transitional models

The issue of transitional care needs have also been raised in the literature [137]. With a growing population of paediatric cancer survivors it is unrealistic for ongoing LTF care to be provided in the paediatric setting where acute treatment occurred [138]. Transitional care programs often use collaborative care models, drawing on expertise from both oncology and primary care providers, and maintain many of the benefits of the specialised LTF clinics, with the added benefit of care providers with expertise in adult medicine [13].

Facilitating a smooth transition from paediatric to adult health services have reported to be challenging for both services because of the need for not only medical transition but also that psychosocial, educational and vocational needs often have to be addressed during this transitional period [137]. A need for skills training prior to transition from paediatric to adult health services has been reported which includes training in the areas of self-advocacy and the ability to negotiate services independently; education about general adolescent health issues such as substance abuse, mental health, exercise and sexual health; educational and vocational issues, particularly career exploration, work experience and disclosure; and parenting issues [137, 138]. These issues are also echoed in the literature surrounding transitional care of people with intellectual/developmental disabilities [139].

Box 2: Key elements of transitional care

- An early start – when children enter a paediatric service they should know when to expect to leave it
- A key worker for each individual
- A written transition policy between paediatric and adult services
- A flexible policy on timing of events; a healthcare setting should be chronologically *and* developmentally appropriate
- Skills training in communication, decision making, creative problem solving, assertiveness, self care, self determination and self advocacy for adolescent patients
- An educational program for patients and parents/carers which addresses medical, psychosocial, and educational/vocational aspects of care
- A written individualised healthcare transition plan in place by age 14, created with the young person and family, with regular review and update
- Administrative support, including provision of a medical summary that is portable and accessible
- A training program in adolescent health and transitional care for paediatric and adult team members
- Primary and preventive care involvement and provision

From: McDonagh JE, Viner RM. Lost in Transition? Between paediatric and adult services. British Medical Journal 2006;332:435-436.

One coordinated program is the "Living Well After Cancer" (LWAC) operated at the Abramsom Cancer Centre of the University of Pennsylvania in the U.S. The program is built on the paediatric model of providing coordinated care to survivors of paediatric cancer while recognising the needs of young adults trying to foster independence in caring for their own health needs [138]. The program addresses medical and quality of life issues and provides early intervention related to treatment late-effects or aging [138]. Patients are transitioned from the cancer survivorship clinic operated at the acute hospital to the LWAC program after they reach the age of 22 and are 10 years post-diagnosis. The survivor and the family are introduced to the idea of transition 1-2 years prior to transition and are given a letter of introduction to the LWAC and a summary of their treatment prior to discharge from the survivorship clinic [138].

Other coordinated transitional programs include the After the Cancer Experience (ACE) and the Survivors Taking Action and Responsibility (STAR) program, both in the US [13].

5.2.3 Adult oncology based care

In this model the survivor is transferred to adult oncology services for ongoing LTF when they reach adulthood. Advantages of this system include monitoring for

disease recurrence in a system that is specialised in adult medical care, and accessibility to care in the local community [13]. However there are clear disadvantages of placing LTF of paediatric cancer survivors solely in the care of adult services; many adult oncology staff are not familiar with the possible late-effects of paediatric cancer treatment and survivors are not likely to receive lifetime follow-up [13].

5.2.4 Community based care

Community based LTF care places responsibility of LTF with a general or primary physician who maintains ongoing communication with the original oncology paediatric treatment team [13]. Studies have indicated that LTF of paediatric cancer survivors can be successfully managed by community based physicians provided that an appropriate level of support and guidance is available [127]. The advent of the COG and the SIGN guidelines provide easy access for community based physicians to quality evidenced-based information [127]. There have been reported psychological and social benefits moving LTF care away from the acute setting. Community based LTF care can facilitate a shift to independence in the survivor and their family and the development of a relationship with a community based provider who is aware of their overall healthcare requirements, provides a more holistic or cohesive approach, as well as being more easily accessible [13].

However, there has been some suggestion that the complexities of the late-effects experienced by paediatric cancer survivors can demand a level of knowledge that is beyond the range of a general physician or family doctor, or even medical oncologists [14]. Many community based physicians may have inadequate formal training in this area and a lack of knowledge of the specialised care required [132]. Furthermore monitoring and management of the complex physiological and psychological needs of the survivors is time consuming and often cannot be easily integrated into a busy community practice [127]. Coordination between primary and multiple speciality areas of care may not be possible, health education may be less rigorously provided and access to psychosocial services may be limited [127].

5.3 Barriers to long term follow-up

There are a number of barriers to LTF including survivor characteristics (e.g. social or cultural background) and their healthcare providers (e.g. attitudes and beliefs) [6]. One significant and important obstacle is a lack of knowledge of cancer risks and LTF care needs, among survivors and non-specialist clinicians [6]. Healthcare structure and policy as well as funding restrictions also pose significant barriers to optimal LTF of paediatric cancer survivors. Low institutional commitment toward the provision of survivorship care, lack of capacity to care for the increasing population of survivors and difficulty with ongoing communication with community physicians were also identified as significant barriers to running a comprehensive LTF program by program directors [136].

6 Summary and conclusions

As treatment for paediatric cancers continue to improve there have been a growing number of long-term paediatric cancer survivors. However, with this growing number of survivors comes an increase in the number of survivors experiencing adverse late-effects of treatment. There have been reports of up to 60% of paediatric cancer survivors experiencing at least one adverse late-effect of treatment and estimates that 20% of survivors have three or more chronic or life threatening late-effects. Late effects have been identified across a broad range of modalities; physical, cognitive, social and psychological. The range of late-effects experienced by survivors strongly supports the need for specialised LTF. However, little high-quality evidence exists about what LTF care is needed, who should deliver it, where, how and how often [134]. The guidelines developed by COG and SIGN provide a detailed reference of the issues that should be considered when providing LTF care to paediatric cancer survivors. However, these guidelines do not (and cannot without further research) detail the optimum care, method and timeframe of delivery. Unfortunately even more limited is research examining LTF or late effects of Australian paediatric cancer survivors. There is also a notable lack of information available on the views of the survivors and their families about their experiences and preferences regarding models of care [134].

A number of LTF models of care have been discussed. These range from specialised LTF clinics, which utilise a specialised multidisciplinary approach, to transitional models, which coordinate care between paediatric and adult systems via a specialised LTF clinic, to entirely community based LTF. Unfortunately, there is no clear evidence to suggest that one model of care is better than the others [134]. The literature on models used across a number of countries appears to reflect the systemic or economic pressures of each health system with LTF care often shaped according to these pressures. Realistically these pressures must be accounted for and future models developed within a sustainable context.

The ideal LTF strategy will be one that captures the largest numbers of long-term survivors by ensuring that appropriate clinical and psychosocial care, health education and health promotion advice are delivered in an appropriate manner at an appropriate location, while taking advantage of important research opportunities that will benefit future generations of survivors [134].

There appears to be consensus about the need for LTF care to be conducted by appropriately knowledgeable and experienced health professionals, utilise a multidisciplinary approach to care, foster independence in the survivors and their family and be wellness focussed rather than relapse driven.

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