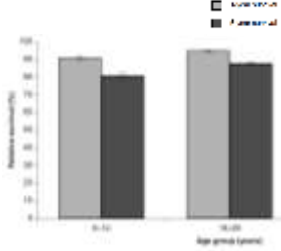


Late Effects: What can we learn from childhood cancer?

Dr Michael Osborn
Youth Cancer Service SA/NT
FCIC Survivorship Conference, 2015

50 years ago late effects in childhood cancer survivors was not an issue...

SHOULD WE TREAT LEUKEMIA IN CHILDHOOD?
By Jane H. Cameron and A. C. Williams
From the Children's Hospital, Melbourne



Childhood Cancer Survival in 2004-2010. Source: AHW (2011)

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Late effects of cancer treatment: Conceptualisation of cancer survivorship as a "chronic illness"

Late Mortality Experience in Five-Year Survivors of Childhood and Adolescent Cancer: The Childhood Cancer Survivor Study
By Jane H. Cameron, Joseph F. Fraley, and others

- 19 x ↑ risk of second malignancy
- 8 x ↑ risk of cardiac death
- 9 x ↑ risk of pulmonary death

Chronic Health Conditions in Adult Survivors of Childhood Cancer
62% of adult survivors of childhood cancer have at least 1 chronic condition (RR 3.3)
28% had a severe or life-threatening condition (grade 3 – 4) (RR 8.2)

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Cancer

Health Status of Adolescent and Young Adult Cancer Survivors

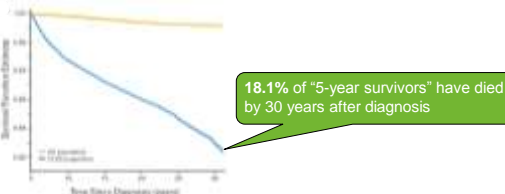
Tai et al, *Cancer*, 2012

	Survivors of Cancer at age 15-29 years	No History of Cancer
Risk Behaviour		
Current Smoking	26%	18%
Obesity	31%	27%
Chronic Condition		
Cardiovascular disease	14%	7%
Hypertension	25%	10%
Disability	36%	18%
Poor Mental Health	20%	10%

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Late effects of cancer treatment: Associated with an increased risk of death

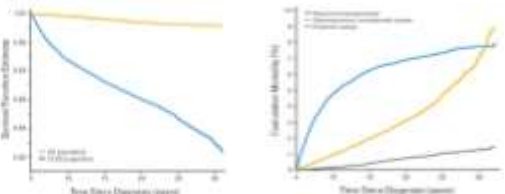
Late Mortality Among 5-Year Survivors of Childhood Cancer: A Summary From the Childhood Cancer Survivor Study
By Jane H. Cameron, Joseph F. Fraley, and others



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Late effects of cancer treatment: Associated with an increased risk of death

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Many survivors are unaware of the risks

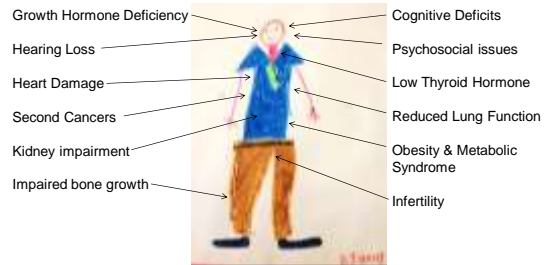
Childhood Cancer Survivors' Knowledge About Their Past Diagnosis and Treatment Childhood Cancer Survivor Study

- 72% accurately named their diagnosis
- 70% who had radiotherapy knew the site of irradiation
- 30 – 52% knew they received daunorubicin or doxorubicin
- 35% knew about late effects



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Late effects may occur in a number of different organ systems



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Heart Problems



Anthracycline chemotherapy

- eg doxorubicin, daunorubicin
- Cardiomyopathy & congestive heart failure
- Risk depends on cumulative dose
 - <10% if <500 mg/m² vs 36% if >600 mg/m²
- ↑ risk if young (<5 years), female, pre-existing heart disease & concomitant mediastinal irradiation ± ? genetic polymorphisms

Mediastinal irradiation

- Constrictive pericarditis, cardiomyopathy, valvular heart disease, coronary artery disease, & conduction abnormalities
- 21% risk of coronary artery disease at 20 years
 - Usually other cardiac risk factors, eg. dyslipidemia, hypertension, obesity, smoking

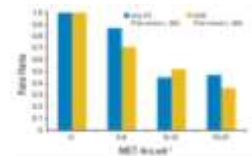
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Heart Problems



Prevention

- Limit cumulative anthracycline dose
- Dexrazoxane
- Smaller radiation fields & risk-adapted use of radiotherapy
- Avoid smoking, obesity, & other modifiable cardiac risk factors
- Exercise (Jones *et al.*, 2014)



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Heart Problems



Prevention

- Limit cumulative anthracycline dose
- Dexrazoxane
- Smaller radiation fields & risk-adapted use of radiotherapy
- Avoid smoking, obesity, & other modifiable cardiac risk factors
- Exercise (Jones *et al.*, 2014)

Prediction

- Genetic polymorphisms: SLC28A3 & UGT1A6 (Visscher *et al.*, 2013)
- Biomarkers: B-type natriuretic peptide (Lawson *et al.*, 2014)

Surveillance

- Echocardiogram every 1 - 5 years

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Neurocognitive Problems



Radiotherapy involving the brain

- Especially at age <5 years
 - Always try to avoid if ≤ 3 years
- Brain tumours mainly; previously ALL & NHL

Learning problems usually appear 1 – 2 years later

- Often progressive
- Increasing difficulty keeping up with peers

Surveillance

- Neurocognitive assessment
- Monitor school reports
- Several charities offer tutoring
 - eg Ronald McDonald, Red Kite, Childhood Cancer Association

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Growth, Development & Obesity

Growth & Development

- Brain irradiation can cause short stature
 - Hypothalamus / pituitary gland control growth hormone release
 - Growth hormone treatment helps if epiphyses still open
- Spinal irradiation → ↓ vertebral growth
- Assymetrical growth after unilateral irradiation
- Gonadal radiation in prepubertal boys → ↓ testosterone



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Obesity & Metabolic Syndrome

- 11 – 40% of Acute Lymphoblastic Leukaemia survivors overweight
- ↑ risk of metabolic syndrome
 - ↑ glucose, dyslipidemia, hypertension

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Fertility



Males

- Radiotherapy, surgery & chemotherapy (alkylating agents)
- Risk depends on type of chemotherapy
 - but absolute risk not well defined by research
- Recommend sperm banking prior to treating
- ? Role of testicular aspiration in "azospermic" patients

Females

- Radiotherapy, surgery & chemotherapy (alkylating agents)
- Premature ovarian failure
 - 13 x ↑ risk of early menopause
 - Anti-Mullerian hormone
- Ideally cryopreserve oocytes before treatment
- ? Role of zoladex (GnRH analogue during treatment)
- Donor eggs after treatment

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Fertility



www.futurefertility.com.au

Info@futurefertility.com.au



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Second Malignant Neoplasm

10 x ↑ risk of subsequent cancer

- 15% at 20 years

Treatment Related MDS / Acute Myeloid Leukaemia

- 2% at 15 years
- Etoposide (early), Alkylating agents (late)



Treatment Related Solid Tumours

- Breast Cancer
 - 20% by age 45 year in Hodgkins survivors
 - Mediastinal Radiation
 - Surveillance from 8-years post Rx or 25 years old
 - Mammogram vs Breast MRI
- Thyroid, Brain, Bone, Lung cancer



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Other Late Effects

Organ	Problem	Cause
Lungs	Pulmonary Fibrosis Restrictive pulmonary deficit	Bleomycin Radiotherapy
Kidneys	Electrolyte abnormalities Impaired Renal Function	Cisplatin, Ifosfamide, Methotrexate Radiotherapy, Surgery
Bladder	Haemorrhagic cystitis Impaired function	Alkylating agents Surgery, Radiotherapy
Thyroid	Hypo- or hyperthyroidism Thyroid nodules & tumours	Radiotherapy
Hearing	Inner ear damage	Cisplatin Radiotherapy

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Guidelines for Surveillance



The world's childhood cancer experts

International Late Effects of Childhood Cancer Guideline Harmonization Group

- Breast Cancer Surveillance
 - Mulder *et al*, Lancet Oncology, 2013
- Cardiac Surveillance
- Transition

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The challenge of long-term follow-up of survivors of childhood cancer

"Epidemic of survival"

1 in 640 adults are childhood cancer survivor



Who will look after them?

Paediatric oncologists?

Not developmentally appropriate
Lack knowledge of adult diseases

General physicians?

Medical Oncologists / Haematologists?

Too busy with new patients to see the healthy majority
Lack knowledge of primary disease
Not well informed re screening guidelines for late effects

GPs?

? Capacity / willingness to deal with complex late effects

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Risk stratified model



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Treatment Summary

Surveillance Road Map

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Late Effects of Childhood Cancer

Significant **Morbidity & Mortality**

Awareness – patients & their family, specialists, GPs

Aim to prevent or minimise when planning treatment

Lifelong Surveillance

Need to personalise according to risk

Challenge of determining **who** will look after these patients

Collaborative, risk-stratified approach

Importance of **empowering the patient**

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Acknowledgements

