Medical Aspects of the Adolescent and Young Adult Cancer Experience

Geoff Cuvelier MD, FRCPC

Pediatric Oncologist
Director of Pediatric Blood and Marrow Transplant
CancerCare Manitoba
Associate Professor, Dept of Pediatrics and Child Health

Disclosures

- None
- I will not be discussing off-label use of medications.

Objectives

- To understand in AYAs, the cancer experience as it relates to:
  - Delays in Diagnosis (Lag Time)
  - Clinical Trial Accrual
  - The Importance of Long-Term Follow Up *YEARS* after completion of treatment.

Cancer Occurs in AYA

Table. Incidence of All Invasive Cancer by Age[a]

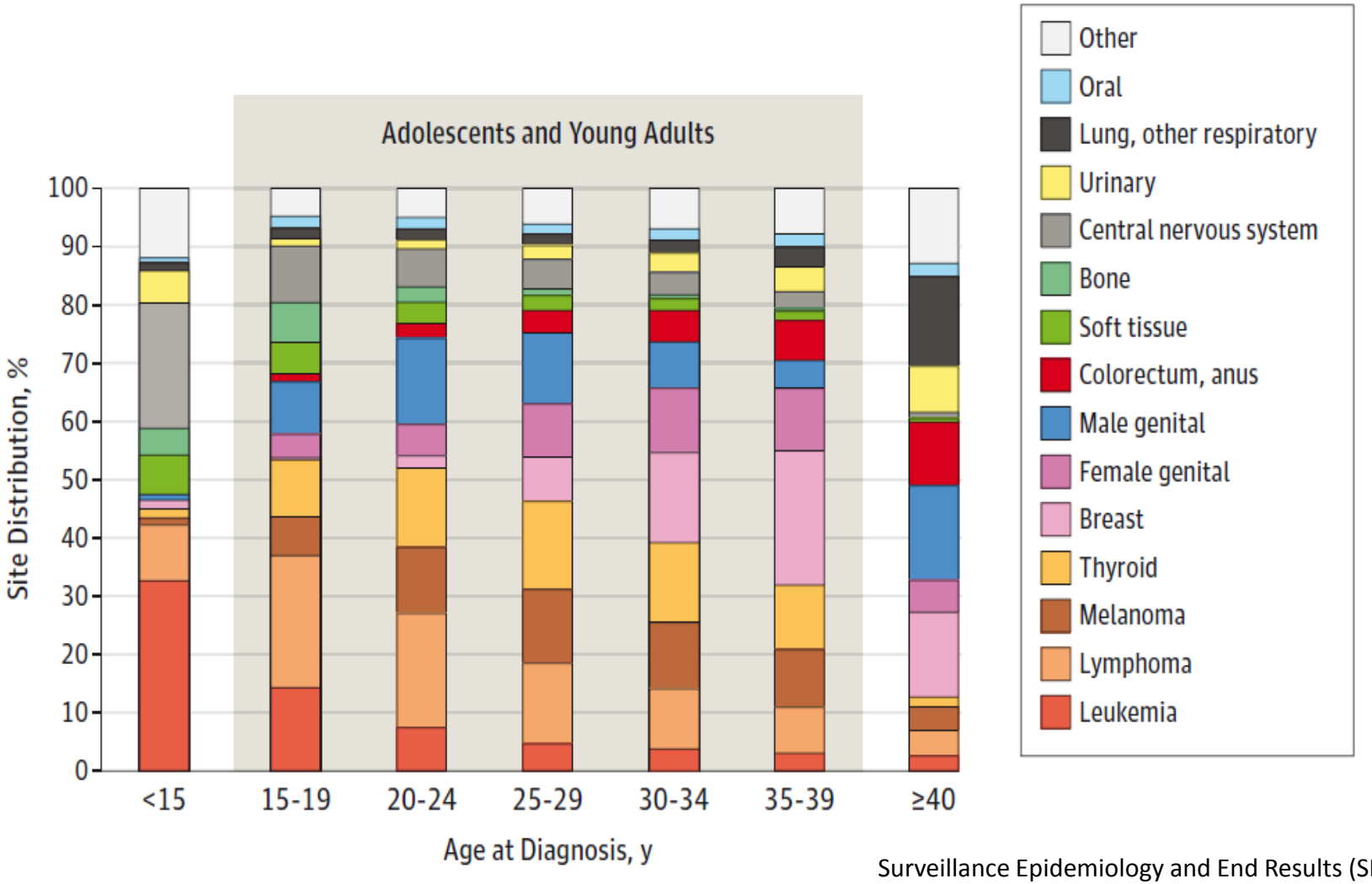
Age, y	Incidence, No.
0-4	200
5-9	110
10-14	125
15-19	200
20-24	350
25-29	550
30-34	830
35-39	1300

[a] Per million per year.[7]

Barr R et al. JAMA Pediatr 2016; 170: 495-501.

Types of Cancer Affecting AYA

Somewhere Between Children and "Older" Adults



Surveillance Epidemiology and End Results (SEER), 2000-2011

"Delay in Diagnosis"

Frequent Concern From Patients and Families

Many *presumed* factors:

- Cancer is a mimicker of other diseases.
- AYA may not recognize importance of symptoms and signs – or may *deny* them.
- Primary health care workers do not consider cancer in the differential diagnosis.
- Lack of access to primary care.

- Lack of insurability. ** Proof of this occurring in the USA
  - Martin et al. Delays in cancer diagnosis in under-insured young adults and older adolescents . Oncologist. 2007. 12: 816-824.

Two Examples – Both "Experiential" Cases From My Practice

Case One: 15 year old female. 1 week history of high fevers and decreased appetite. Small (1-2 cm) palpable lymph nodes in anterior and posterior cervical chains. Seen at walk in clinic. Monospot negative.

-Returns to same walk in clinic 2-weeks later but sees a different doctor. Still having fevers. Not eating much and losing weight. No change on exam. Complete Blood Count: Normal. Diagnosed with probable viral infection. Prescribed antibiotics nonetheless.

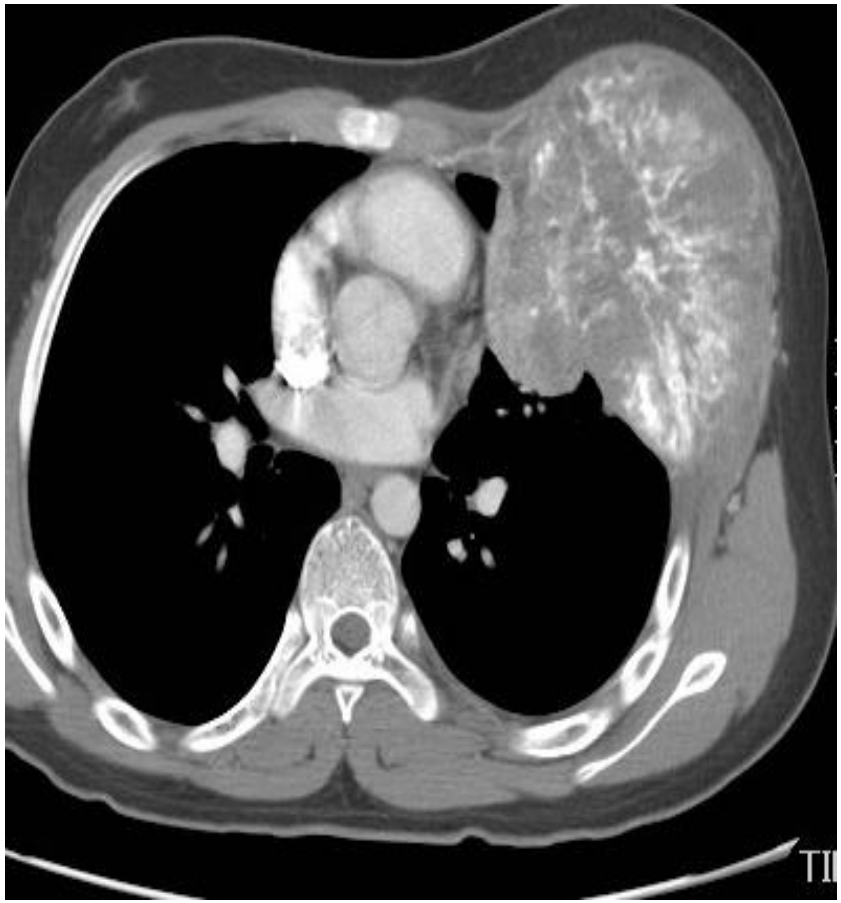
-Emergency room visit 1-week later. Still having fevers. Now with night sweats. Still with palpable lymph nodes in head and neck region.

-CXR – Large Anterior Mediastinal Mass.

-Dx: Hodgkin Lymphoma.

-Family was upset that it took one month to come to this diagnosis.

Two Examples – Both "Experiential" Cases From My Practice



Case Two: 16 year old male playing volleyball. Mother watching the game, noted he was not really using left arm that well.

•Young man admitted to having a painful "lump" left side of chest for 8 months but had not told anyone.

•Osteogenic sarcoma.

Lag Time instead of "Delay in Diagnosis"

- Lag time is less prejorative than "delay in diagnosis".
- 2 components to Lag Time:
  (1) Time from symptom / sign onset to first medical contact.
  (2) Time from first medical contact to diagnosis.

While it is clear that *LONGER* lag time (particularly for point #2) results in less patient satisfaction (and lawsuits), the effect on OUTCOME is not as clear.

For certain cancers – shorter lag time associated with better event-free survival (AYAs - sarcomas, breast cancer).

For many other cancers – no known association.

Type of Cancer	Lag Time (wk)	
	Mean	Median
Leukemia	4.2	2.7
Kidney tumors	7.4	2.0
Neuroblastoma	5.9 (5.4)	3.3 (3.0)
Non-Hodgkin lymphoma	7.3 (7.1)	3.8 (3.7)
Hodgkin lymphoma	12.5 (14.0)	6.7 (7.0)
Germ cell tumors	9.9	5.9
Rhabdomyosarcoma	7.2	6.4
Retinoblastoma	16.7	8.0
Medulloblastoma	12.8	7.9
Low-grade astrocytoma	34.0	16.1
Bone tumors	20.7	14.1
Soft tissue sarcoma†	26.1	13.1
Ganglioglioma	135.2	220.1

Figures in parenthesis are taken from Pollock et al.[18]
*Assembled from Brasme et al.[4]
†Except rhabdomyosarcoma.

Most interesting: There has been no shortening of lag time in cancer diagnosis time for the past 40 years.

Barr et al. Journal of Pediatric Hematology/Oncology. 2014; 36(3):169-172.

Access To Clinical Trials for AYA

Generally Very Poor

- In pediatrics: Children's Oncology Group (COG)
- COG forms the basis for care of childhood cancers.
- Many of these trials will enroll up to age 30 years – *but there are many barriers to enrollment*.

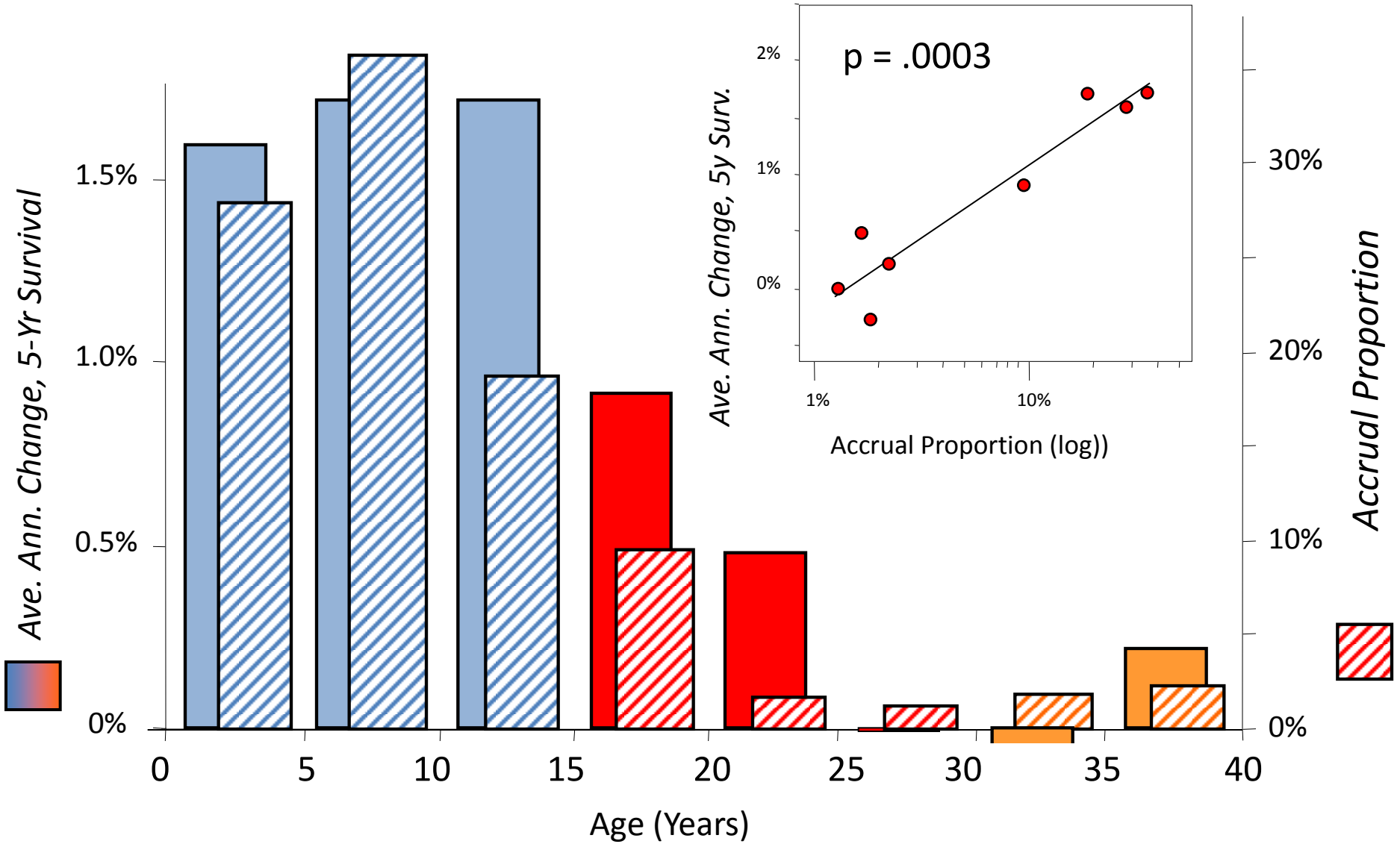
- In adults: Many different collaborative groups.
- Canadian Example: Canadian Cancer Clinical Trials Group (CTG)

- A great example of integration of groups to help AYAs:

"Pazopanib Neoadjuvant Trial in Non-Rhabdomyomatous Soft Tissue Sarcomas. A Phase II/III Randomized Trial of Preoperative Chemoradiation or Preoperative Radiation Plus or Minus Pazopanib"

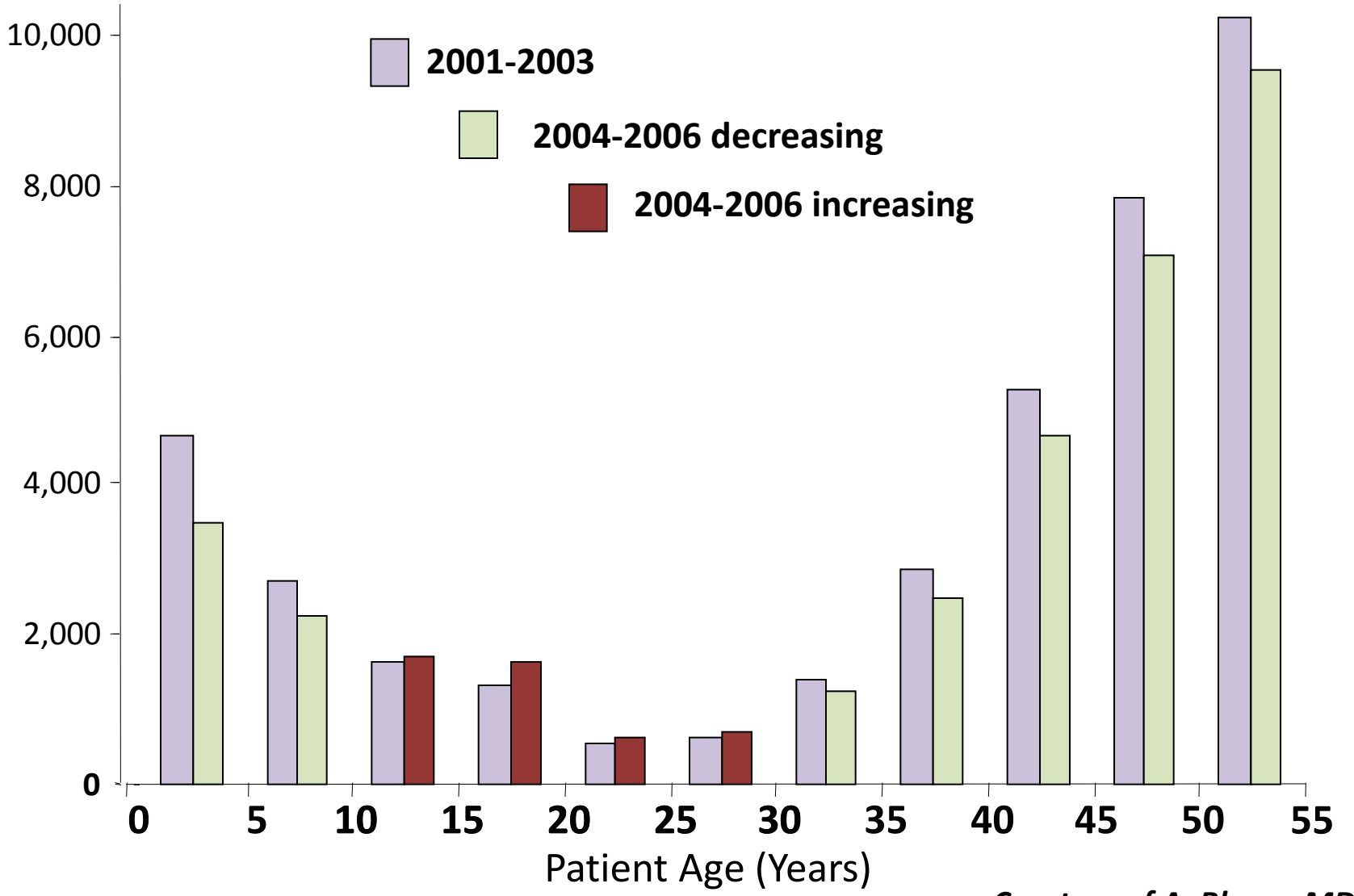
  - Intergroup study between the Children's Oncology Group, National Cancer Institute, Alliance, ECOG-ACRIN, SWOG, and Canadian Cancer Clinical Trials Group.

Survival improvement is correlated with clinical trial participation (Courtesy of Dr Archie Bleyer)



Clinical trial accrual in the U.S.

(Courtesy of Dr Archie Bleyer)



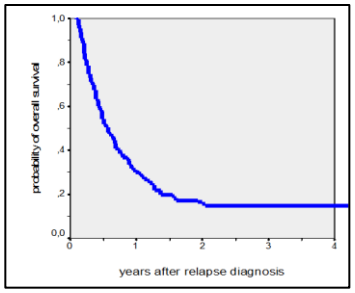
Courtesy of A. Bleyer. MD

Enrollment on Clinical Trials in Canada for AYA is Dismal

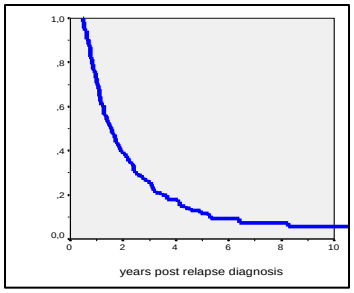
Province	Age range (years)	Year	Accrual (%)	Source
Alberta	15–29[a]	2000–2009	11.7	Alberta Cancer Registry[b]
British Columbia	15–19	1990–1994	29.3	Children, Adolescent, Young Adult
		1995–1999	12.1	Cancer Survivorship research program
		2000–2004	7.4	
		2005–2010	8.2	
	20–24	1990–1994	22.2	
		1995–1999	3.1	
		2000–2004	2.3	
		2005–2010	6.9	
	25–29	1990–1999	2.3	BC Cancer Agency
		2000–2010	2.6	
Manitoba	15–17	2003–2013	7.0	CancerCare Manitoba
	18–30	2003–2013	0.4	
Ontario[c] (pediatric centres)	15–17	2010–2013	12.2	Pediatric Oncology Group of Ontario
Ontario[c] (adult centres)	15–29	2013	4.7	Ontario Institute for Cancer Research
		2014	3.5	

Hay et al. *Current Oncology* 2016; 23: 81-85.

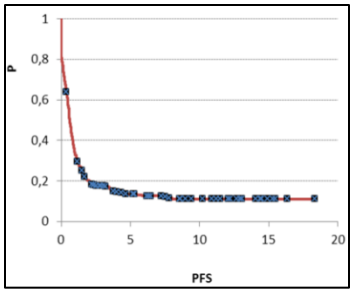
ALL-HR



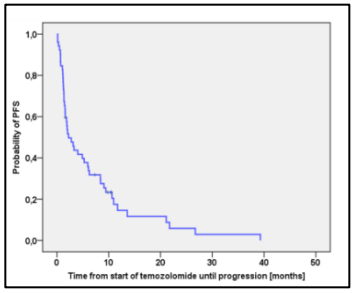
ALL post-SCT



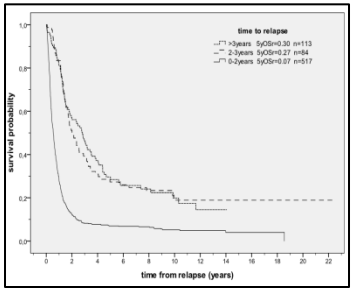
AML



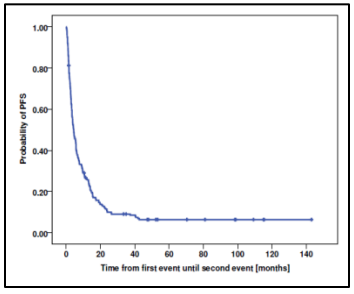
Brain Tumors



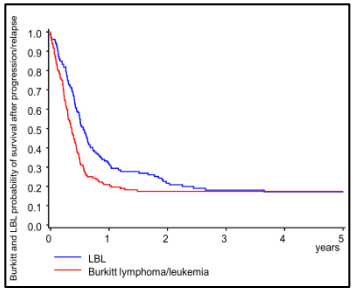
Ewing Sarcoma



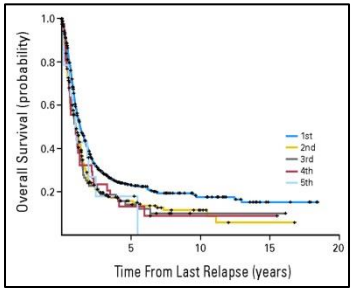
Neuroblastoma



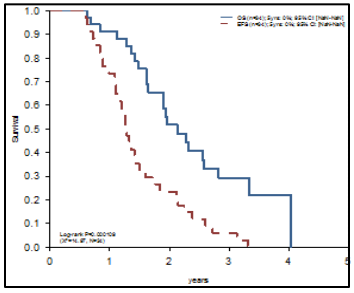
NHL



Osteosarcoma



Rhabdomyosarcoma



Dr. Stefan Pfister, DFKZ, Heidelberg

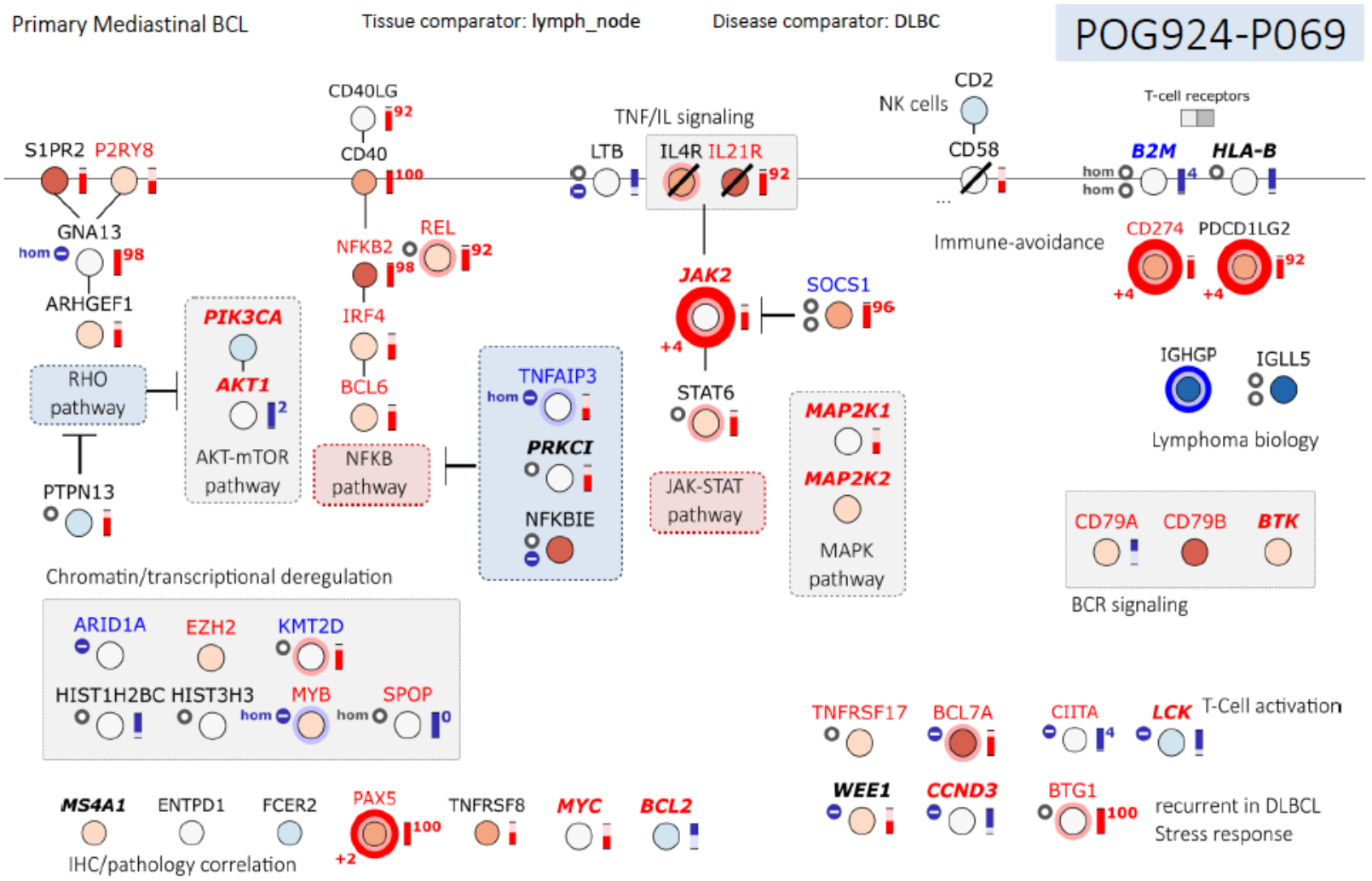
TERRY FOX
PROFYLE
PRECISION ONCOLOGY FOR YOUNG PEOPLE

PROFYLE Project

- Across Canada – now open in Manitoba.
- Enrolls patients between 0-29 years of age –great desire to enrol AYAs.
- Patients with “hard to treat” cancers:
  - Defined as projected 5-year EFS <30%
  - Often in the relapse setting but also in the upfront setting.
  - Examples in AYA: Metastatic Breast Ca, Various sarcomas, relapsed ALL, relapsed AML.

- Goal is to “molecularly profile” – using whole genome, whole exome, transcriptomics, proteomics – an individual’s cancer.
- Understand the pathways that drive that individual’s cancer so that drugs already available might be used.
- “Personalized medicine”.

Example Where PROFYLE Helped an AYA Patient



Based on This Information – Entirely New Treatment Was Considered With Immune Checkpoint Inhibitor

GENOMIC CASE NOTES

POTENTIAL THERAPEUTIC TARGETS

POTENTIAL THERAPEUTIC OPTIONS

Drug Target		Biomarker		Notes
JAK2	JAK-STAT pathway		amplification high percentile LoF mutation	Inactivation of SOCS1 is inferred (multiple mutations)
PDCD1	Immune-checkpoints	CD274 PDCD1LG2	amplification high expression outlier amplification high expression outlier	Multiple events in immune-avoidance. Efficacy of this approach is uncertain. JAK2 amplification, CD58 mutated, B2M hyperrmutated.
PIK3CA	AKT-MTOR	GNA13	LoF mutation	Hypothetical. RHO pathway inactivation is thought to promote PIK3CA signalling. No clear evidence that AKT-mTOR pathway is a central driver.
EZH2	Chromatin	ARID1A	LoF mutation	Hypothetical. ARID1A iLoF mutation is heterozygous.
NFKB2	NFKB pathway	TNFAIP3	LoF mutation	Multiple genomic events indicating activation of NFKB signalling.

POTENTIAL CHEMORESISTANCE

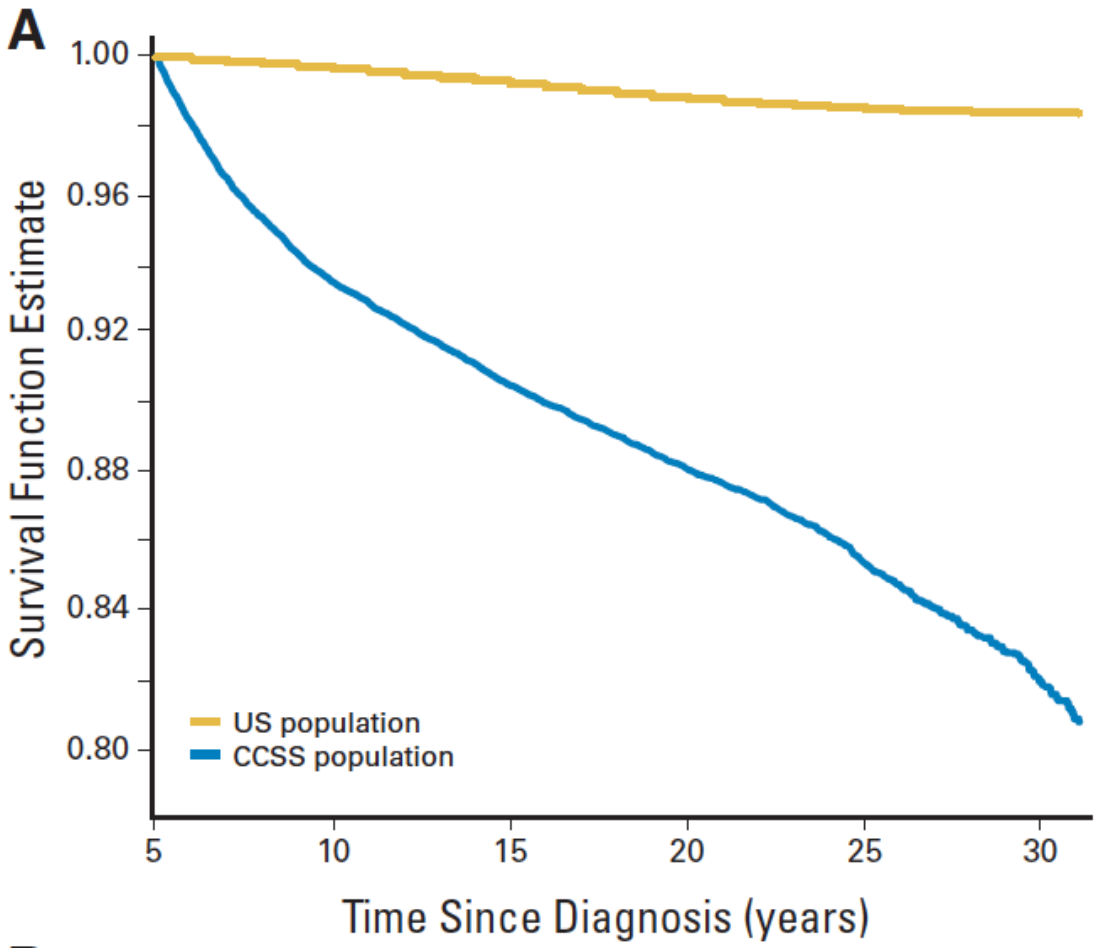
Resistance To	Biomarker		Notes
immunotherapy	B2M	LoF mutation	Inactivating mutations in B2M are an emerging resistance marker for anti-PD1-based therapies. The mutations in this tumour are however VUS.

The Importance of Long Term Follow Up of Childhood and AYA Cancers

- Family physicians / nurse practitioners play a major role.
- Less emphasis on return of the cancer – and more about long-term side effects.
- Beyond the scope of this talk to discuss in great detail.
- The type and frequency of long-term follow up is dictated by (1) the disease (2) treatments.
- Highest risk:
  - High cumulative doses of anthracycline chemotherapy (>250mg/m^2) (doxorubicin, daunorubicin, mitoxantrone) – cardiomyopathy
  - Radiation – Total Body Irradiation (e.g. allogeneic stem cell transplant) or local radiotherapy (many sarcomas, breast ca) – second malignancies, cataracts.
  - Corticosteroids – Bone health, easy fractures.
  - Alkylating agents (cyclophosphamide in particular) - infertility

- Major concerns for AYA: Oncofertility, premature ovarian failure.

Childhood Cancer Survivors Have Poorer Overall Survival Compared to the General Population



Armstrong et al. *J Clin Oncology* 2009; 27: 2328-2338.

What Are Long-Term Survivors Dying From?

Data from Childhood Cancer Survivor Group Study

	Second Malignancy	Cardiac Disease
	RR (95% CI)	RR (95% CI)
Years since Diagnosis		
5-9	2.7 (2.1-3.5)	2.2 (1.3-3.6)
10-14	1.9 (1.5-2.5)	1.7 (1.0-2.7)
15-19	1.4 (1.1-1.8)	1.5 (1.0-2.3)
20+	1.0	1.0
History of Radiation		
Yes	2.9 (2.1-4.2)	3.3 (2.0-5.5)
No	1.0	1.0
Cumulative Anthracycline Dose (mg/m^2)		
Not Exposed		1.0
1-100		2.5 (0.7 – 9.2)
101-250		2.3 (0.9-6.0)
251-400		2.2 (1.3-4.0)
401+		3.1 (1.6-5.8)

All $p<0.05$

Armstrong et al. *J Clin Oncology* 2009; 27: 2328-2338.

Children's Oncology Group

Long-Term Follow-Up Guidelines

for Survivors of Childhood, Adolescent, and Young Adult Cancer

Version 4.0 – October 2013

www.survivorshipguidelines.org

CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

Frequent Echocardiograms Are Commonly Recommended to Family Doctors

RECOMMENDED FREQUENCY OF ECHOCARDIOGRAM (or comparable cardiac imaging)			
Age at Treatment*	Radiation with Potential Impact to the Heart§	Anthracycline Dose†	Recommended Frequency
<1 year old	Yes	Any	Every year
	No	< 200 mg/m^2	Every 2 years
		≥ 200 mg/m^2	Every year
1-4 years old	Yes	Any	Every year
	No	<100 mg/m^2	Every 5 years
		≥100 to <300 mg/m^2	Every 2 years
		≥300 mg/m^2	Every year
≥5 years old	Yes	<300 mg/m^2	Every 2 years
		≥300 mg/m^2	Every year
	No	<200 mg/m^2	Every 5 years
		≥200 to <300 mg/m^2	Every 2 years
		≥300 mg/m^2	Every year
Any age with decrease in serial function			Every year

*Age at time of first cardiotoxic therapy (anthracycline or radiation [see Section 81], whichever was given first)
§See Section 81
†Based on doxorubicin isotoxic equivalent dose [see conversion factors on previous page, "Info Link (Dose Conversion)"]

What Actually Happens in Manitoba in terms of Long-Term Follow Up of Patients?

If treated in Pediatric Oncology (<17 yrs at time of diagnosis):

-Followed by primary pediatric oncologist until 5-years from ending therapy.

-After this – sent to Long-Term Follow Up Clinic at CancerCare Manitoba – once per year follow up.

-If high risk (radiation, anthracyclines) – we follow until age 30. Then discharge to family doctor.

-If low risk – may follow for few years then discharge to family doctor.

If treated by one of the Disease Specific Groups (DSG) in Adult Medical Oncology (17 years or greater at time of diagnosis):

-Highly variable. Most are sent back to their family doctors for long-term follow up.

Practical Points For Community Oncology

- Promoting healthy lifestyles
  - Avoiding smoking.
  - Exercise.
  - Proper Diet.

- Sunscreen and Hat – high rates of melanoma in many of our childhood and AYA survivors of cancer.

- Close monitoring of blood pressure.
- Careful thyroid exam for nodules. Yearly monitoring of TSH and fT4 in patients who have had neck radiation.
- Following guidelines for ECHO monitoring.

Primary Care of Adult Survivors of Childhood Cancer

DEAN A. SEEHUSEN, LTC, MC, USA, *Evans Army Community Hospital, Fort Carson, Colorado*
DREW BAIRD, CPT, MC, USA, *Carl R. Darnall Army Medical Center, Fort Hood, Texas*
DAVID BODE, CPT, MC, USA, *Brooke Army Medical Center, Fort Sam Houston, Texas*

American Family Physician Volume 81, Number 10 • May 15, 2010

Survivorship Issues in Adolescent and Young Adult Oncology

Linda Overholser, MD, MPH[a,*], Kristin Kilbourn, PhD, MPH[b], Arthur Liu, MD, PhD[c]

Med Clin N Am 101 (2017) 1075–1084

Questions?