Long-Term and Late Effects Following AYA Cancer

Addressing the Needs of Adolescent and Young Adults with Cancer
IOM / NCPF Workshop
July 15, 2013

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Terminology

• Long-term and late effects
• Excess risk: relative, absolute, attributable
• Are all comorbidities = late effects?
• Chronic health conditions
  • Physical
  • Psychosocial
AYA Cancer and Late Effects

Bleyer A, et al. 2006
Factors Contributing to Risk of Late Effects

- Aging
- Premorbid conditions
- Genetic
  - BRCA, ATM, p53 polymorphisms
- Host Factors
  - Tobacco
  - Diet
  - Alcohol
  - Exercise
  - Sun
  - Age
  - Gender
  - Race
- Treatment Events
  - Surgery
  - Chemotherapy
  - Radiation therapy

Hudson MM. Cancer, 2005
Late Effects Following AYA Cancer

Factors Contributing to Risk of Late Effects

“Accelerated Aging”

Aging
Premorbid conditions
Genetic
BRCA, ATM, p53 polymorphisms
Tumor Factors
Histology
Site
Biology
Response

Health Behaviors
Tobacco
Diet
Alcohol
Exercise
Sun

Host Factors
Age
Gender
Race

Treatment Factors
Surgery
Chemotherapy
Radiation therapy

Treatment Events

Hudson MM. Cancer, 2005
<table>
<thead>
<tr>
<th>System</th>
<th>Exposures</th>
<th>Potential Late Effects</th>
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<tbody>
<tr>
<td>Cardiovascular</td>
<td>Radiation therapy</td>
<td>Myocardial infarction or stroke</td>
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<td>Anthracyclines</td>
<td>Congestive heart failure</td>
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<td>Cisplatin</td>
<td>Valvular disease</td>
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<td>Hypertension</td>
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<td>Pulmonary</td>
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<td>Restrictive lung disease</td>
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<td>Bleomycin</td>
<td>Pulmonary fibrosis</td>
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<td>Carmustine/Lomustine</td>
<td>Exercise intolerance</td>
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<td>Renal insufficiency or failure</td>
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<td>Hemorrhagic cystitis</td>
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<td>Alkylating agents</td>
<td>Infertility and gonadal dysfunction</td>
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<td>Dyslipidemia</td>
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<td>Insulin resistance and diabetes</td>
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<td>Learning disabilities</td>
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<td>Cognitive dysfunction</td>
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<td>Cancer</td>
<td>Post-traumatic stress</td>
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<td>Employment &amp; educational problems</td>
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<td>Insurance discrimination</td>
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<td>Adaptation/problem solving</td>
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<td>Second malignancies</td>
<td>Radiation therapy</td>
<td>Solid tumors</td>
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<td>Leukemia</td>
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<td>Epipodophyllotoxins</td>
<td>Lymphoma</td>
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</table>
Late Effects Following AYA Cancer

Cumulative incidence of chronic physical health conditions

Childhood Cancer Survivor Study

73.4% with at least one chronic condition

42.4% with a severe or life-threatening condition or death

By age 45

95.5% with a chronic health condition
80.5% with a grade 3-4 condition
Late Effects Following AYA Cancer

Cumulative incidence of chronic physical health conditions

Examples in Survivors of AYA Cancer

• Cardiovascular disease and metabolic syndrome in testicular cancer survivors
• Breast cancer in AYA Hodgkin lymphoma survivors treated with chest radiation
• Infertility and gonadal dysfunction in AYA cancer survivors
• AYA allogeneic stem cell transplant recipients and multiple morbidities
Late Effects Following AYA Cancer

Cardiovascular Disease

- Lymphomas: 20%
- Invasive Skin: 15% (76% Melanoma)
- Male Genital System: 11% (99% Testis Cancer)
- Female Genital System: 9%
- Endocrine System**: 11% (96% Thyroid)
- Central Nervous System Cancers: 6%
- Leukemias: 6%
- Breast: 5%
- Digestive System: 4%
- Bones & Joints: 3%
- Oral Cavity & Pharynx: 2%
- Urinary System: 2%
- Respiratory System: 2%

Other: 1%
Late Effects Following AYA Cancer

Cardiovascular Disease in Testicular Cancer Survivors

- Norway, 1962-1997  
  Fossa et al. British J Cancer 2004  
  - Circulatory-deaths: **SMR = 1.2** (95% CI, 1.0-1.5)  
  - No difference in SMR or AER after intro of cisplatin

- Netherlands, 1965-1995  
  - CVD in platinum w/o radiation: **HR = 1.7** (1.2-2.4)  
  - Median survival post CVD = 4.7 yrs

- United Kingdom, 1982-1992  
  - CVD **RR = 2.6** (1.2-5.8) in chemo only vs surgery

- Norway, 1980-1994  
  Haugnes HS et al. J Cancer Surviv 2008  
  - Cisplatin > 850 mg with **OR = 3.4** (1.3-8.7) compared with surgery only
Late Effects Following AYA Cancer

Incidence of CVD Risk Factors Following Therapy

- Hypertension
- Hypercholesterolemia
- BMI > 27.8

- 25% with metabolic syndrome (MetS)
- 2.2-fold increased risk of MetS vs health controls
- Survivors with MetS with increased carotid IMT
- MetS associated with decreased testosterone level

Late Effects Following AYA Cancer

Development of Cardiovascular Disease

Late Effects Following AYA Cancer

Development of Cardiovascular Disease

Cisplatin
Bleomycin

Hypogonadism

16% of all incident cancers are an SPN
Breast Cancer Following Chest Radiation

By age 50
- HL: 35%
- BRCA1: 31%
- SEER: 4%

- Hodgkin lymphoma
- BRCA1 Carrier
- SEER Benchmark
Breast Cancer Risk, Ovarian Radiation


with ovarian radiation, risk decreases
Late Effects Following AYA Cancer

**Age at Radiation Exposure**

32,591 HL patients in 16 population-based registries

<table>
<thead>
<tr>
<th>Age at HL</th>
<th>RR</th>
<th>AER</th>
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<td>&lt; 21 yrs</td>
<td>14.2</td>
<td>18.6</td>
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<td>21-30</td>
<td>3.7</td>
<td>12.9</td>
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<tr>
<td>31-40</td>
<td>1.2</td>
<td>2.6</td>
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Characteristics of Breast Cancer

• Median age is young
• Interval from radiation to breast cancer is often short (10-20 yrs)
• Upper outer quadrant (inner quadrant)
• Updated CCSS data
  • 26% bilateral: 12% synchronous, 14% asynchronous
  • 55% w/ bilateral mastectomy at time of 1st diagnosis
Late Effects Following AYA Cancer

Outcomes of Breast Cancer

• 5-yr survival strongly associated with stage at diagnosis (women with early stage disease have good outcomes)

• Limitations in therapy
  • Further radiation?
  • Anthracyclines (doxorubicin)
1. Incidence and excess risk of breast cancer following chest radiation

2. Clinical characteristics and the outcomes following breast cancer

3. Harms and benefits associated with breast cancer surveillance

Late Effects Following AYA Cancer

**Radiation-Gene Interactions**

- Identified two variants at chromosome 6q21 associated with radiation-induced SMN in Hodgkin’s lymphoma survivors


- Identified a genetic profile for breast cancer following Hodgkin’s Lymphoma

Late Effects Following AYA Cancer

Breast Cancer Risk Prediction Model

**Treatment-related factors**
- RT dose/volume, chest
- RT dose fractionation
- RT, pelvis or abdomen
- Alkylating agent
- Age at exposure
- Interval from primary cancer diagnosis
- Primary cancer diagnosis

**Gail model predictors**
- Age
- Age at menarche
- Age at first live-birth
- # of first degree relatives with breast cancer
- # previous breast bx
- Biopsy with atypical hyperplasia

**Other potential risk factors**
- Age at menopause
- Years of intact ovarian function after radiation
- Oral contraceptive/ HRT
- BMI at breast cancer diagnosis
Late Effects Following AYA Cancer

Breast Cancer Risk Prediction Model

R01CA136783

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Late Effects Following AYA Cancer

Infertility

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- Invasive Skin*: 15%
  *76% Melanoma
- Male Genital System+: 11%
  *99% Testis Cancer
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- Digestive System: 4%
- Soft Tissue: 3%
- Bones & Joints: 3%
- Oral Cavity & Pharynx: 2%
- Urinary System: 2%
- Respiratory System: 2%
- Other: 1%
Acute Ovarian Failure in AYA Cancer Survivors

Infertility in Female AYA Cancer Survivors

At age 35 – 40%

Late Effects Following AYA Cancer

Early Menopause in AYA Cancer Survivors

Factors Associated with Infertility

Females
- Alkylating agents
- Radiation to the ovaries
- Stem cell transplant

Males
- Alkylating agents
- Radiation to the testes
- Stem cell transplant
Late Effects Following AYA Cancer

Multiple Chronic Conditions and AYA Cancer Survivors

- Bones & Joints: 3%
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*Memorial Sloan-Kettering Cancer Center*
Late Effects Following AYA Cancer

Multiple Chronic Conditions post Allogeneic SCT

Prior therapy

Preconditioning chemotherapy

TBI

GVHD

• Gonadal dysfunction
• SMN
• Endocrinopathies
• Osteoporosis
• Osteonecrosis
• Renal insufficiency
• Pulmonary complications
• Cataracts
• Gait and balance disturbances
• Hypertension
• Metabolic obesity (thin/fat)
• Insulin resistance / diabetes
• Dyslipidemia / fatty liver
• Coronary artery disease
Late Effects Following AYA Cancer

Maximizing the Cure – Minimizing the Cost
<table>
<thead>
<tr>
<th>Lorene (mom)</th>
<th>Lauren</th>
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<tbody>
<tr>
<td>HL, Stage IIIB</td>
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<tr>
<td>1975, Age 20</td>
<td>2002, Age 15</td>
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<tr>
<td>46 Gy Mantle</td>
<td>21 Gy IFRT</td>
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<tr>
<td>36 Gy Para-aortic</td>
<td>21 Gy Para-aortic</td>
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<td>BEACOPP</td>
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<td>Thyroid CA, Age 51</td>
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<td>2-v CABG, Age 53</td>
<td>Allo BMT</td>
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<td>Asplenic</td>
<td>Ovarian failure</td>
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<td>Diabetes</td>
<td>AVN, hips</td>
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<td>Fatty liver</td>
<td>Hypothyroidism</td>
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<td>Dyslipidemia</td>
<td>Insulin resistance</td>
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<td>Iron overload</td>
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Lorene (mom)  Lauren

HL, Stage IIIB  HL, Stage IIIB
1975, Age 20  2002, Age 15
46 Gy Mantle  21 Gy IFRT
36 Gy Para-aortic  21 Gy Para-aortic
BEACOPP

The remains an urgency to understand, predict, prevent and manage late effects in AYA cancer survivors.

Restrictive lung dis  Dyslipidemia
Musculoskeletal  Iron overload
Future Directions

- Better estimates across cancers and exposures
- Mechanisms
- Gene*Exposure*Lifestyles
- Risk prediction / risk stratification
- Interventions