Cancer Prevention & Control in Adolescent & Young Adult Survivors

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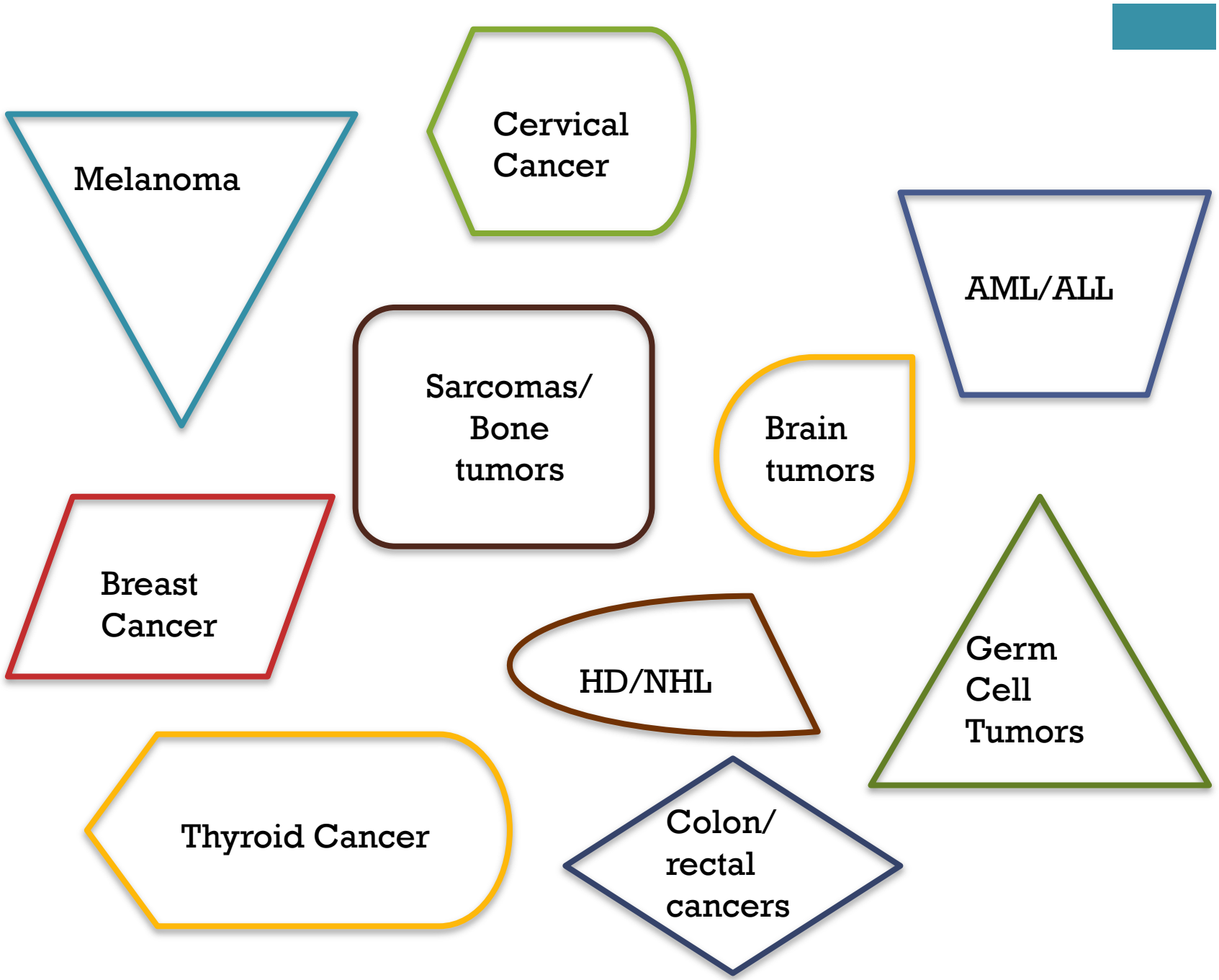
Overview

- Why focus on surveillance for cancer recurrence and secondary cancers in AYA survivors?
- What exposures and other factors put them at risk for another episode of cancer?
- Monitoring, screening, and prevention strategies for the AYA survivor population—clinical and policy implications.

General Considerations Regarding Cancer Surveillance in AYAs

- Heterogeneity of cancer types and prognoses
- Broad age range: 15 to 39 years
- Great potential for life years to save, especially if recurrence or secondary cancers detected early
- A high-risk population by definition—must consider the value of prevention!


Melanoma
Cervical Cancer
AML/ALL
Sarcomas/ Bone tumors
Brain tumors
Breast Cancer
HD/NHL
Germ Cell Tumors
Thyroid Cancer
Colon/ rectal cancers

Heterogeneity of cancer types—recurrence surveillance strategies

- Rapid vs. slow growing cancers
  - Implications for frequency/intensity of monitoring & type of tests
- Paucity of evidence-based guidelines, but disease-specific strategies exist
  - e.g., tumor markers and imaging in testes cancer survivors
- Most relevant for diseases that can be cured at the time of recurrence

Divergent patterns of recurrence

- Local vs. metastatic, for solid tumors and sarcomas
  - Careful clinical examinations and scans; some tumor markers
- Hematological malignancies are particularly common in this population; pattern of widespread hematogenous recurrences
  - Focus on imaging, blood markers and bone marrow examinations

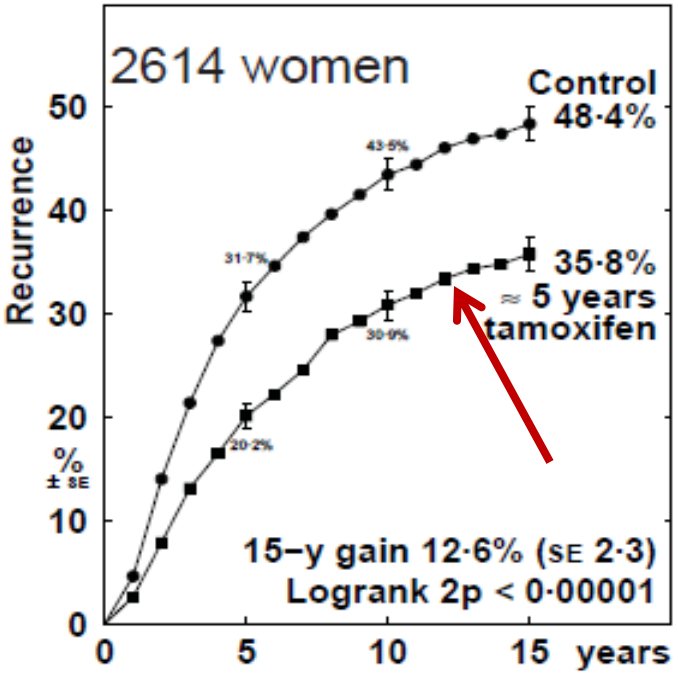
AYAs have few competing causes of death

- Recurrent cancer is the most significant threat…..
- Successful treatment varies substantially, with respect to cure
  - Highly successful: germ cell tumors, Hodgkin lymphoma, thyroid, high grade NHL

BCa Recurrence & Mortality in Women <45, ER+

p 5: 15-year outcomes, age at entry <45 years, ER+ disease: ~5 years tam.

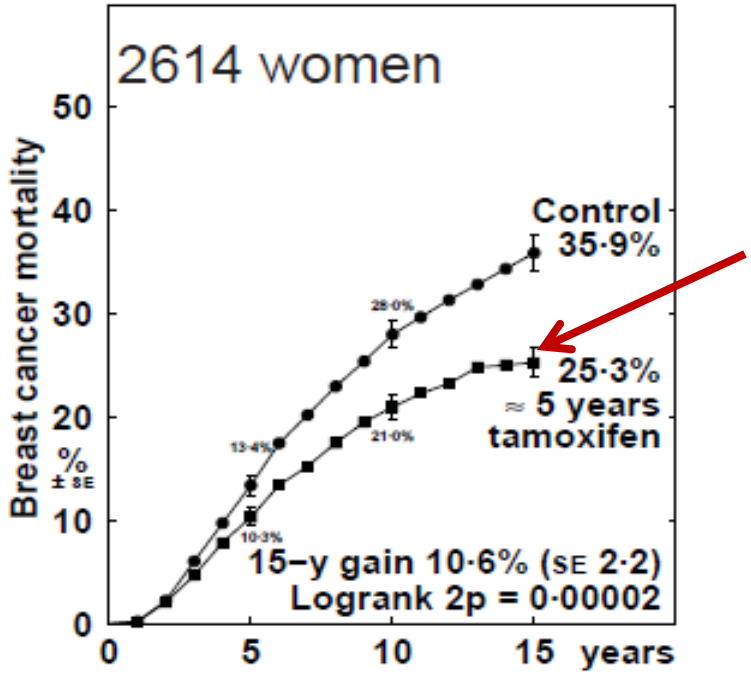
≈ 5 years tamoxifen vs. Not
RECURRENCE
Entry age < 45, ER+



Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Years 10 – 14	Year 15+
Tamoxifen	4·57 (259 / 5668)	3·03 (114 / 3760)	1·60 (30 / 1870)	0·54 (3 / 559)
Control	7·57 (407 / 5373)	3·62 (126 / 3299)	1·90 (30 / 1575)	1·99 (9 / 452)
Rate ratio, from (O–E) / V	0·58 SE 0·06 −82·5 / 152·9	0·75 SE 0·12 −15·9 / 56·6	0·82 SE 0·24 −2·9 / 14·5	0·27 SE 0·33 −3·7 / 2·9

≈ 5 years tamoxifen vs. Not
BREAST CANCER MORTALITY
Entry age < 45, ER+



Death rates (% / year: total rate − rate in women without recurrence) & logrank analyses

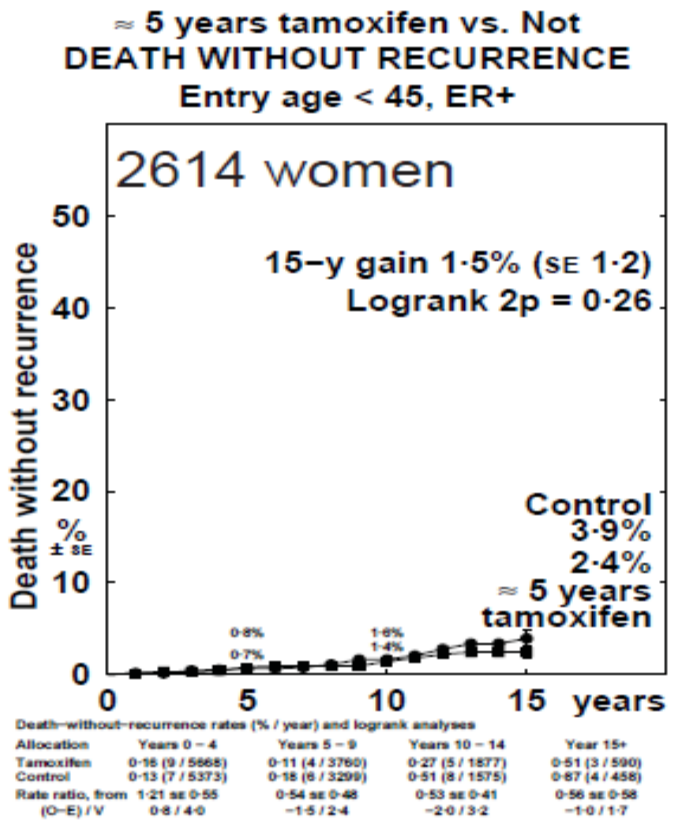
Allocation	Years 0 – 4	Years 5 – 9	Years 10 – 14	Year 15+
Tamoxifen	2·15 SE 0·19	2·63 SE 0·25	1·29 SE 0·24	0·98 SE 0·37
Control	2·60 SE 0·21	3·74 SE 0·30	2·39 SE 0·35	0·65 SE 0·38
Rate ratio, from (O–E) / V	0·76 SE 0·10 −19·9 / 71·9	0·69 SE 0·10 −23·7 / 63·8	0·56 SE 0·18 −10·5 / 18·1	1·07 SE 0·61 0·2 / 2·8

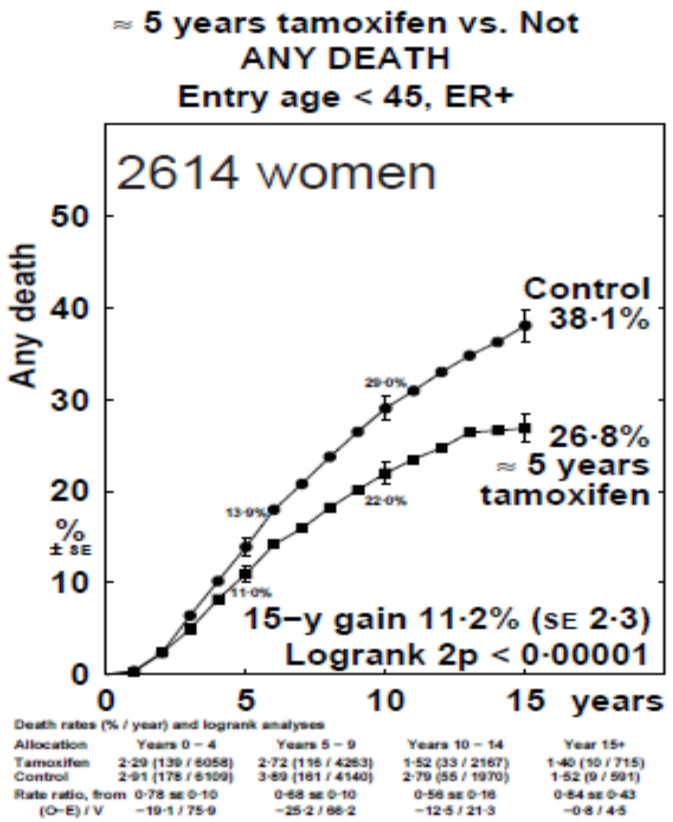
*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

Lancet, 2011

Overall Mortality, women <45, ER+

Most deaths are from Breast Ca





*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

Lancet, 2011

What Do We Know About Surveillance Testing after Breast Cancer?

- Breast cancer adjuvant clinical trials abandoned routine monitoring with chest films, radionuclide liver and bone scans in the 1990s---recurrence detection rare before clinical symptoms.

- Two randomized trials conducted in the 1990's did not find a difference in survival outcomes for women who had routine clinical office visits and mammograms compared to women who had more intensive monitoring with blood work, chest films, scans and ultrasounds.

ASCO Guidelines 2006, 2013
Rojas et al. Cochrane Review 2005

What Do we Know About Surveillance Testing after Breast Cancer?

- No RCT data to support use of tumor markers for breast cancer monitoring (CEA, CA 15-3, CA 27.29) for effect on survival outcome, i.e. that detection of recurrence earlier makes a difference.

- The rate of false negative or false positive findings for these markers is not known.

- Normal or abnormal tumor marker results can contribute to false reassurance and/or increased anxiety for patients, as well as unnecessary medical evaluations.

What about Imaging Tests?

Chest and abdominal CT scans or whole-body PET scans have not been evaluated as surveillance strategies for follow-up of early-stage breast cancer.

With the low prevalence of distant recurrence in early-stage breast cancer, and the high risk of false positive and incidental findings, ***there is no evidence to support the use of routine imaging tests.***

What Surveillance is Recommended after Curative Treatment of Breast Cancer?

- ***Patients are at high risk for an ipsilateral local recurrence, and/or a new primary in the conserved breast or contralateral breast.***

- Clinical breast examination and annual mammographic screening play an important role in detecting local recurrence and new primaries.

- Breast MRI screening is only recommended in very high-risk women, such as those with *BRCA1/2* mutations.

- Need to encourage adherence to mammography screening in breast cancer survivors.

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ASCO SPECIAL ARTICLE

American Society of Clinical Oncology Identifies Five Key Opportunities to Improve Care and Reduce Costs: The Top Five List for Oncology

Lowell E. Schnipper, Thomas J. Smith, Derek Raghavan, Douglas W. Blayney, Patricia A. Ganz, Therese Marie Mulvey, and Dana S. Wollins

Choosing Wisely®

An initiative of the ABIM Foundation

4. Don't perform surveillance testing (biomarkers) or imaging (PET, CT and radionuclide bone scans) for asymptomatic individuals who have been treated for breast cancer with curative intent.[12,20-23]

- Surveillance testing with serum tumor markers or imaging has been shown to have clinical value for certain cancers (e.g. colorectal). However, for breast cancer that has been treated with curative intent, several studies have shown there is no benefit from routine imaging or serial measurement of serum tumor markers in asymptomatic patients.
- False-positive tests can lead to harm through unnecessary invasive procedures, over-treatment, unnecessary radiation exposure, and misdiagnosis.

Sources:

- Locker GY, Hamilton S, Harris J, et al: ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. J Clin Oncol 24:5313-5327, 2006.
- Desch CE, Benson AB 3rd, Somerfield MR, et al: Colorectal cancer surveillance: 2005 update of an American Society of Clinical Oncology practice guideline. J Clin Oncol 23:8512-8519, 2005.
- Carlson RW, Allred DC, Anderson BO, et al: Breast cancer. J Natl Compr Canc Netw 7:122-192, 2009.
- Khatcheressian JL, Wolff AC, Smith TJ, et al: American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guideline in the adjuvant setting. J Clin Oncol 24:5091-5097, 2006.
- Harris L, Fritsche H, Mennel R, et al: American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. J Clin Oncol 25:5287-5312, 2007.

What factors increase the likelihood of second cancers in AYAs?

- Hereditary predisposition genes
- Treatment exposures
  - Radiation
  - Chemotherapy
- Risks from diagnostic imaging procedures?

Hereditary Predisposition for Cancer

- Li-Fraumeni Syndrome (p53 mutations): childhood leukemia, sarcoma, brain and breast cancers, adrenal cortical carcinomas
- HNPCC/Lynch Syndrome: colon cancer, uterine cancer, ovarian cancer, urinary tract cancer
- Familial Adenomatous Polyposis (FAP) syndrome: colon cancer
- *BRCA1/2:* breast cancer, ovarian cancer, melanoma, pancreatic and prostate cancers
- **ALL ASSOCIATED WITH EARLY ONSET CANCERS IN AYA POPULATION!!!**

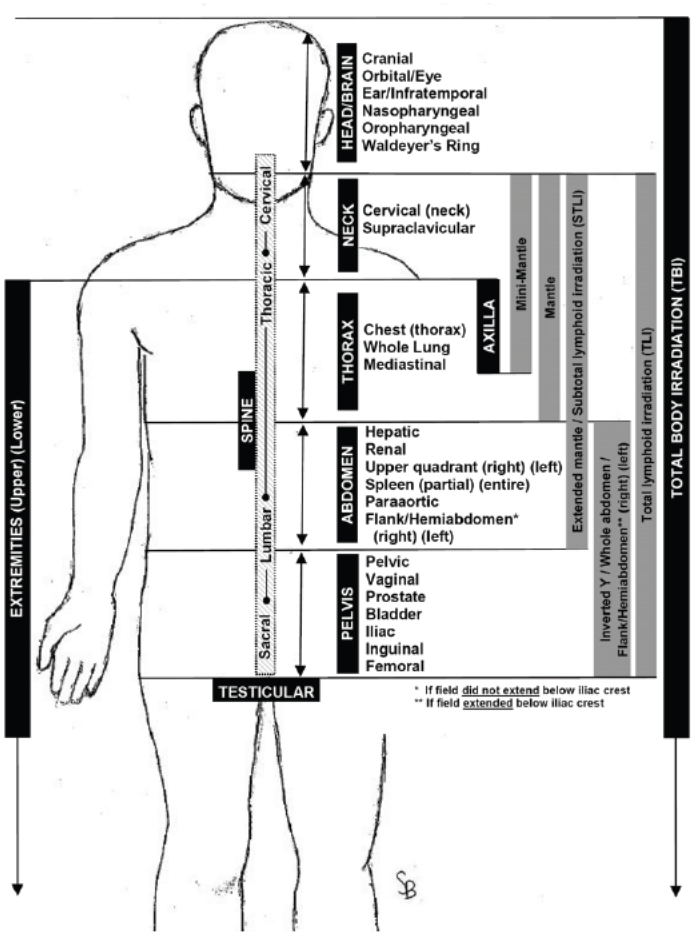
Recognizing these syndromes is critical for secondary prevention!

There are important opportunities for risk reducing surgery and intensive surveillance in this setting.

Treatment Exposures
Radiation

- One of the most important risk factors for secondary cancers
- Often 10-20 years after initial exposure
- Affected areas in radiation field; monitoring and screening directed to these areas
  - Examples: breast cancer after chest RT; thyroid cancer after neck RT; GI tract after abdominal RT; basal cell ca in skin fields
  - GI malignancies after radioactive iodine for thyroid cancer

Radiation Treatment Exposure History is Critical



Radiation Fields by Anatomic Region

- Need to have dose, field, age of exposure
  - e.g., breast tissue is most at risk between 10-30 yrs
- Type of radiation may also be a factor
  - Total body irradiation
  - Radio-immunotherapy

http://www.survivorshipguidelines.org/ COG long term follow-up guidelines

RADIATION

POTENTIAL IMPACT TO GI/HEPATIC SYSTEM (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
78	≥ 30 Gy to: **Spine (thoracic, lumbar, sacral, whole)** **Extended Mantle** **Hepatic** **Renal** **Upper quadrant (right, left)** **Spleen (partial, entire)** **Paraaortic** **Flank/Hemiabdomen (right, left)** **Whole abdomen** **Inverted Y** **Pelvic** **Vaginal** **Prostate** **Bladder** **Iliac** **Inguinal** **Femoral** **TLI** **STLI** **TBI*** **Info Link:** ***Important:** Reports of colorectal cancer in cohorts of long-term survivors suggest that radiation likely increases risk; however, the risk related to TBI alone has not been established. Therefore, monitoring of patients who received TBI without additional radiation potentially impacting the colon/rectum should be determined on an individual basis. (See Info Link in next column)	**Colorectal cancer** **Info Link:** Reports of colorectal cancer in cohorts of long-term survivors suggest that radiation likely increases risk, but the median age of onset is not as well established as that of secondary breast cancer following chest radiation. The expert panel agreed that early onset of screening is likely beneficial, and that a prudent course would be to initiate screening for colorectal cancer for those at highest risk (abdominal, pelvic, and/or spinal radiation ≥ 30 Gy) at age 35, or 10 years post radiation, whichever occurs last. Surveillance should be done via colonoscopy as per recommendations for populations at highest risk, with information from the first colonoscopy informing the frequency of follow-up testing.	**Host Factors** Current age ≥ 50 years **Treatment Factors** Higher radiation dose to bowel Higher daily dose fraction Combined with chemotherapy (especially alkylators) **Medical Conditions** Obesity **Health Behaviors** High fat/low fiber diet	**Host Factors** Personal history of ulcerative colitis, gastrointestinal malignancy, adenomatous polyps, or hepatoblastoma Familial polyposis Family history of colorectal cancer or polyps in first degree relative	**SCREENING** **Colonoscopy** Every 5 years [minimum] beginning at 10 years after radiation or at age 35 years [whichever occurs last]; more frequently if indicated based on colonoscopy results; Per the ACS, begin screening earlier for the following high-risk groups - HNPCC: at puberty; FAP: at age 21 years; IBD: 8 years after diagnosis of IBD; Information from the first colonoscopy will inform frequency of follow-up testing.	**Health Links** **Colorectal Cancer** **Considerations for Further Testing and Intervention** Surgical and/or oncology consultation as needed. **SYSTEM = SMN** **SCORE = 2A**

- This section is only applicable to patients who:
  1) Received radiation to any of the specified fields at ≥ 30 Gy
  OR
  2) Received a combination of radiation to any of the specified fields **plus** relevant spinal radiation **and/or** TBI, the sum of which is ≥ 30 Gy
- See dose calculation rules on page 48 for patients who received: (a) radiation to more than one of the specified fields, or (b) more than one planned course of treatment to the same field.
- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

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JOURNAL OF CLINICAL ONCOLOGY

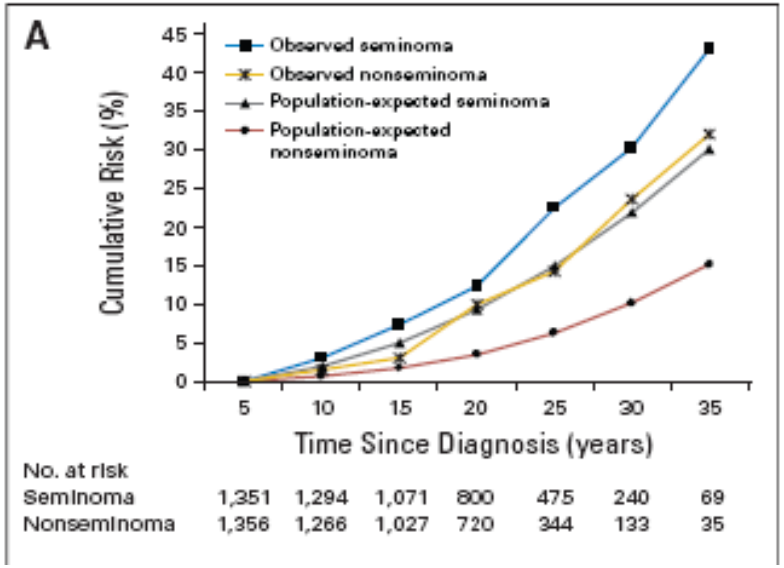
ORIGINAL REPORT

Treatment-Specific Risks of Second Malignancies and Cardiovascular Disease in 5-Year Survivors of Testicular Cancer

Alexandra W. van den Belt-Dusebout, Ronald de Wit, Jourik A. Gietema, Simon Horenblas, Marieke W.J. Louwman, Jacques G. Ribot, Harald J. Hoekstra, Gabey M. Ouwens, Berthe M.P. Aleman, and Flora E. van Leeuwen

	10 yrs since dx	20 yrs since dx	30 yrs since dx	Difference Cum Incidence compared to surgery alone at 20 yrs
All treatments combined	**2.2**	**8.2**	**19.1**	**---**
Surgery only	**0.7**	**3.9**	**---**	**---**
Sub diaphragmatic RT	**2.3**	**8.3**	**22.0**	**4.4**
Sub diaphragmatic & mediastinal RT only	**2.5**	**10.0**	**---**	**6.1**
CT, no RT	**3.1**	**8.0**	**---**	**4.1**
RT & CT	**4.3**	**13.9**	**---**	**10.0**

Cumulative Incidence of SMN according to treatments received.



Seminoma patients, who predominantly received RT, have greatest cumulative risk for SMN.

Treatment Exposures
Chemotherapy

- Major risks are second hematological malignancies: AML, MDS, non-Hodgkin lymphoma
- Other malignancies:
  - Cyclophosphamide, Ifosfamide: bladder cancer

Risks from diagnostic imaging?

C. Daly et al., Imaging in Young Adult Long-term Survivors, ASCO Quality of Care Symposium 2012

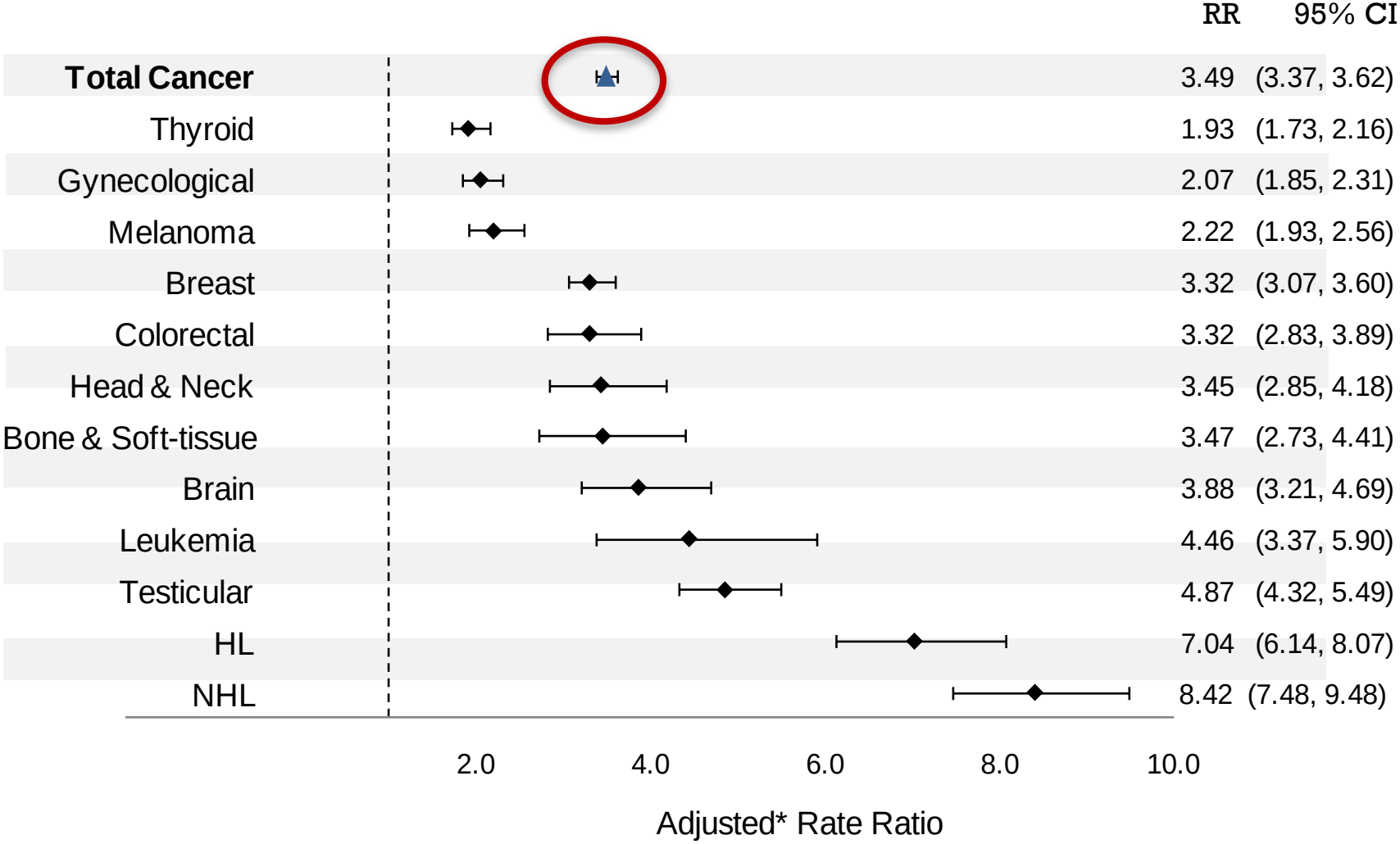
- Population-based cohort of 20-44 yo at Dx; young adult survivors from Ontario, Canada
- More than 5 yr disease-free without recurrence
- Matched 1:5 to population controls from general Ontario population
- Imaging studies identified from claims
- Dose estimates for CT scans
- 20,911 survivors, median follow-up 14.2 yrs
- Observational study with case-control design

J Clin Oncol 30, 2012 (suppl 34; abstr 69)

Mean No. of Imaging Studies in Years 5-15 after diagnosis

Malignancy Type	Imaging Studies Per Person Year			
	CT		Ultrasound	
	Survivor	Control	Survivor	Controls
Total Cancer	0.30	0.08	0.65	0.47
Breast	0.32	0.10	0.85	0.59
Gynecological	0.21	0.09	0.71	0.58
Thyroid	0.15	0.08	0.87	0.57
Melanoma	0.17	0.07	0.50	0.43
Hodgkin Lymphoma	0.45	0.07	0.49	0.37
Non-Hodgkin Lymphoma	0.73	0.09	0.56	0.41

Rate Ratios of CT scans, Survivors to Controls



J Clin Oncol 30, 2012 (suppl 34; abstr 69)

Cumulative Dose

- 5-year recurrence-free survivors received mean dose = 24 mSv
  - ~1,300 chest x-rays
- Linear regression showed that survivors received a 4.6-fold higher dose (95% CI: 4.39, 4.81) than controls

J Clin Oncol 30, 2012 (suppl 34; abstr 69)

Questions raised by this study

- Why are disease-free, AYA, long term survivors receiving so many imaging studies?
- How can we reduce the number of unnecessary procedures and increased radiation exposure?
- Will explicit survivorship care plans make a difference?
- How effective will guidelines be in reducing unnecessary testing?

Monitoring, screening, and prevention strategies for the AYA survivor population

- Who is taking charge?
  - Need for coordination of care; care planning; avoidance of unnecessary imaging and radiation exposure
- How do we educate and empower AYA survivors?
  - Need for evidence-based guidelines
- How do we improve the uptake of prevention strategies?
  - Education of primary care providers
  - Identification of high risk groups and provision of counseling

Clinical and Policy Implications (1)

- **Urgently needed**:
  - Development of an evidence-base for recurrence surveillance, e.g. use of clinical trial data to support or refute intensive surveillance across most common AYA cancer sites
  - Rational use of imaging tests with limitation of radiation exposure; focus on frequency of testing as well as number of years of follow-up
  - Guidance statements on recurrence surveillance for the most common AYA cancers

Clinical and Policy Implications (2)

- **Standardized approaches to screening for second malignancies are needed**
  - Consider exposure based approach, using COG guidelines as a model
  - Recognize and test for genetic predisposition
  - Focus on risk for multiple organ-based primaries (e.g. breast, GI tract)
  - Actively pursue risk reduction strategies, including chemoprevention and surgical prophylaxis

Clinical and Policy Implications (3)

- **Implement behavioral and lifestyle risk factor reduction strategies**
  - Second cancer prevention mitigation through avoidance of additional environmental exposures e.g., tobacco, alcohol, solar exposure
  - SERMs after chest radiation exposure in women
  - Management of energy balance: reduce obesity and increase physical activity
  - Need to collaborate with primary care providers
  - Managing a vulnerable population!