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Adverse effects of chemotherapy and radiotherapy

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ESMO Preceptorship on Adolescents and Young adults with cancer
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Adverse effects of treatment in AYA

- Defined as the effects of antineoplastic treatment (chemotherapy and radiotherapy) occurring during and after completion of treatment.
- A huge emerging issue as approximately three quarters of adolescents achieve long-term survival.
- Caused by the cancer, and the delivery of intense multimodality treatment to AYA.
- They can affect every aspect of patient's health, quality of life and psychological well being.

Woodward et al 2011

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Adverse effects by Surgery

- Disabling surgery is a cause of late effects interfering with patient's quality of life.
  - Mutilating surgery in the limbs, head and neck or torso causes disfigurement with resultant functional disabilities
  - This may not always be necessary, such as limb-sparing surgery with modern endoprostheses has enabled preservation of functional limbs

Hollis R et al. Lancet Oncology 2001

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Effects of Chemotherapy

Table 2 Common late effects of cytotoxic drugs

Drug	Late effect	Cumulative dose (mg/m^2)[a]
Doxorubicin	Cardiomyopathy	550
Cyclophosphamide	Cardiomyopathy	>1550 daily for 3–4 days
	Pulmonary toxicity	6500 in a few days
Mitoxantrone	Cardiomyopathy	160
Mitomycin	Cardiomyopathy	70 as monotherapy, 30 in combination with anthracycline
Paclitaxel	Neurotoxicity	1000
Bleomycin	Pulmonary fibrosis	360 units
	Skin pigmentation	270 units
Nitrosoureas	Pulmonary fibrosis	700 for Carmustine
	Encephalopathy	
Busulphan	Pulmonary toxicity	500
	Encephalopathy	16 mg/KBΣ in a few days
Methotrexate	Pulmonary fibrosis	
	Hepatic fibrosis	Unknown
Vincristine	Neurotoxicity	16 mg within 4 months
Etoposide	Myelodysplasia	2000
Ifosfamide	Encephalopathy	Unknown
	Pulmonary toxicity	16 g/m^2 within a few days
	Cardiotoxicity	20 g/m^2
Cisplatin	Neurotoxicity	400–600
	Renal toxicity	

[a] Doses in mg/m^2 unless stated otherwise.

Pentheroudakis G and Pavlidis N Cancer Treat Rev 2007

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Effects of Chemo: Alkylating agents and heavy metals

- Mechlorethamine, melphalan, nitrosoureas, busulfan, chlorambucil
- Cyclophosphamide, ifosfamide, platinum analogs

- ✓ Mutagenic and carcinogenic (secondary AML)
- ✓ Associated with infertility (amenorrhea, azoospermia)
- ✓ Lung injury (High dose busulphan)
- ✓ Renal injury (with acquired Fanconi's syndrome)
- ✓ Neurotoxicity, ototoxicity (irreversible if not diagnosed early)

Pentheroudakis G and Pavlidis N Cancer Treat Rev 2007

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Effects of chemo: Anthracyclines

Adriamycin, epirubicin, daunorubicin, idarubicin

- Late cardiotoxicity (free-radical damage of cellular nucleic acids, lipids and proteins):
  - Myocardial cell injury
  - Increased afterload
  - Left ventricular systolic dysfunction
  - Congestive heart failure
- The cumulative anthracycline dose seems to be the most important determinant of the incidence of cardiotoxicity
- Increased risk by chest irradiation, smoking, hypertension, diabetes, dyslipidemia, cardiotoxic agents

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Effects of chemo: cardiomyopathy

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Pentheroudakis G and Pavlidis N Cancer Treat Rev 2007

Risk Factor	Anthracycline	Trastuzumab
Cumulative dose >550 mg/m^2	Yes	
Age	Yes (≥64 years)	Yes (≥50 years)
Hypertension	Yes	Yes
Previous heart disease	Yes	
Previous radiation therapy	Yes	
Concurrent chemotherapy	Yes	Yes[a]
Hematopoietic cell transplantation	Yes	
Host susceptibility[5]	Yes	
Obesity (BMI ≥30)		Yes
Diabetes	Yes	No[b]

Blank cells in the table denote characteristics that are not risk factors or are inconclusive.
BMI, body mass index.
[a]Especially with concurrent anthracycline use.
[b]Small study suggests association in elderly women with diabetes.[6]

Risk of Cardiotoxicity Associated With Chemotherapy

Pentheroudakis G and Pavlidis N Cancer Treat Rev 2007

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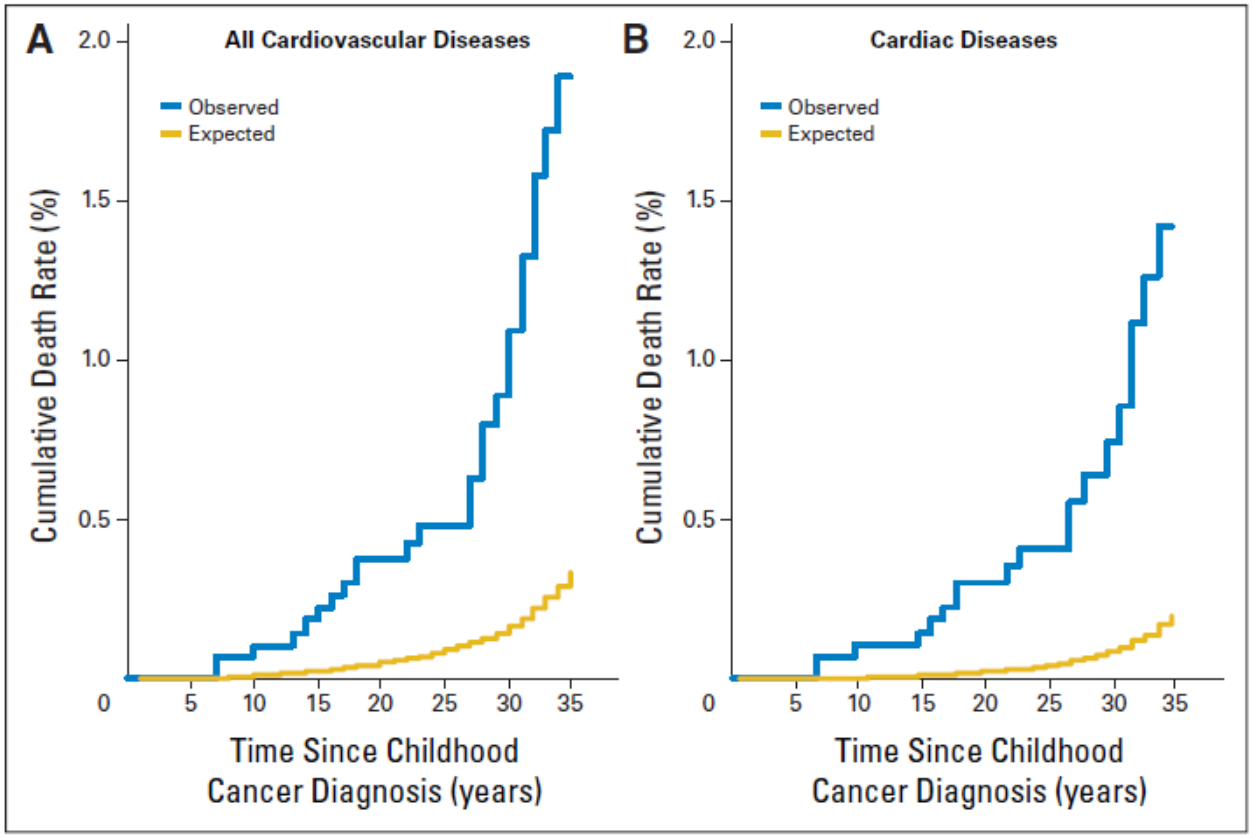
Mortality due to cardiovascular event x6 after childhood cancer

2nd cause of late toxicity



Cumulative rate of death

4122 survivors after 5 y

Treated between 1942 - 1986

Before age 15

France and U.K.

Tukenova, JCO, 2010

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Main cardiotoxicities after cancer treatment in childhood and adolescence

- Cumulative rates at age 45 y
  - Ischemia 5.3% vs. 0.9%
  - Clinical cardiac failure 4.8% vs. 0.3%
  - Valvular disease 1.5% vs. 0.1%
  - Arythmia 1.3% vs. 0.4%

10.724 survivors more than 5 y after cancer treatment before 21 y in USA and Canada between 1970 and 1986 vs. 3159 brothers and sisters

Armstrong, JCO, 2013

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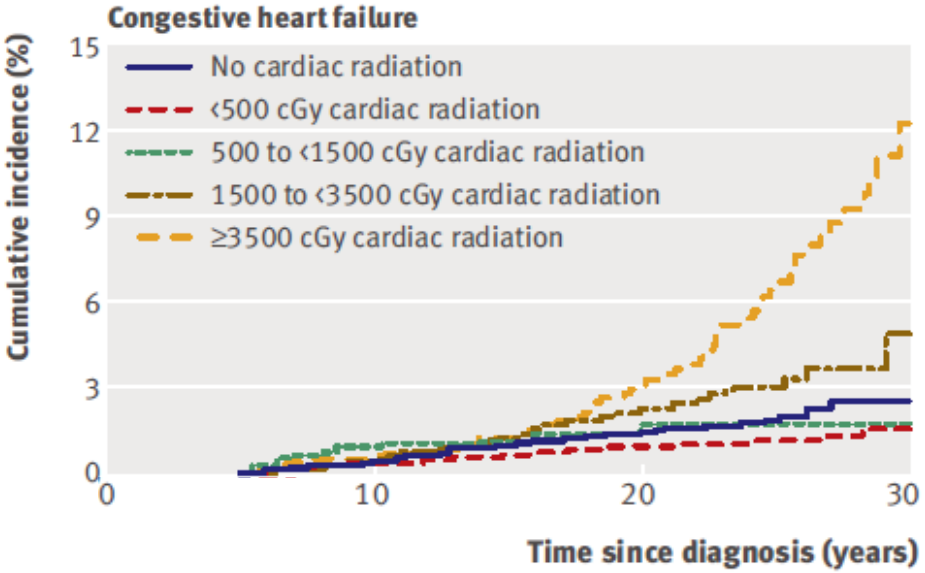
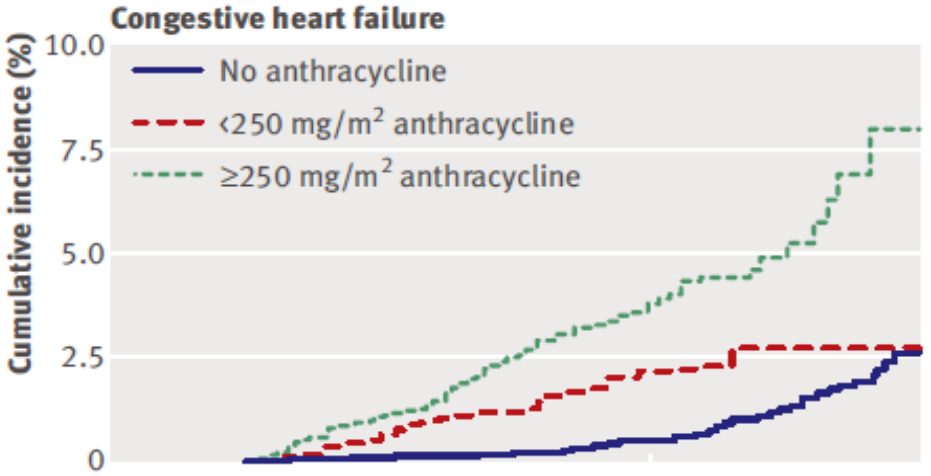
Congestive heart failure
Role of treatment





Mulrooney, BMJ, 2009

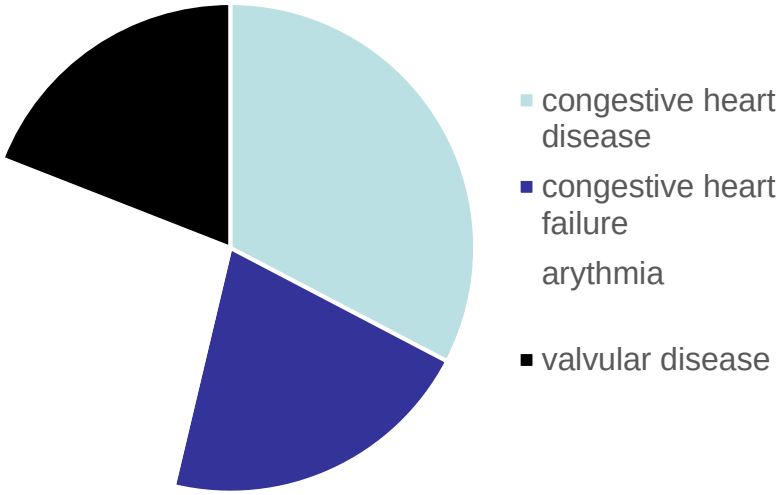
Cardiovascular disease after treatment for Hodgkin's lymphoma: an analysis of nine collaborative EORTC-LYSA trials

6039 patients treated for Hodgkin in LYSA/EORTC trials between 1964 and 2004

Median age : **30.y** **Median follow-up 9 y**

Life situation questionnaire

1238 cardiac events in 703 patients



Maralda , Lancet Oncol 2017

Van Nimwegen, JCO, 2015

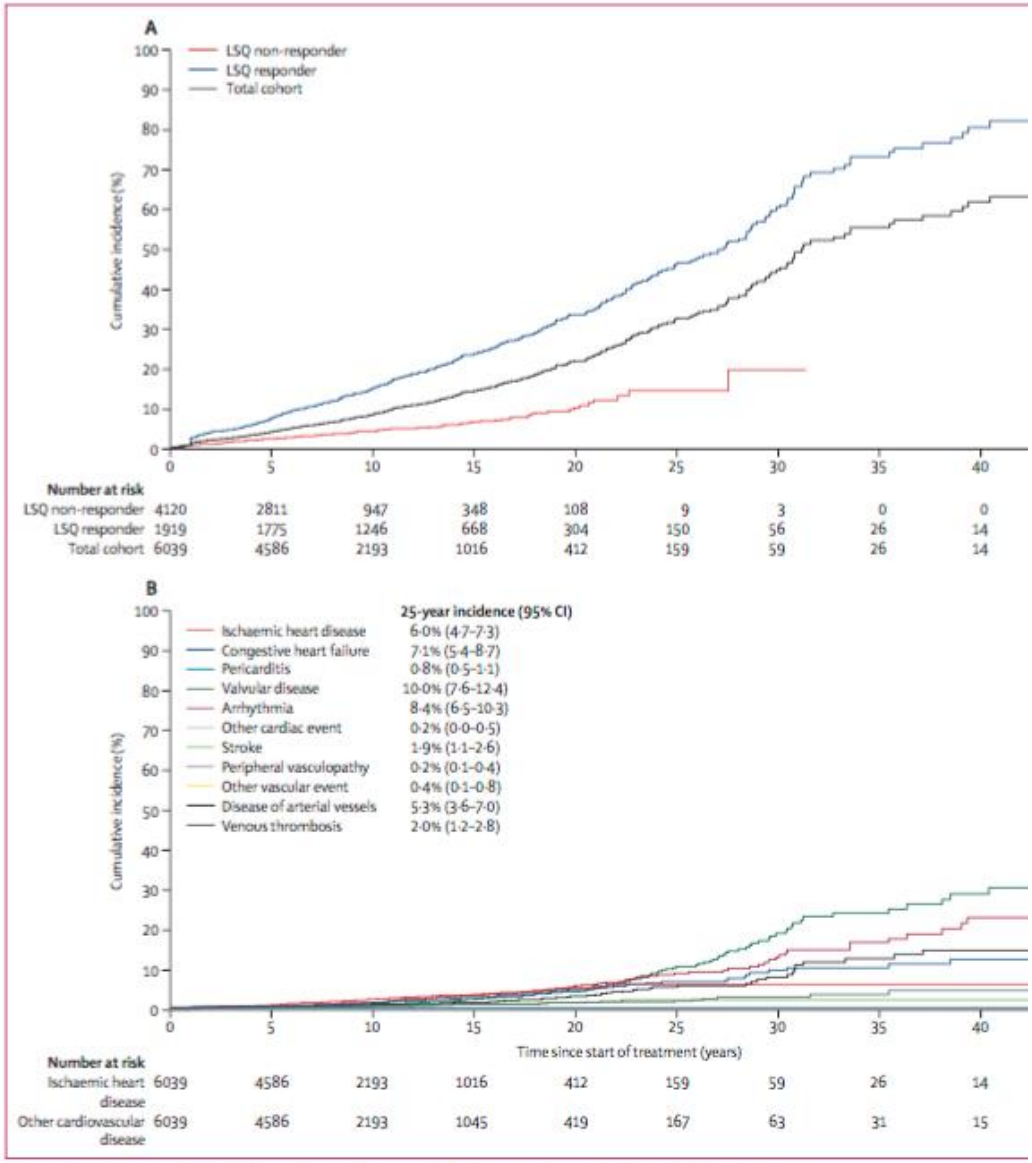


Figure 2: Cumulative incidence of first cardiovascular disease by LSQ-responder status and by individual diagnoses

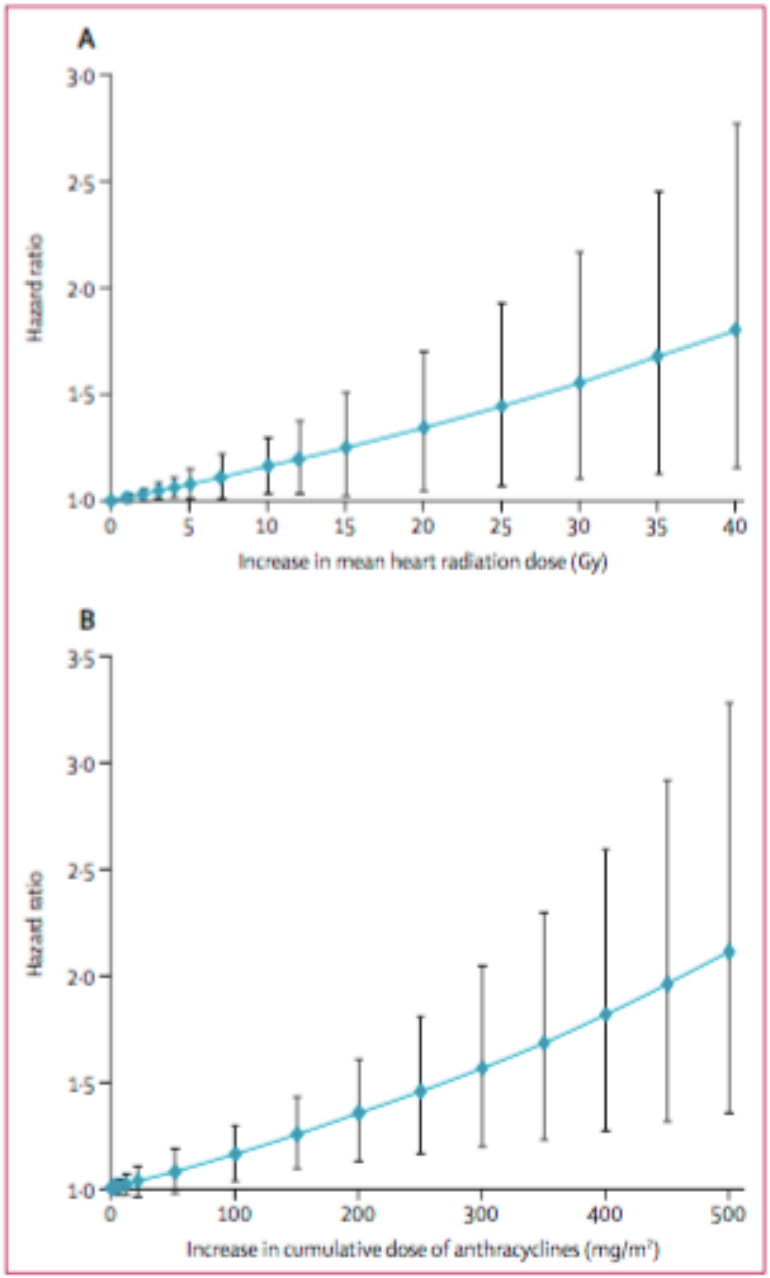


Figure 3: Estimated hazard ratio for cardiovascular events according to (A) mean heart radiation dose and (B) cumulative dose of anthracyclines in doxorubicin-equivalents

Management of treatment-induced cardiotoxicity

- Pretreatment assessment,
- Risk reduction,
- Surveillance and early treatment of cardiotoxicity during therapy,
- Post-treatment surveillance

Surveillance for cardiotoxicity

- For whom?

  For patients treated with anthracyclins or cardiac irradiation

- How?

  Cardiac Tripplex U/S

		Irradiation de l'aire cardiaque (dose max)	
		< 20 Gy	≥ 20 Gy
Dose cumulée d'anthracyclines	< 300 mg/m²	/ 5 ans	/ 3 ans
	≥ 300 mg/m²	/ 3 ans	/ an

Role of early treatment with Enalapril

- 200 pts with LVEF < 45% after anthacycline treatment
- Treatment with enalapril and whenever possible carvedilol as soon as decrease of LVEF was detected
- 42% of patients were responders and had a decrease risk of cardiac events

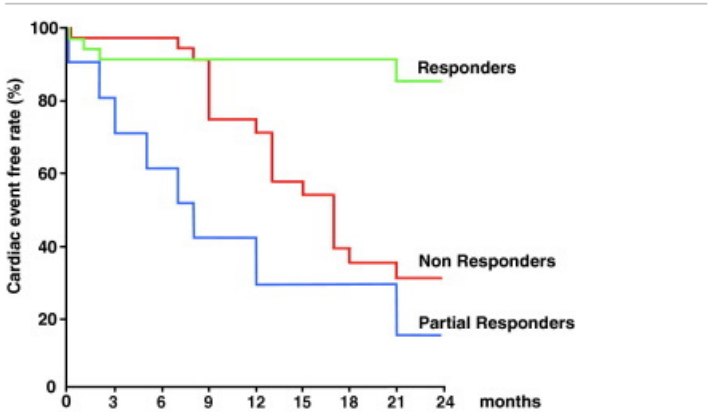


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Figure 2. Cumulative Cardiac Event Rate During the Study Follow-Up

2-year Kaplan-Meier analysis for major adverse cardiac events in the 3 study groups. p = 0.0003 (log-rank test).

Cardinale 2010

Stroke after irradiation of Willis circle arteries

- **3172 adults treated for a tumor before age 16 between 1942 and 1985 in France (FCCSS) ; median follow- up 26 y**

- **54 patients with a stroke**
  - 38 ischémic
  - 16 hemorragic
  - 1 both

    Cumulative incidence at age 50 = 6.8% (SIR = 6.9)

- **Among 442 patients treated for a brain tumor**

  26 stroke

  Cumulative incidence at age 50 = 26.7%

Fayech, 2018

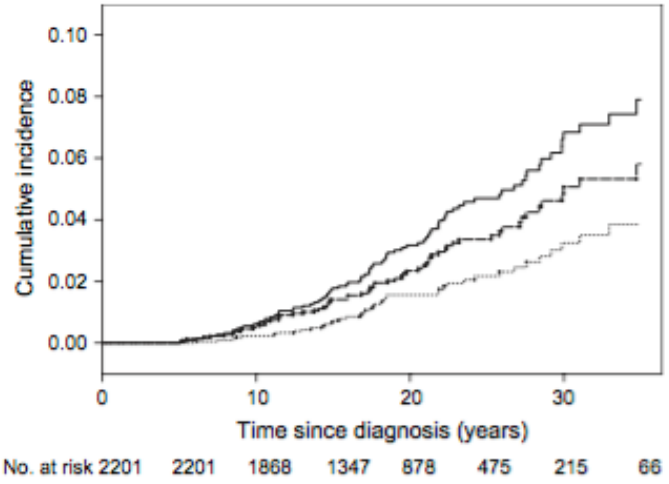
Irradiation of Willis circle arteries: a major risk factor

	Patients	All strokes (n=54)		Ischemic strokes (n=39)		Hemorrhagic strokes (n=16)	
		n	RR* (95%CI)	n	RR* (95%CI)	n	RR* (95%CI)
Average radiation dose to the cerebral arteries (Gy)							
No radiotherapy	970	4	1 (ref‡)	2	1 (ref‡)	2	1 (ref‡)
< 1	1,267	12	1.5 (0.5-4.9)	6	1.5 (0.3-7.5)	6	1.5 (0.3-8.1)
1 < 10	300	9	5.0 (1.4-17.4)	7	6.6 (1.3-34.7)	3	2.0 (0.3-12.6)
10 < 40	386	13	7.9 (2.5-24.6)	13	14.5 (3.2-65.2)	0	
40 and +	249	16	15.7 (4.9-50.2)	11	19.0 (3.9-92.2)	5	12.6 (2.1-78.0)

Fayech, 2018

Stroke after Hodgkin lymphoma

- 2251 HL treated before age 51 between 1965 and 1995
- Median follow-up 17.8 y
- 96 cerebrovascular diseases (55 strokes, 31 TIA, 10 both)
  - Carotid 76%
  - Vertebro-basilar 13%
  - Both 7%
- Median age at stroke 51 y
- Outcome
  - 9 died
  - 2 svere symptoms
  - 29 mild symptoms
  - 48 complete recovery
- Radiation to the neck and mediastinum was an independent risk factor (HR = 2.5, 95%CI1.1 -5.6) vs without radiotherapy



De Bruyne, JNCI, 2009

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PREVENTION of CARDIOVASCULAR COMPLICATIONS

- AVOID RISK FACTORS
  - Tobacco
  - Overweight
  - Hypercholesterolemia
  - Diabetes
  - **Hypertension**
- PHYSICAL ACTIVITY

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Suggested follow-up

- For all patients with cerebral radiotherapy

Brain MRI angiography every 5 years

- Irradiation cervical > 20 Gy :

Ultrasonography of carotid vessels every 3-5 years

Effects of chemo: Antimetabolites and Topo-inhibitors

1. Antimetabolites: Methotrexate, mercaptopurine, cytarabine gemcitabine
1. Topo-inhibitors: etoposide, irinotecan, topotecan
2. Anticancer Antibiotics: bleomycin

- Osteopenia (High-dose methotrexate)

- Secondary 11q23 AML

(Etoposide>2 g/m^2, 5-10% probability)

- Lung injury, pulmonary fibrosis, respiratory failure

(Bleomycin >300-360 IU, <2% of adolescents)

Pentheroudakis G and Pavlidis N Cancer Treat Rev 2007

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Effects of chemo: steroids

- Hyperglycemia➔ insuline resistance➔diabetes
- Hypertension
- Skin changes , hypertrichosis
- Myopathy, muscular atrophy
- Immunosuppression,
- Osteopenia, osteoporosis, bone necrosis (aseptal femoral head necrosis)
- Mood disturbances (agitation, depression, anxiety)

Pentheroudakis G and Pavlidis N Cancer Treat Rev 2007

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Effects of treatment: Osteopenia

- Multifactorial, may lead to clinically significant osteoporosis in adult life:
  - Irradiation
  - Chemotherapy-associated hypogonadism
  - Pituitary dysfunction (Cranial irradiation)
  - Hypothyroidism
  - Steroid-induced bone resorption
  - Renal calciuresis and vitamin D deficiency
  - Poor diet and nutrition

Bhatia S et al. JCO 2003

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Effects from irradiation:

Cranial/Neck/Chest Rx

- Reduced intellectual capacity-cognition is rare
- Subclinical verbal, non-verbal, visual-spatial and attention-concentration deficits
- Neuroendocrine dysfunction

(GH, GnRH, TSH, ACTH low. Prolactin high)

- Hypothyroidism
- Cardiopulmonary disease
- Lung/breast/thyroid cancer

Gurney JG et al. Cancer 2003, Bhatia S et al. JCO 2003, Travis et al. JNCI 2005

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Effects from irradiation:

Abdomino-pelvic Rx

- Chronic enteritis
- Chronic malnutrition
- Intestinal fibrosis (5%)
- Tubular and glomerular dysfunction
- Hypertension (8%)
- Renal impairment (11%)
- Calciuresis-osteopenia
- Bladder fibrosis (rare)
- Gastric/Colorectal/Pancreatic/Bladder cancer

Gurney JG et al. Cancer 2003, Bhatia S et al. JCO 2003, Travis et al. JNCI 2005

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"Take home" messages

- Surgery, chemotherapy and irradiation can be associated with substantial toxicity from many target organs, depending on the timing, intensity and combination of regimens
- These toxicities are of particular concern for AYA because of their young age and very long life expectancy
- Care of AYA with cancer should be always directed in maximizing efficacy and cure potential and at the same time minimizing short and long term toxicities that can significantly impair young patients' quality of life

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Thank you for your attention!