



Prevention and screening of long term side effects

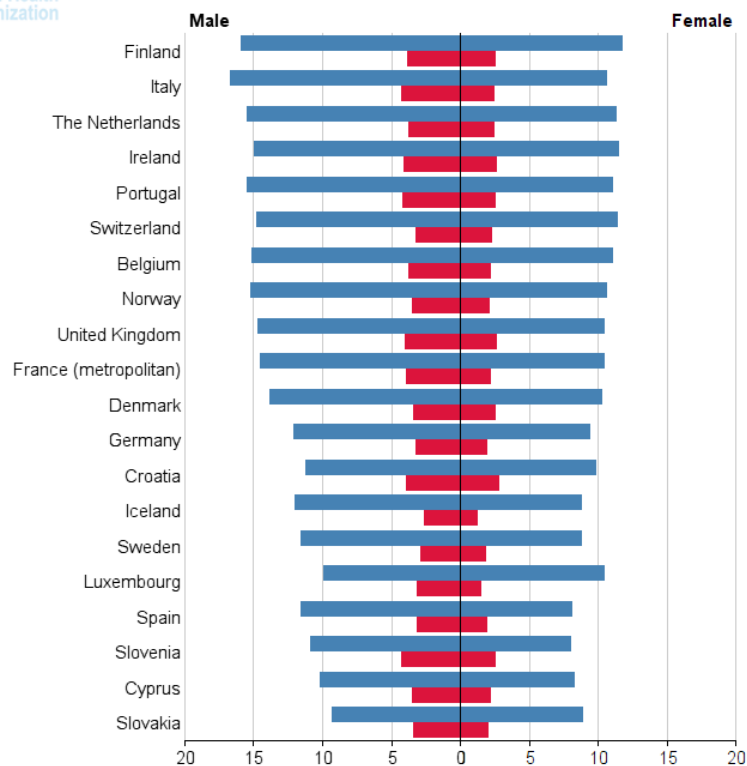
Lena Specht MD DMSc
Professor of Oncology
Depts. Of Oncology and Haematology
Rigshospitalet, University of Copenhagen
Denmark



Incidence and mortality of lymphoma in Europe

Age standardized rates and absolute numbers

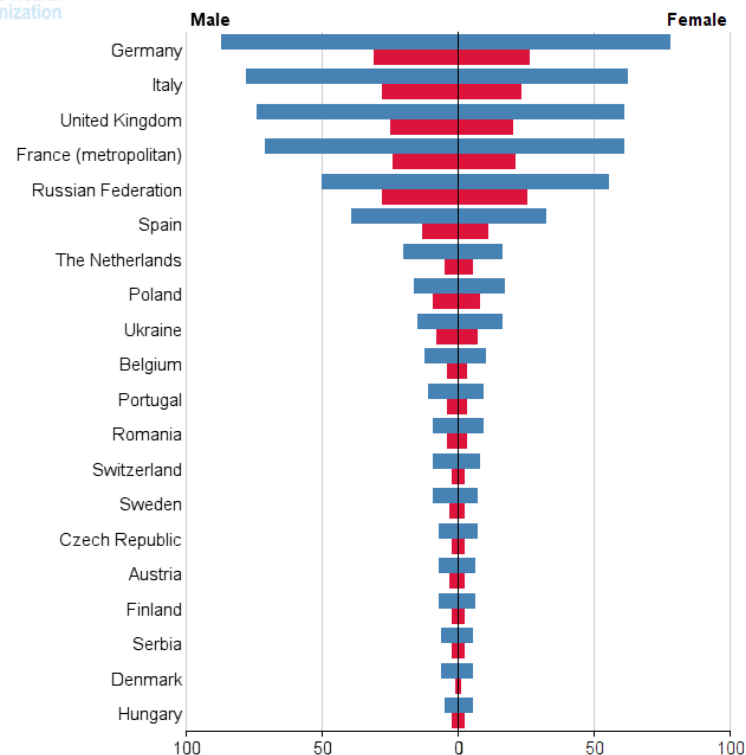
International Agency for Research on Cancer
Hodgkin lymphoma, Non-Hodgkin lymphoma
ASR (W) per 100,000, all ages



GLOBOCAN 2012 (IARC) (22.11.2015)

■ Incidence
■ Mortality

International Agency for Research on Cancer
Hodgkin lymphoma, Non-Hodgkin lymphoma
all ages



(x100)

■ Incidence
■ Mortality

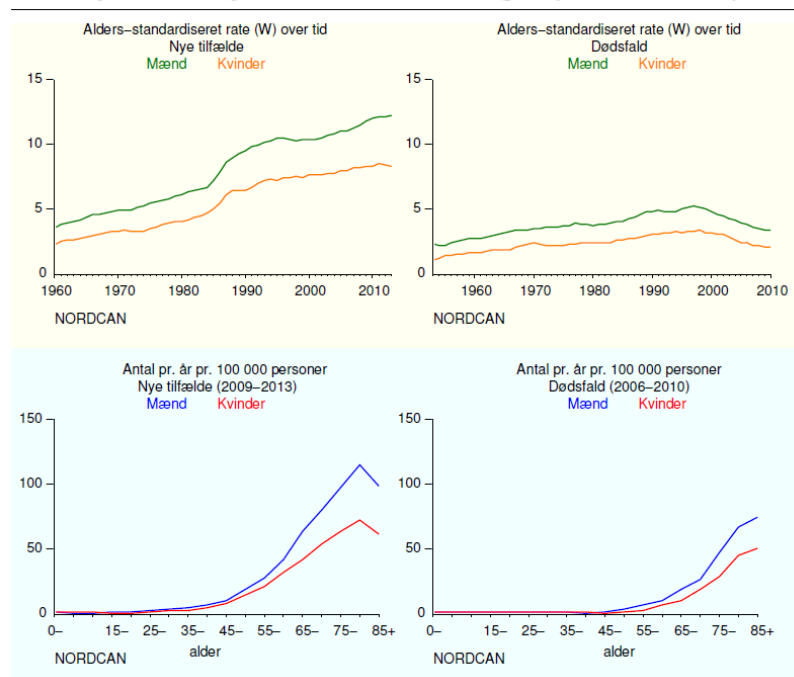
GLOBOCAN 2012 (IARC) (22.11.2015)

Long term survivors in Scandinavia

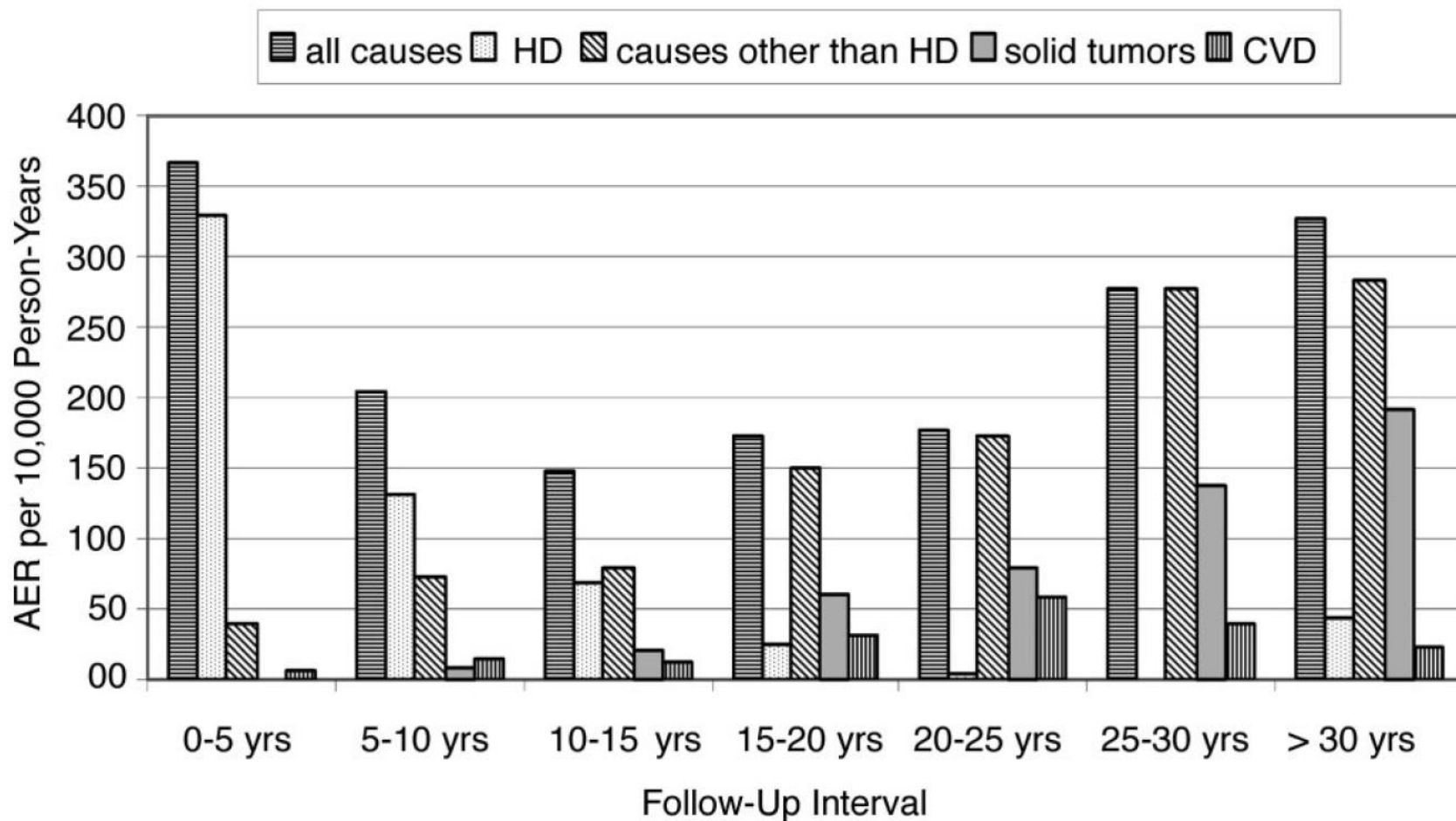


Kræftstatistik: Nøgletal og figurer Norden – Non- Hodgkin lymfom

	Mænd	Kvinder
Antal nye tilfælde pr. år (incidens 2009–2013)	2760	2229
Andel af alle kræfttilfælde (pct)	3.5	3.1
Andel af alle kræfttilfælde bortset fra anden hudkræft (pct)	3.7	3.3
Risiko for at få sygdommen før 75-års alderen (pct)	1.4	1.0
Alders-standardiseret incidensrate (W)	12.2	8.5
– Estimeret årlig ændring de sidste 10 år (pct)	+1.5	+0.9
Antal dødsfald pr. år (2006–2010)	926	812
Andel af alle kræftdødsfald (pct)	3.0	2.8
Risiko for at dø af sygdommen før 75-års alderen (pct)	0.4	0.2
Alders-standardiseret dødsrate (W)	3.6	2.3
– Estimeret årlig ændring de sidste 10 år (pct)	–3.6	–4.7
Personer, der lever med diagnosen ved udgangen af 2013 (prævalens)	22775	20008
Antal personer, der lever med diagnosen, ud af 100 000	174	152



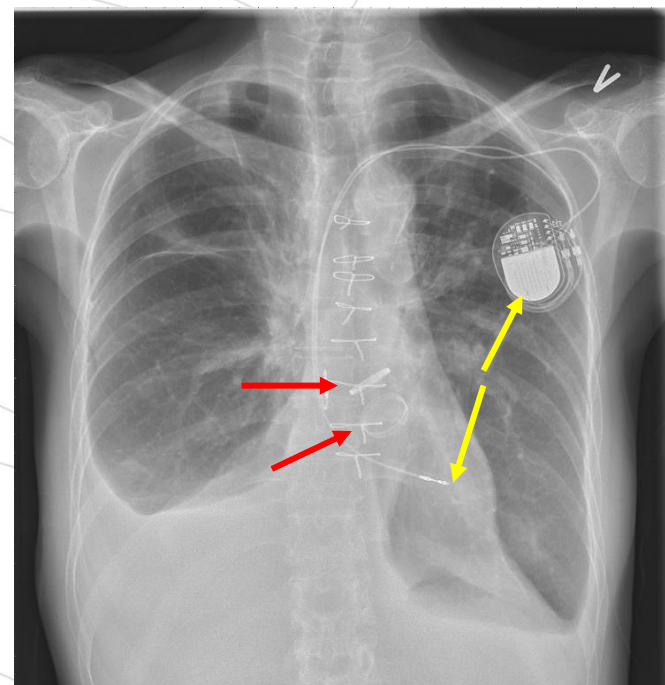
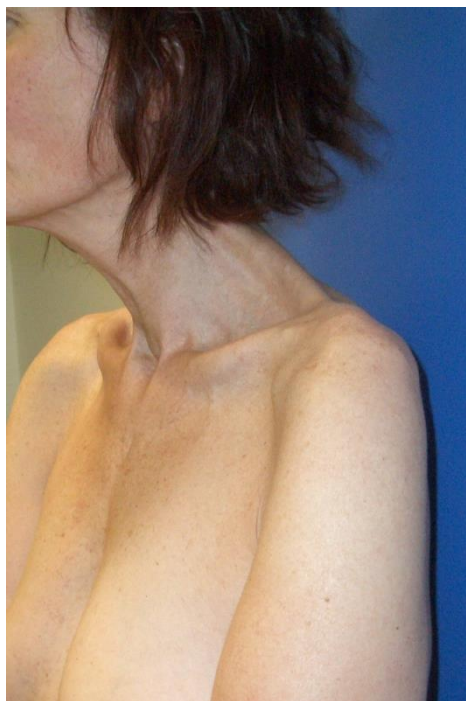
Absolute excess risk of death from different causes in a Hodgkin lymphoma cohort study (Aleman et al. 2003)



Facts about radiotherapy in lymphomas

- Most lymphoma types are highly radiosensitive and lower radiation doses (30-40 Gy) sufficed compared to solid tumours (60-80 Gy)
- Radiotherapy was the first modality to cure lymphomas
- Very extensive radiation fields were used in the past (extended field radiotherapy)

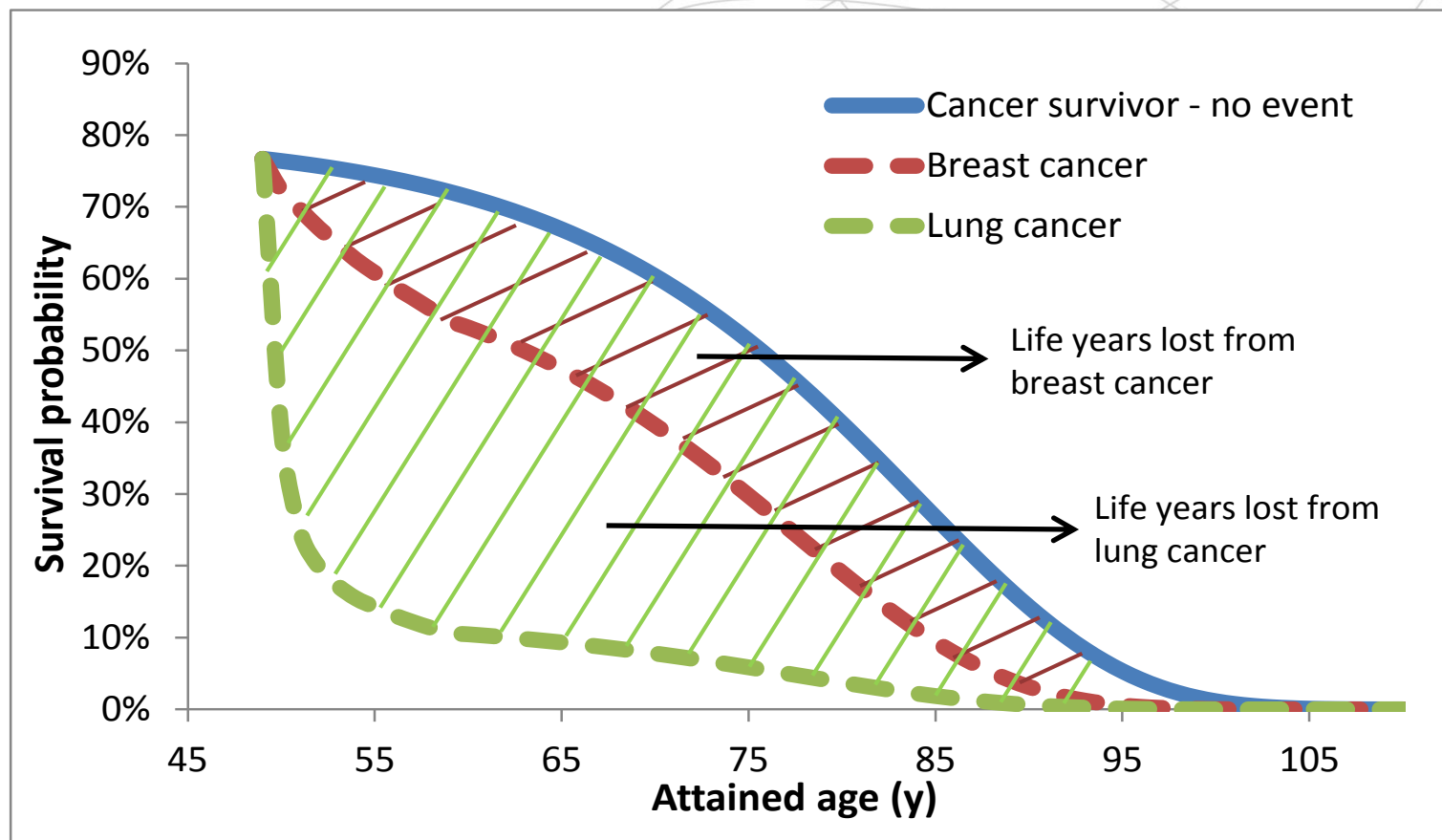
Radiotherapy to the very large volumes used in the past caused serious long-term sequelae in patients surviving many decades



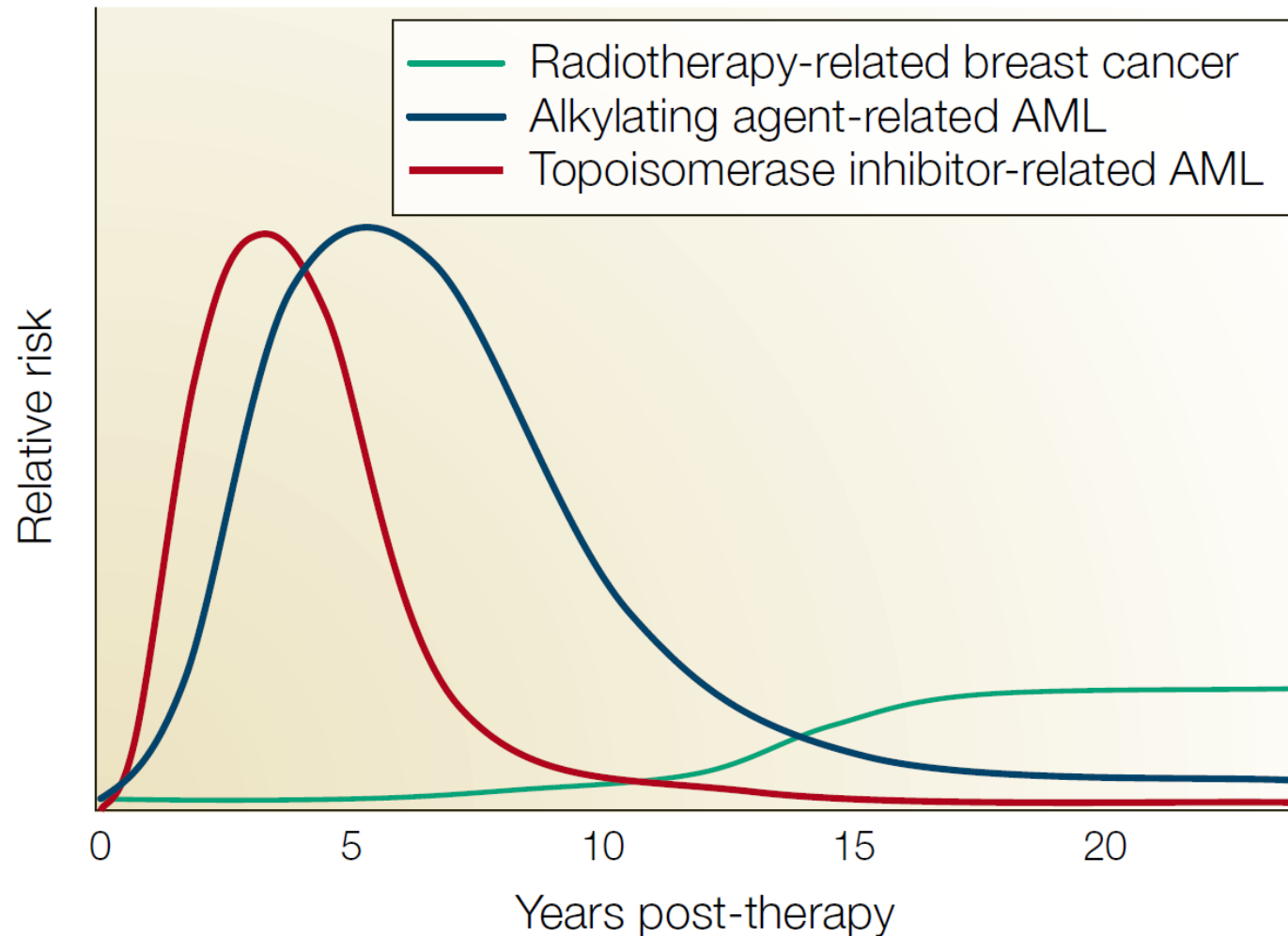
Quantifying risks from several competing adverse endpoints

- Find the age-specific excess hazard ratio (hr_{excess}) of cancer survivors compared to the general population for each endpoint
- Find the hr_{excess} dependency on the radiation or chemotherapy dose
- Excess hazard (h_{excess}) attributable to each endpoint:
- Probability of surviving, after having contracted an endpoint, is then taken into account

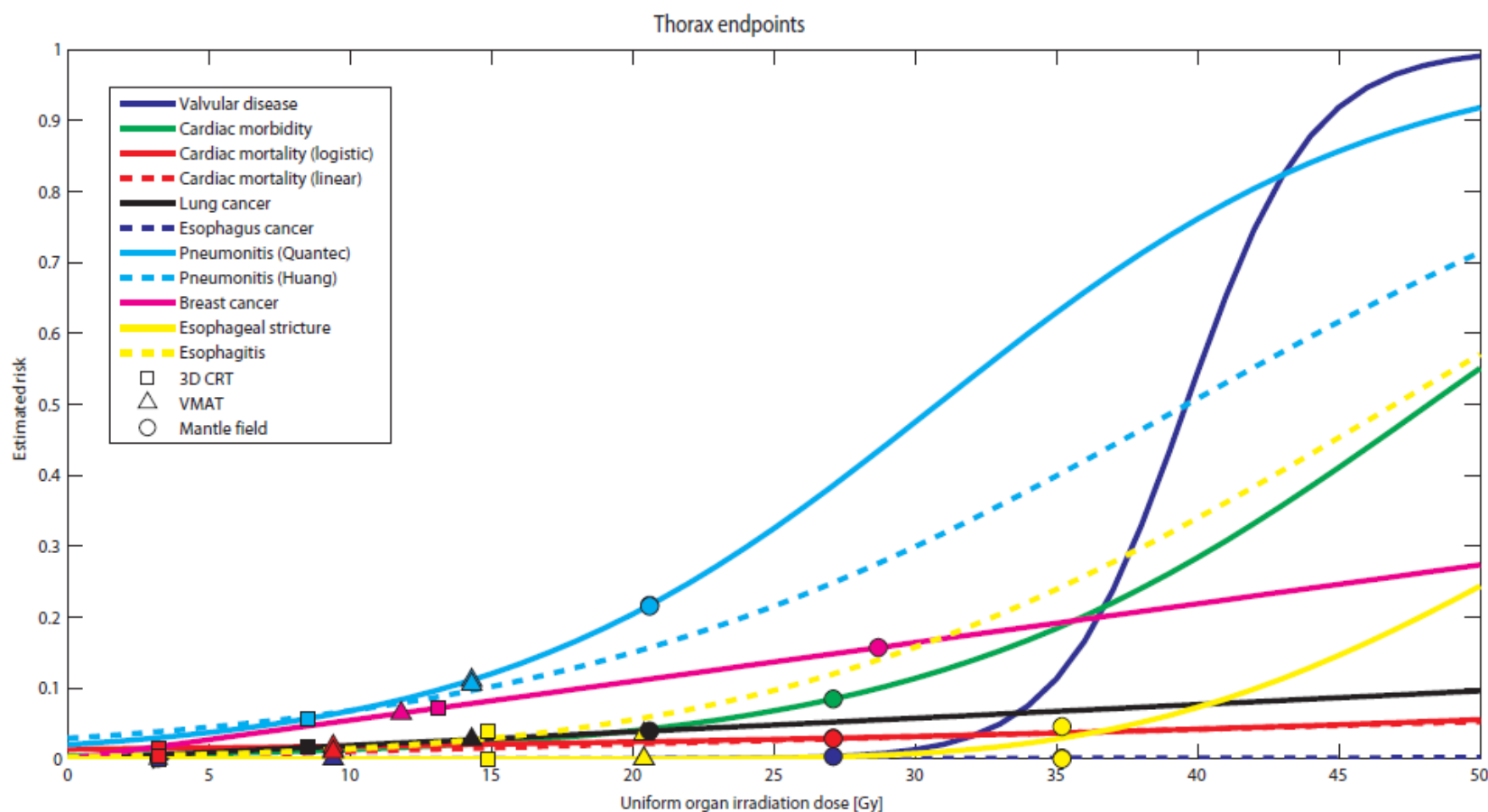
Not only the risk but also the gravity of a late effect must be taken into account



Time to excess risk must also be taken into account



Ideally, normal tissue complication probability models for all relevant risk organs should be combined for each treatment strategy



Secondary malignancies, how to avoid them

- Maintain high cure rate with no more therapy than is strictly necessary
 - Cure with first treatment is important
 - Recurrence is usually treated with high dose chemotherapy and stem cell transplantation
 - These patients experience much more acute and long term toxicity
 - Only about 50 % achieve long term remission
- Modern radiotherapy is associated with much less long term complication probability than the extended fields of the past
 - Highly conformal radiotherapy based on advanced imaging and treatment planning and delivery
 - Special techniques, e.g., respiratory adapted radiotherapy
 - Lower doses
- Chemotherapy is also associated with long term complications, but less data are available
 - Limit alkylating (and other) agents
- Biological treatments: very little is known of long term complications

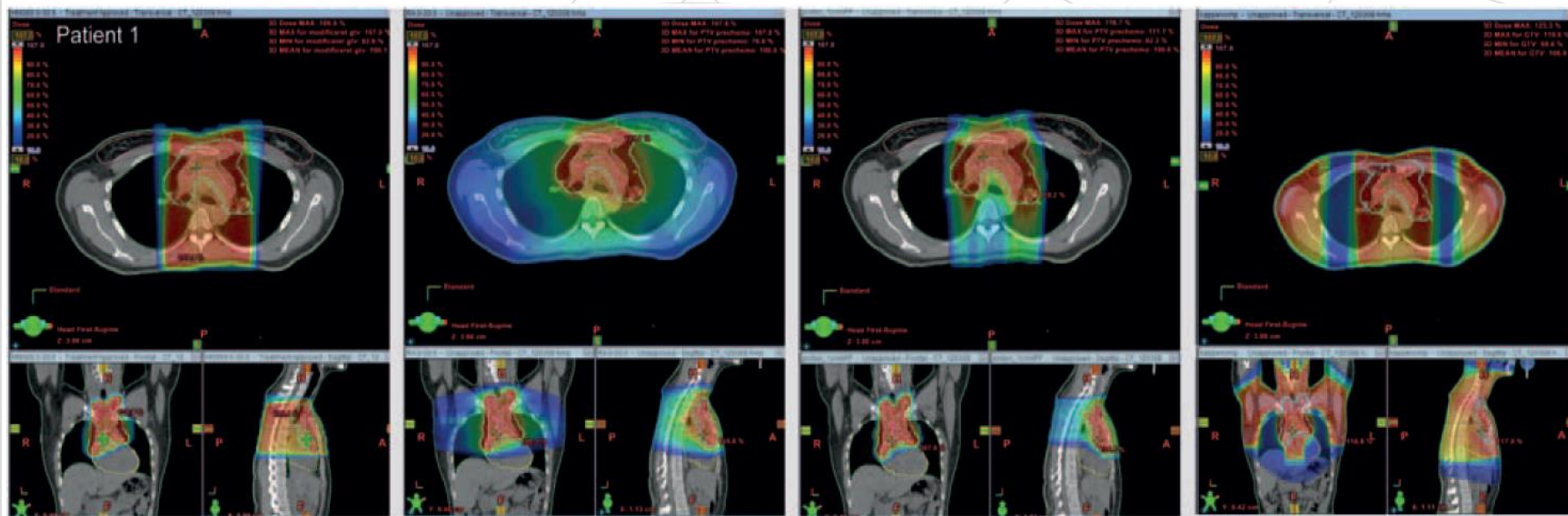
Different modern techniques vs. extended fields of the past

AP-PA

IMRT

IMPT

Mantle field



Maraldo M et al. Ann Oncol 2013; 24: 2113-8

Guidelines (interventions have rarely been tested in randomized trials)

- After radiotherapy including breast in women < 30:
 - start mammography (MRI?) 8-10 years after treatment
- After alkylating agents and radiotherapy including lung:
 - Stop smoking
 - Annual chest imaging for patients at increased risk of lung cancer
- Immune compromised patients:
 - Sun-safety practice
 - Regular self-examination and annual skin examination by dermatologist
- After radiotherapy to the abdomen:
 - Selected patients (e.g. family history) colonoscopy screening every 5 years starting 10 years after treatment

Cardiovascular disease, how to avoid it

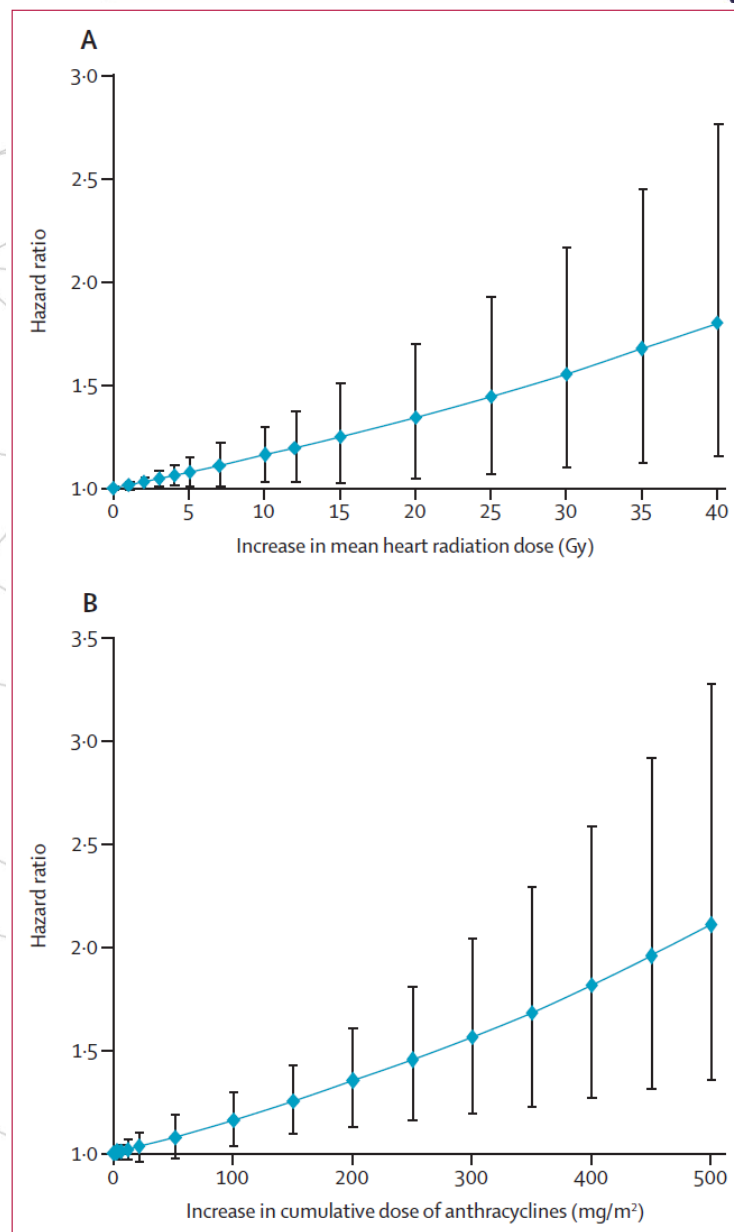
- Radiotherapy:
 - Limit dose and volume to the heart
 - Highly conformal treatment to involved site only
 - Treatment in deep inspiration breath hold
- Chemotherapy:
 - Free-radical scavenging cardioprotectant (Dexrazoxane), but concern about possible interference with anticancer activity
 - Some indications of possible benefit from ACE-inhibitors and beta-blockers (no evidence yet)



Dose-response data for cardiotoxicity

- Hazard ratio for cardiac event:
 - 1.015 per 1 Gy mean heart dose
 - 1.077 per 50 mg/m² doxorubicin
- 5 Gy mean heart dose corresponds to 1 cycle of ABVD

Maraldo MV et al. Lancet Haematol (e-print ahead of publ.)





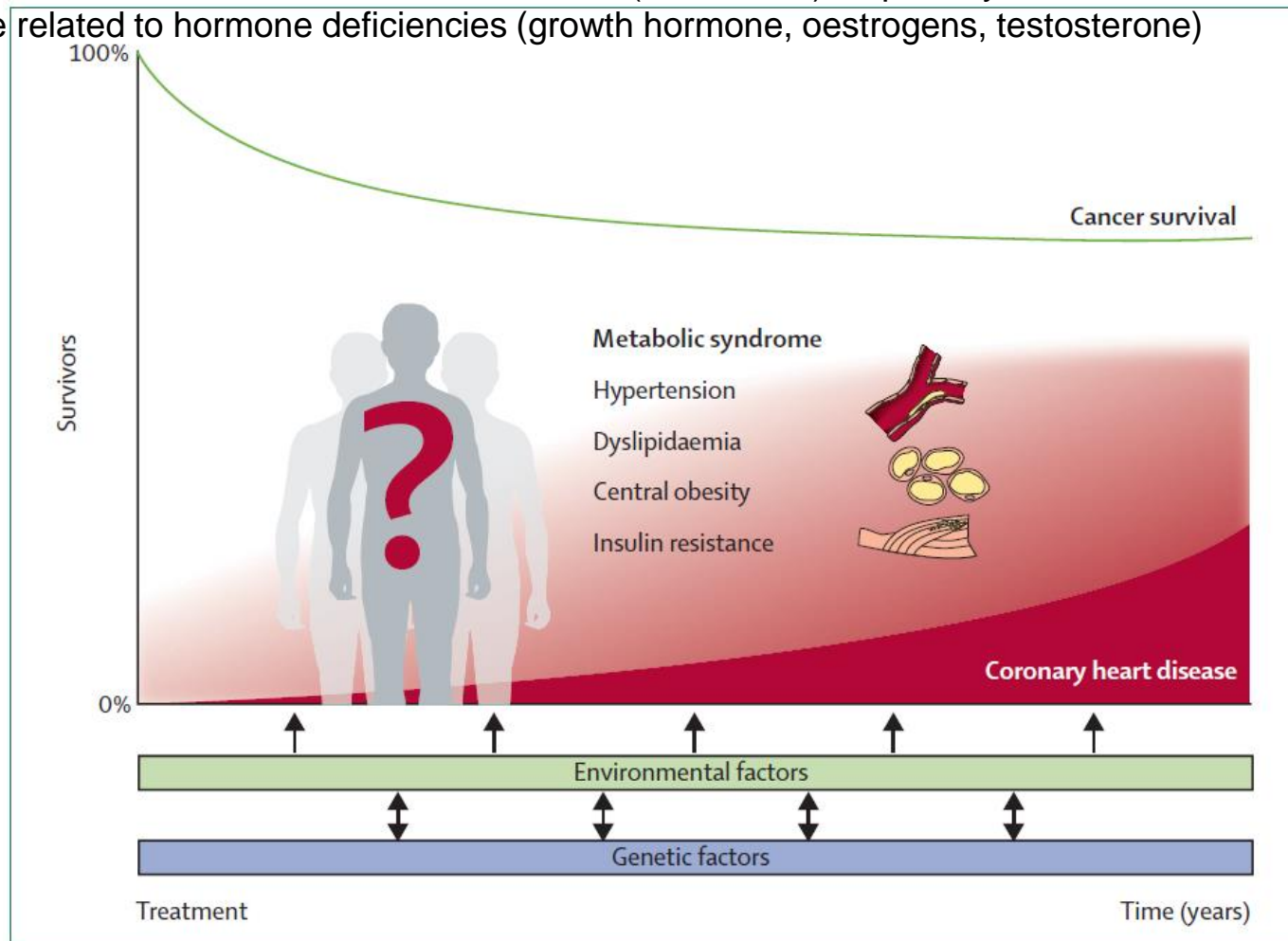
Guidelines for cardiac follow-up

- Annual blood pressure, serum glucose, lipid screening
- Consider baseline echocardiogram at 10 years
- Possible screening tools (evidence for use as standard is still lacking):
 - Serial endocardial biopsy
 - Serial BNP and troponin level testing
 - Serial MUGA or radionuclide angiography
 - Exercise testing
 - Echocardiogram

Carver JR et al. ASCO guidelines.
JCO 2007; 25: 3991-4008

Metabolic syndrome

- Cluster of cardiovascular risk factors
- Associated with increased risk of type 2 diabetes and atherosclerotic disease
- Associated with cancers and cancer treatment (RT and CT), especially in children
- May be related to hormone deficiencies (growth hormone, oestrogens, testosterone)



Endocrine function

- Chemotherapy (alkylating agents), radiotherapy to pelvic area:
 - Options for preserving fertility prior to treatment initiation
 - Sperm banking
 - Ovarian or egg freezing
 - Effect of hormonal suppression during chemotherapy uncertain
- Radiotherapy to the neck:
 - Annual TSH

Peripheral neuropathy

- Overall incidence in patients treated with multiple agents around 38 %
- Higher incidence with treatments including platinum drugs and vinca alkaloids
- Partially reversible in 80%, resolves in around 40 % after 6-8 months.

Peripheral neuropathy

Prevention of CIPN

- There are no established agents recommended for the prevention of CIPN in patients with cancer undergoing treatment with neurotoxic agents. This is based on the paucity of high-quality, consistent evidence and a balance of benefits versus harms.
- Clinicians should not offer the following agents for the prevention of CIPN to patients with cancer undergoing treatment with neurotoxic agents:
 - Acetyl-L-carnitine (ALC)
 - Amifostine
 - Amitriptyline
 - CaMg for patients receiving oxaliplatin-based chemotherapy
 - Diethyldithio-carbamate (DDTC)
 - Glutathione (GSH) for patients receiving paclitaxel/carboplatin chemotherapy
 - Nimodipine
 - Org 2766
 - All-*trans*-retinoic acid
 - rhuLIF
 - Vitamin E

Venlafaxine is not recommended for routine use in clinical practice. Although the venlafaxine data support its potential utility, the data were not strong enough to recommend its use in clinical practice, until additional supporting data become available. No recommendations can be made on the use of *N*-acetylcysteine, carbamazepine, glutamate, GSH for patients receiving cisplatin or oxaliplatin-based chemotherapy, goshajinkigan (GJG), omega-3 fatty acids, or oxycarbazine for the prevention of CIPN at this time.

Hershman DL et al. ASCO guidelines.
JCO 2014; 32: 1941-67

Peripheral neuropathy

Treatment of CIPN

- For patients with cancer experiencing CIPN, clinicians may offer duloxetine
No recommendations can be made on the use of:
- ALC, noting that a positive phase III abstract supported its value, but this work has not yet been published in a peer-reviewed journal, and a prevention trial suggested that this agent was associated with worse outcomes.
- Tricyclic antidepressants; however, based on the limited options that are available for this prominent clinical problem and the demonstrated efficacy of these drugs for other neuropathic pain conditions, it is reasonable to try a tricyclic antidepressant (eg, nortriptyline or desipramine) in patients suffering from CIPN after a discussion with the patients about the limited scientific evidence for CIPN, potential harms, benefits, cost, and patient preferences.
- Gabapentin, noting that the available data were limited regarding its efficacy for treating CIPN. However, the panel felt that this agent is reasonable to try for selected patients with CIPN pain given that only a single negative randomized trial for this agent was completed, the established efficacy of gabapentin and pregabalin for other forms of neuropathic pain, and the limited CIPN treatment options. Patients should be informed about the limited scientific evidence for CIPN, potential harms, benefits, and costs.
- A topical gel treatment containing baclofen (10 mg), amitriptyline HCL (40 mg), and ketamine (20 mg), noting that a single trial indicated that this product did decrease CIPN symptoms. Given the available data, the panel felt that this agent is reasonable to try for selected patients with CIPN pain. Patients should be informed about the limited scientific evidence for the treatment of CIPN, potential harms, benefits, and costs.

Cognitive, emotional and psychosocial function

- Counseling on health habits and psychosocial issues
- Psychoactive drugs have been tested, e.g., Methylphenidate (stimulant), not for routine practice
- Rehabilitation
- Survivorship clinics

Survivorship: Healthy Lifestyles, Version 2.2014

Clinical Practice Guidelines in Oncology

GENERAL PRINCIPLES OF HEALTHY LIFESTYLES

- All survivors should be encouraged to achieve and maintain a healthy lifestyle with attention to weight management (SNWM-2*), physical activity (SPA-1), and healthy dietary habits (SNWM-1*).
- Healthy lifestyle habits have been associated with improved overall health and quality of life. For some cancers, a healthy lifestyle has been associated with a reduced risk of recurrence and death.
- For a healthy lifestyle, all survivors should be encouraged to:
 - ▶ Achieve and maintain a healthy body weight throughout life (SNWM-2*)
 - ◊ Pay attention to calories consumed versus calories expended via diet and exercise
 - ◊ Calculate and monitor body mass index (BMI) (SNWM-A*)
 - ▶ Engage in physical activity regularly (SPA-1)
 - ◊ Avoid inactivity and a sedentary lifestyle
 - ◊ Strive for at least 150 minutes of moderate or 75 minutes of vigorous activity per week, spread out over the course of the week.
 - ▶ Maintain a healthy diet high in fruits, vegetables, and whole grains (SNWM-1*)
 - ▶ Minimize alcohol intake
 - ◊ Limit intake to 1 drink per day for a woman and 2 drinks per day for a man
 - ▶ Avoid tobacco products
 - ◊ Attempt tobacco cessation if currently smoking or using smokeless tobacco
 - ▶ Practice sun safety
 - ◊ Use a sunscreen with an SPF of at least 30 that protects against UVA and UVB rays and is water resistant
 - ◊ Apply generously and reapply every 2 hours or after swimming/excessive sweating
 - ◊ Consider using physical barriers whenever possible (eg, hats, shirts with sleeves, avoidance of direct sun during peak hours)
 - ▶ Follow up with primary care physician regularly
 - ◊ Adhere to age-appropriate health screening, preventive measures (SIMIN-1*), and cancer screening recommendations (See NCCN Guidelines for Detection, Prevention, & Risk-Reduction[†])
- Routine use of dietary supplements is not recommended for the purposes of cancer control (SSUP-1*)

Thank you for your attention

